Society for Cardiothoracic Surgery in Great Britain and Ireland

Perspectives in Cardiothoracic Surgery

The SCTS Ionescu University Volume III

Series Editor
Paul Modi

Invited Editor
Marian Ion Ionescu

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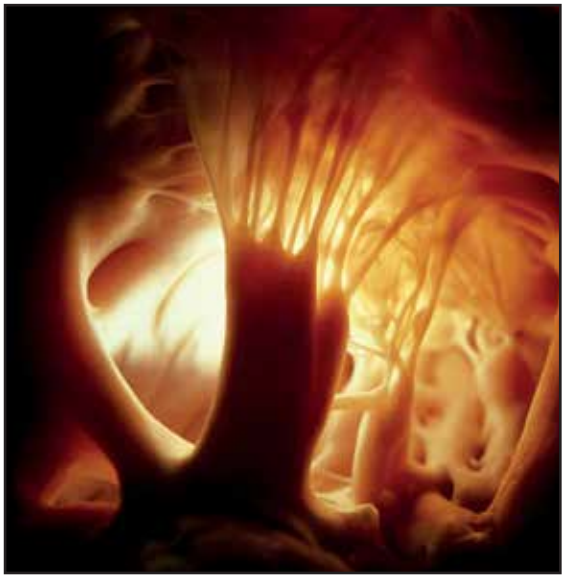

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Perspectives in Cardiothoracic Surgery: The SCTS-Ionescu University, Volume III

ISBN 978-0-9957260-1-7

First published in Great Britain in 2018 by Society for Cardiothoracic Surgery in Great Britain and Ireland, SCTS 5th Floor, Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE.
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Cover photo by Lennart Nilsson

Designed, typeset and printed by CPL Associates, London, UK.

Perspectives in Cardiothoracic Surgery

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Volume III

Edited by Paul Modi

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Section I: Cardiac Surgery

Guest Editors *Yasir Abu-Omar, Cambridge, UK.*
Mark Field, Liverpool, UK.

Section II: Thoracic Surgery

Guest Editors *Steven Woolley, Liverpool, UK.*
Michael Shackcloth, Liverpool, UK.

Society for Cardiothoracic Surgery in Great Britain and Ireland

SCTS Ionescu UNIVERSITY

Preface

"Vides ut alta stet nive candidum"

Quintus Horatius Flaccus
65-8 BC
From Carmina ode I, 9

It is, once again, a pleasure to introduce the third volume in the series 'Perspectives in Cardiothoracic Surgery'. In this volume, the highlights of the third SCTS Ionescu University, held in Belfast on 12th March 2017, are published. This was the most successful SCTS Ionescu University to date with 473 delegates. The twelve streams of the University addressed the key, contemporary issues in cardiac and thoracic surgery. Their presentation as edited, scholarly articles in the printed form we believe enhances their educational value and makes 'Perspectives' one of the important educational tools available to the cardiothoracic surgeons of today and tomorrow.

We are grateful to the authors of the chapters for their time and scholarship. The Section Editors Yasir Abu-Omar, Mark Field, Steven Woolley and Michael Shackcloth have all been essential contributors to the production of the book. Paul Modi as Series Editor has, once again put in much hard work bringing the project to fruition.

It is always a pleasure to recognise the contribution of Mr Marian Ionescu both for his inspiration as Invited Editor and for his support for the University itself and for the publication of this book.

We very much hope that you enjoy reading this third volume of 'Perspectives' and that it imparts pleasure as well as education.

Graham Cooper
President 2016-18

Richard Page
President Elect 2018-20

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Quid Est Veritas

About Intellectual Humility

Almost two thousand years have passed and, as the Romans used to say 'Gramaticans certant'. Thinkers, philosophers, priests, politicians and many who tried to decipher and explain the real meaning of truth as a phenomenon, as an element of thought, have given us a variety of differing interpretations of the words uttered by Pontius Pilatus on that fatidic Friday, the third of April in the year 33AD, according to many Scriptures. Most of the answers and interpretations hit the Wailing Wall and perished. From Francis Bacon to Fredrich Nietzsche, from Mikhail Bulgatov to J L Austin and David Lodge and Ludwig Andreas Feuerbach, etc. etc., the meaning of the notion 'truth' remains open to interpretation. On the other hand, the banal knowledge of being true or untrue is clear. There is nothing to argue about that.

In spite of the highly intellectual questions of the notion of truth, my curiosity pushed me to try to find an explanation. I was told that somewhere outside logical thought and outside the known world of ours, I should try to find the Great Wizard on whom no mortal has ever set eyes. He should be a sage, a hermit or a sorcerer who might know the ways of the occult as well as of the enlightenment.

Suddenly, an arrow of fire crossed the morning mist of the valley. The gates of a new day flung open and light began to flow in waves. I had to start my journey. The path I took was narrow, it led towards the old woods where light and shadow replaced each other in turn as the old trees darkened the twisting trail. Fear began to envelop my being. I stopped from time to time to listen to the stillness. Then I heard my heartbeat as a muffled sound, as my heart would beat not in my chest but deep somewhere under ground.

During my long journey I saw in daylight, in a prairie, Beauty dancing with Zephyr, Favonius and with autumn leaves. Occasionally I caught a glimpse of a flock of angels in flight crossing the diagonal of the sky. At dusk, the lights of a warm sunset were leaning over the earth from the windows of a unique crepescule. At night, shadows moved swiftly between the crooked tree trunks giving the impression of an entire army on the move. In the dark I saw many bugs flying around but only a few fireflies. I was reassured, I was still on our planet.

Suddenly, the firmament broke into pieces. The storm arrived on its giant wings with mighty winds, which shook the whole forest and thunder and lightening proclaimed the majesty of the sky. Shortly after, peace and serenity restored, my journey continued until, with a sound of a soft song, a sunny green prairie opened its smiles to me. From a sanctuary in a cave, a creature covered in rags appeared, dancing on a hieratic song in a sacred language spoken two millennia ago around the Gulf of Corinth. She seemed to be a seeress. Very friendly she told me that today is Wednesday, the third day, call me Tamserku. And if I had arrived the day before, I asked her, what would be your name? She quickly answered Heautontimoromenos, and tomorrow will be Kumbi-ila. She was the last descendant of Pythia of Delphi. I had barely asked her about Quid est Veritas when she said that she cannot talk about the past. Her duty was, and remains, to tell the future and to tell it in cryptic verses, to be interpreted only by the great priests and, if you want an answer to your question, you should go to the Vault Keeper beyond the green river, in the dark, cold woods. I bid her good day and took my journey under my arm and carried on walking. Before the

sunset I reached the bank of the green river. I had to wait for nightfall when the river becomes completely still and the water takes the colour of emerald. Then, one could walk on the solid green water safely to cross to the other side.

The morrow was clear and cool. I walked steadily in the company of two ravens which appeard from nowhere and showed me the way. At the old vault carved in granite, the two heavy gates were ajar. At one of the side pillars was, growing out of the rock, the Keeper. He appeared to have been born, together with time, at the beginning of eternity. His beard touched the ground and his feet seemed to be attached to the rock. He had to lift his eyelashes and eyebrows with his staff to be able to see me. 'What made you take this long journey, what do you search for ?' he asked. 'Quid est veritas' I replied. His answer was simple. 'I cannot tell you. I am here only to guard the souls of those who tried to vanquish death, to be united with a loved one. They rode in the night on wild horses, as fast as they could, but they were caught by the first sunrays and their souls had to enter and remain here. They will wander alone somewhere in the invisible gulag inside the labyrinth with a single exit, towards nowhere'.

Those words might have been just sea waves from a sealed memory that keeps the ledger of our yesterdays and also of all ancient times. 'Do not loiter around here. The Great Priest, the one of the other realm, the Great Wizard may answer your question. Go over the slow River of Regrets, deep in the moving woods and find him.' With these words the old Keeper became again a part of the rock from which he emerged.

I must have approached the end of the world. Somewhere in the middle of motionless time, where even the sun stood still, I journeyed on and I saw from a distance a thin spun-out thread of smoke. It was a cauldron where Datura Stramonium, Mandrake and Emerald powder were boiled, together with some, unknown to me, wild herbs by a priest, like an old man, an anachoret or a sorcerer. He was in fact the Great Wizard who reigns over the land of our dreams. He holds counsel with the trees, with the birds and the beasts of the forest. He is a sorcerer, a thing free, a spirit that envelops the earth and moves in the empty spaces. The vapours from the boiling potion became dense, enveloping the Wizard's whole being. He appeared now like a Byzantine fresco.

'What do you want from me stranger ?' he asked. 'I came to you, Great Spirit, and I found that your shadow is a light to me. I walked a long and difficult path in quest of the ultimate knowledge. What is the meaning of *Quid est veritas*? I want to understand the meaning of the word truth, as used by Pontius Pilatus on that fatidic day of the year 33 of our era.' Following a long silence, the Wizard spoke. 'You will find the roots of truth and untruth and the good and the evil, all entwined together in the silent heart of the earth. You will find them also in yourself.'

'Stranger, lover of unreachable heights, why seek you the unattainable. What storm could you trap in your net ? I cannot give sibylline answers to your need of knowledge. You came to me to talk when you ceased to be at peace with your thoughts, although you knew, in the depths of your heart, that you always knew in thought what you would hear in words. Learned people looked at ancient worlds from afar and believed they could understand their distorted, nebulous look. Veritas-veritatis is a simple latin noun with a simple meaning, nothing else. Vague and nebulous is the beginning of all things, but as we move further back on life's stage, we see the broader picture clearer. Life, and all that lives, is conceived in the mist and not in the crystal, and who knows but crystal is mist in decay.'

As I listened to the Great Wizard I felt as if sinking deeper and deeper in a bizarre

sort of dream within a dream. I still heard his voice. 'Your life oscillates between two contradictions, the duty to speak the truth and the need to hide it. Let your heart decide, you live now in a time of big events and small people. Many people do not know that everything is possible if you really want it. My gift to you at your departure is the truth you will find in the book you carry under your arm without knowing.'

I started the long walk back, hastening towards my world. During the journey, in the autumn drizzle, I felt like the old soldier, under the weight of his wet overcoat, carrying the soul of an entire army defeated in battle.

The sky cleared and everything changed. I stopped and looked back towards sunset. I became the witness of a miracle of light. The last rays of a dying sun reflected their light through the maze of fir tree branches and the whole background of the woods appeared ablaze, like a mysterious stained-glass behind which the agony of an old world unfolded.

The journey of understanding is over. Beautiful and simple, the truth is within us. Days later when I arrived home, indeed and in truth, the third volume of Perspectives had just been published.

Marian Ion Ionescu

December 2017

Section 1

Cardiac Surgery

Yasir Abu-Omar
Mark Field

Chapter 1

Coronary Artery Surgery:
Total Arterial Revascularisation

The Radial Artery as the Second Arterial Conduit

James Tatoulis

The Right Internal Mammary Artery as the Second Arterial Conduit

Umberto Benedetto, David P Taggart

"Nihil quod tetigit non ornavit"

The Radial Artery as the Second Arterial Conduit

James Tatoulis

"Audi alteram partem"

Introduction

The Radial Artery (RA), is a long, robust, and versatile conduit that is assuming greater use in coronary surgery, and is an important conduit in the armamentarium of the coronary surgeon (Figure 1).

Introduced by Carpentier in 1973, the early experience was unsatisfactory with poor patencies at a mean post-operative interval of 18 months. In retrospect, this was due to the inadequate knowledge regarding its muscular wall structure, propensity to spasm, forceful mechanical probe dilatation and lack of anti-spasm medication and spasm prophylaxis protocols[1].

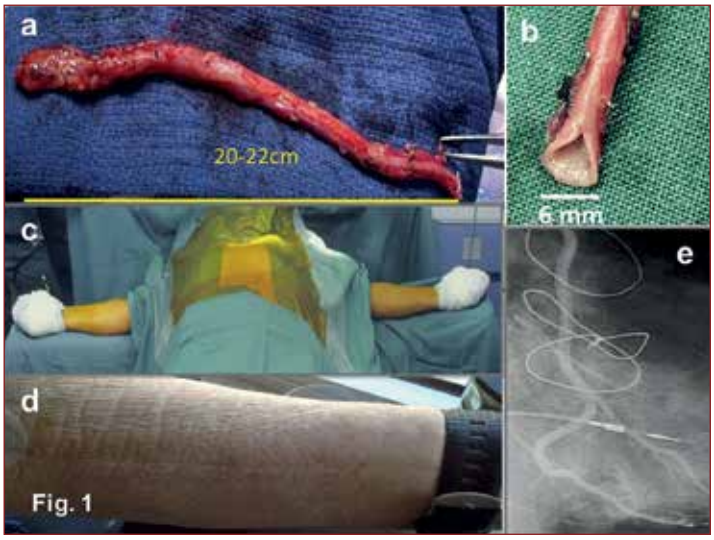


Figure 1:

a. Composite images of a harvested radial artery, 20-22 cm in length.

b. The distal radial artery, prepared for anastomosis. Note excellent quality and good size.

c. Preparation for bilateral radial artery harvest.

d. Healed radial harvest incision 3 months post op.

e. Aorto-coronary radial artery graft to the mid and inferior circumflex marginal.

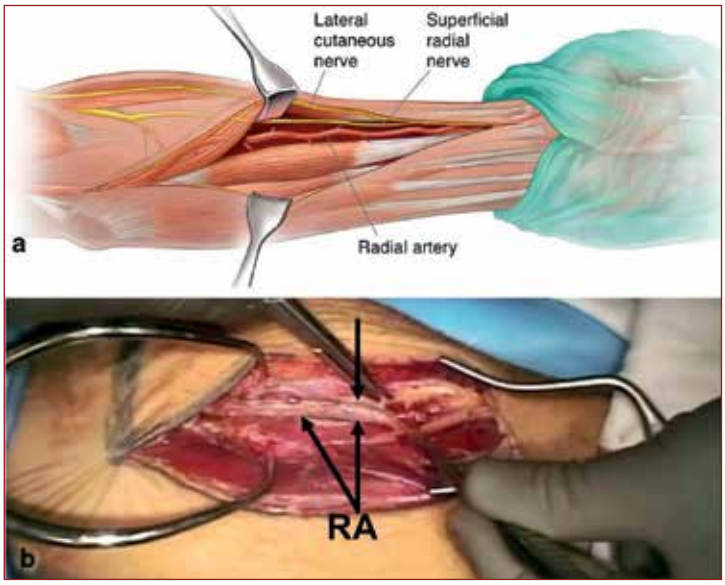


Figure 2:

a. Schematic diagram of the radial artery anatomy in the forearm. Note proximity to the Superficial radial nerve and the Lateral cutaneous nerve of the forearm.

b. Open harvest of the radial artery. Branches are divided between small vascular clips, the adjacent vein is held and there is no direct contact with the radial artery itself.

The RA was re-introduced 20 years later, when Acar noted a substantial number of the original radial artery grafts placed by Carpentier to be patent on subsequent angiography. This led to the concept of a "living", physiologically responsive arterial graft with potential for long-term patency, and improved coronary revascularisation results and patient outcomes if arterial conduit spasm could be avoided or reversed [2].

The RA has been subsequently adopted in routine coronary surgery by an increasing number of units, to the point where it is used routinely in many centres around the world.

Anatomical course and harvest

The RA arises at the elbow and runs between the brachioradialis laterally and the flexor muscles and tendons medially, to the lateral aspect of the wrist where it then contributes to the deep and superficial palmar arches in conjunction with the ulnar artery. Just beyond its origin, there is often a lateral recurrent branch, and a deep interosseous branch (Figure 2a).

The majority of RA branches pass laterally or deeply. There are few or often no branches on the volar/superficial aspect throughout its length. In its upper half, it lies in loose areolar tissue, has few branches, and is easy to mobilize and harvest. Towards the wrist, the branches become more frequent and are shorter before entry into neighbouring structures. Occasionally a relatively large branch may arise 1 – 3 cm above the wrist and run laterally over the radial styloid. Because these branches communicate with the ulnar artery, the distal RA with as many of these branches should be preserved, providing the length of RA conduit required is assured.

Prior to harvest, an Allen's test or similar (index finger arterial wave plethysmography) is essential to ensure adequate ulnar collaterals and hand perfusion [3]. The RA is dominant in 5% of cases and should not be used. Other contraindications to use include severe RA wall calcification. When present, calcification is more pronounced near the wrist and is more frequent in diabetics and older patients. This can be assessed pre-operatively with ultrasound [4]. Generally, calcification does not impinge on the lumen, but may create technical difficulties at the potential distal RA-coronary anastomosis. We try to avoid these

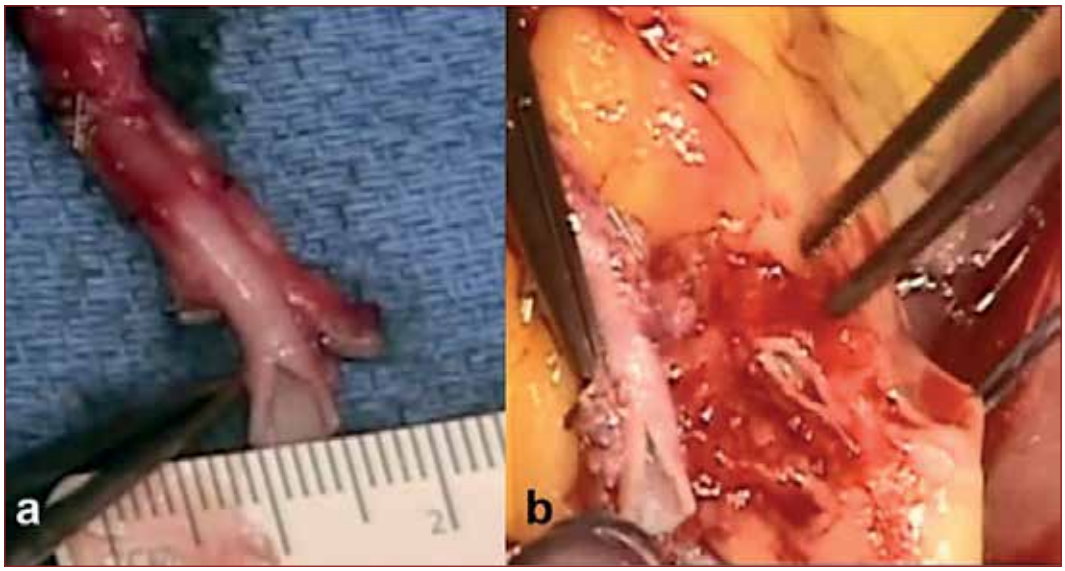


Figure 3:
a. The distal radial artery prepared for anastomosis. 2.5 mm in diameter, 6-7 mm "hood".

b. The distal radial artery held beside the opened posterior descending coronary artery. Note the good size match, with the prepared radial artery hood approximately 25% larger than the PDA arteriotomy.

areas of RA wall calcium. If that is not possible, we orientate the calcification into the hood of the anastomosis. It is often possible to create the distal RA anastomosis between areas of wall calcification, or discarding, or leaving in situ, the calcified components and using the more proximal segment of RA either when a shorter conduit is required or as a Y-graft. We routinely explore the distal RA just above the wrist prior to its harvest to ensure it is of satisfactory size and quality [3]. Other contraindications include collagen diseases such as scleroderma, and in patients who experience intense Raynaud's phenomenon and live in cold climates [3].

The RA may be harvested via either open, or by "endo techniques" [5]. We prefer open harvest as it is less traumatic, and less costly. The "endoharvest" technique is also satisfactory, cosmetically superior, but the endoscopic and "harmonic scalpel" technology is expensive. It is particularly suitable when an experienced operator performs these procedures, in contrast to a teaching hospital environment where trainees rotate through a service every 3-6 months.

The incision for open harvest runs from the wrist to the cubital fossa somewhat medially to avoid the Lateral Cutaneous and Radial nerves. The branches are exposed from distal to proximal via a combination of sharp and diathermy dissection, and the branches divided by scissors between small vascular clips (Figure 2b). After complete mobilisation of the distal half, the distal stump is secured with two medium vascular clips, the RA transected and 3 ml of Papaverine (30mg in 30ml buffered Ringers Lactate), or other vasodilator, in heparinised arterial blood at 37°C is injected into the distal RA with a small bulb end 1mm cannula and

the RA end secured with a vascular clip. Whilst the RA "beats against its occluded distal end" the more proximal branches are divided between vascular clips [3]. Proximally it is important to ensure one is well away from the brachial artery bifurcation. The longitudinal harvest is lateral to, and incorporates, the vena commitantes. The accompanying veins are freed from either side of the proximal RA, and divided between vascular clips. Intravenous 5000 units of Heparin is given, and then the proximal RA is secured with at least 3 medium vascular clips, and a suture ligature of 5/0 Polypropylene. The RA is then transected, haemostasis checked and the RA stored in a Heparinised Papaverine warm arterial blood solution until use. A long "Redivac" drain is left in situ, exiting laterally just below the cubital fossa taking care not to accidentally damage the cephalic vein. The wound is closed in 2 layers and the incision is covered with a waterproof dressing and firmly bandaged, the drain activated, and the arm tucked in by the patient's side with a further sterile drape covering everything from the chest retractor down to the floor. The left internal mammary artery (LIMA), and left RA are harvested simultaneously.

If bilateral RAs are used, they are usually harvested first, the arms put by the patient's side and covered before the sternotomy [6].

Structure, pharmacology and physiology

The RA internal diameter is 2.0 – 2.5 mm distally, 2.5 – 3.0 mm proximally, although it may be less in smaller elderly women. It is slightly larger than internal thoracic artery (ITA). In contrast, the intimal layer is thicker than that of the ITA and has a much thicker (2-3 times) muscular media layer, which is responsible for the greater propensity towards spasm. The distal RA is a good size match, being slightly larger than most coronary artery branches (Figure 3).

To ensure optimum patency, pharmacologic prophylaxis of spasm is essential, and competitive flow must be avoided. The RA shows the best patencies when grafted to occluded or tightly stenosed coronary branches. Vessels with only moderate stenoses are best avoided if possible, and rather (if needed), grafted with an ITA, vein graft or stented, depending on the individual vessel, available options, and patient circumstances [3,10,11].

Deployment

Aorta Coronary

The versatility, length, and size of the RA lends itself to multiple modes of use. The most common is the 1:1 aorta coronary construction and forms the majority of RA use. In our experience, we use this technique in over 70% of patients (Figure 4).

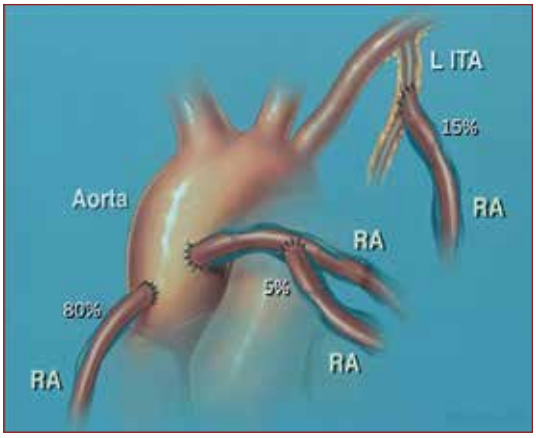


Figure 4: Diagram of potential inflows to radial artery conduits. The internal thoracic artery – radial artery configurations are predominantly used in off-pump coronary surgery.

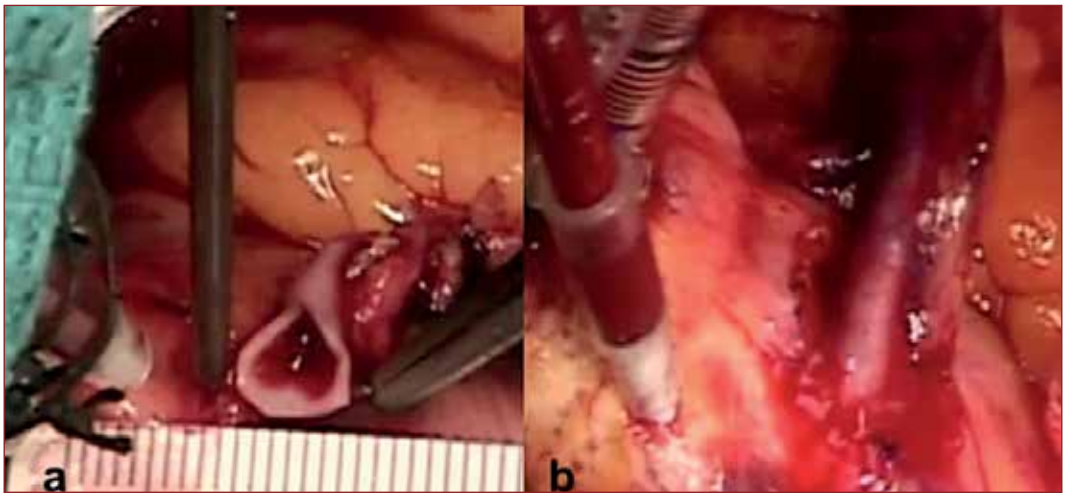


Figure 5:

a. Prepared proximal end of the radial artery graft prior to direct anastomosis to the ascending thoracic aorta. 8-9 mm when opened out, similar in size to a saphenous vein graft.

b. The completed proximal radial artery anastomosis to the aorta, of an aorto-coronary radial artery to circumflex marginal graft.

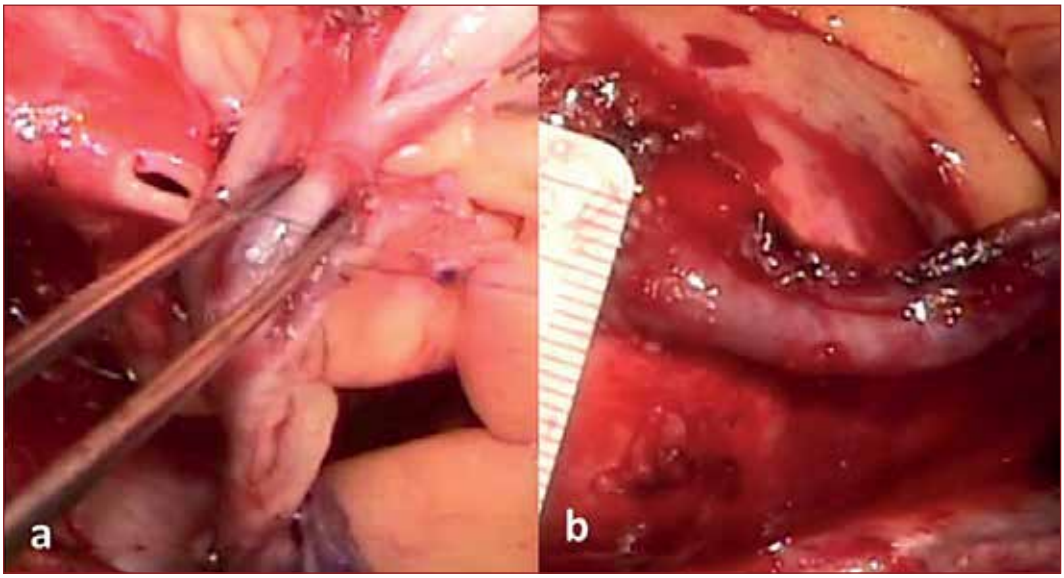


Figure 6:

a. A proximal direct radial artery to aorta coronary anastomosis about to be constructed. The aortic opening has been created with a 3.5 mm aortic punch. The radial artery hood is approximately 30% larger to allow creation of a wide patulous anastomosis.

b. The completed proximal radial artery to ascending thoracic aorta anastomosis (posterior descending coronary graft). 9 mm across, and a wide "hood" ensuring excellent flow into the radial artery graft.

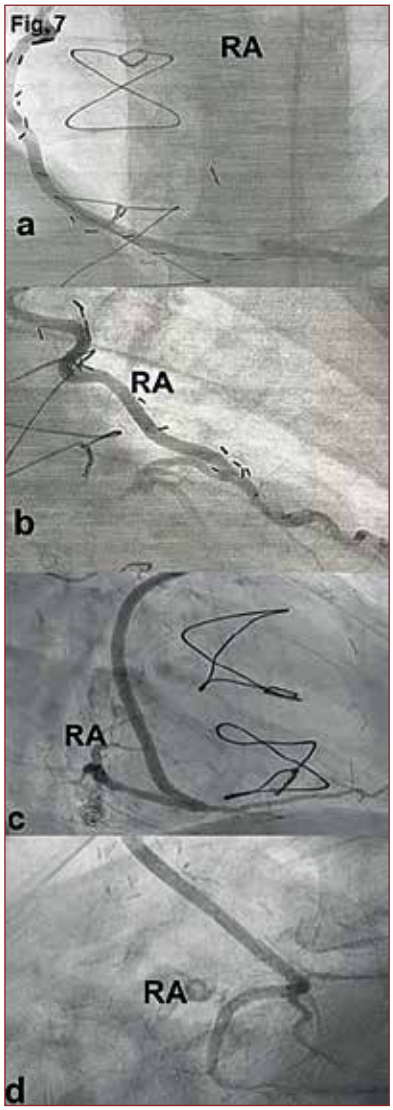


Figure 7:

a. Aorto-coronary radial artery graft to the posterior descending artery.

b. Aorto-coronary radial artery graft to the mid circumflex marginal

c. Aorto-coronary radial artery graft to an inferior circumflex marginal.

d. Aorto-coronary radial artery (RA) sequential graft to the intermediate and diagonal arteries.

All radial artery grafts depicted have been in-situ for 15-20 years. Note the smooth lumen and absence of atheroma in each. This is a typical appearance in patent radial artery grafts.

In RA aorta-coronary grafts, the proximal anastomosis is constructed directly to a standard 3.5 mm aortic punch opening in the proximal ascending thoracic aorta – in exactly the same fashion as one would construct a proximal SVG aorta-coronary anastomosis. The proximal RA is usually 3 – 3.5 mm in diameter and 8 – 9 mm across, when opened out (Figure 5).

In some smaller patients, the RA may be of smaller calibre and more delicate. In these circumstances, a 2.5 mm or 2.8 mm aortic punch is used, and the proximal RA hood is made intentionally longer to mitigate against having a flattened proximal RA inflow hood. Alternatively, inflow can be from the LIMA. A wide patulous anastomosis should be the end result (Figure 6).

Sequential grafts can be readily constructed, because of the excellent size match, robust wall, and length. This technique helps to maximise the number of arterial anastomoses and is associated with excellent survival. RA patencies whether used a single, or sequential grafting appear to be similar. There are some reports however that the most distal segment of the sequential RA graft may have inferior patency and string signs, so ending the sequential graft on a tightly stenosed large distal vessel would seem to be ideal.

The RA is up to 22 cm long, and from the aorta can usually reach any coronary vessel. The aorta coronary format is the commonest use either as a single aorta coronary conduit, or in a sequential fashion (15% of our cases, but often routinely by others). In younger patients (< 70 years), we prefer to use bilateral ITAs with the LIMA to the LAD, and the RITA to the next most significant coronary vessel - usually the circumflex, either by an in situ skeletonised RITA through the transverse sinus to a high circumflex marginal, a LIMA/RITA Y-graft, or a free RITA graft to the circumflex [12]. Hence in such a situation, the RA would be used to the posterior descending, or left ventricular branch, or both (Figure 7a). In general, we prefer not to graft the RCA prior to the crux, as it usually has significant wall disease (even though widely patent on angiography) and new disease often forms at the crux many years post-operatively [3].

In older patients, we place the RA to the circumflex system (Figure 7b). The distal RCA could be grafted (if indicated), with either an additional RA (bilateral RAs) or an SVG – particularly if there had been a prior RCA occlusion and inferior wall scar [6].

In diabetic patients (but not morbidly obese) we would use two skeletonised IMAs, supplemented with an RA to the PDA, or alternatively an LIMA and two radials (Figure 7c, d) [3,6,10, 12].

LIMA–RA Y- or T-grafts

We use this technique in approximately 15% of our cases, particularly if there was conduit shortage, or in anaortic off pump surgery [3]. We construct the anastomosis in a longitudinal (Y) fashion, on the anterior wall of the LIMA either just above or just below the second intercostal branch so that the anastomosis lies within the pericardial cavity and sits on the anterior aspect of the pulmonary trunk. We support the anastomosis by interrupted sutures in the adventitial tissues, and loosely "anchor" the LIMA in the region of the Y-anastomosis to the epicardial fat over the pulmonary trunk. This arrangement allows multiple sequential anastomoses to be constructed with the RA, which can usually reach to the posterior descending. The volar aspect of the RA is preferred for construction of sequential anastomoses as there are usually no branches, allowing placement of the RA arteriotomy at any chosen/ideal location (Fig 8). We prefer to construct the sequential anastomoses in a parallel fashion, if possible, or if not, the orientation is such to allow the best possible lie of the graft (Fig 9a) [3,6,10, 13].

The larger size and thicker wall of the RA make it easier to use in a sequential fashion in grafting intramyocardial coronary vessels, by comparison to the RITA, with less chance of flattening or a "seagull" effect. The sequential anastomosis should be constructed as close to parallel as possible whilst ensuring the best possible lie of the graft.

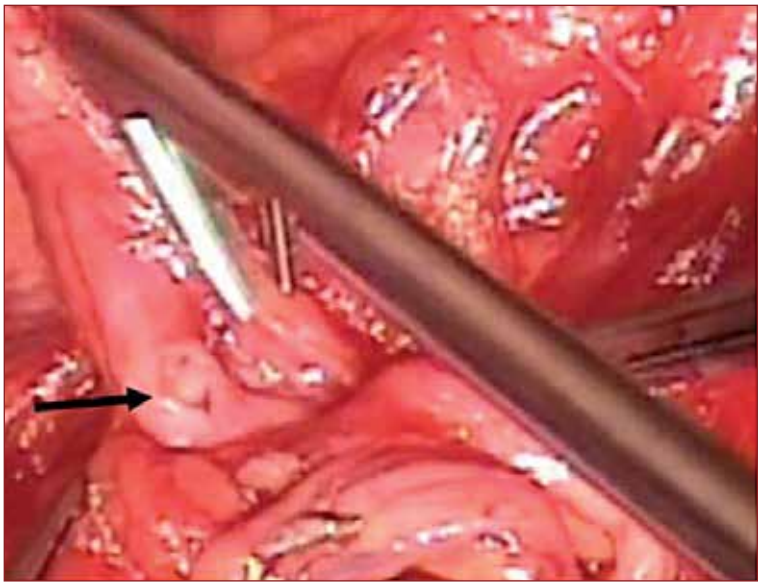


Figure 8: Arteriotomy in the radial artery in preparation for sequential anastomosis. The radial artery is approximately 3 mm in diameter and the arteriotomy approximately 5 mm in length. In general, the volar side of the radial artery is used for sequential anastomoses, as there are usually no or very few branches

"Baby Y-graft"

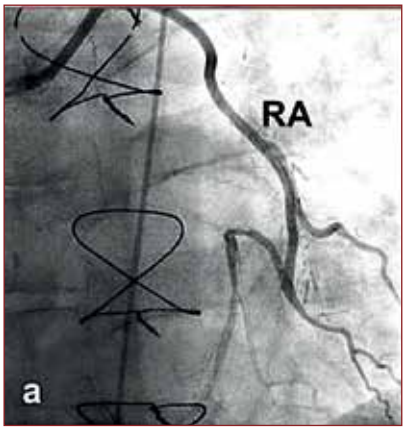
Not infrequently, the location of the stenosis, and wall disease in the circumflex marginals may mitigate against ideal sequential grafting, i.e. the stenotic lesion in the first circumflex marginal is more distal than that in the second. To allow uncompromised selection of the best anastomotic target area, we graft the most distal circumflex vessel at the appropriate site with the main RA graft, and then use a short segment of RA (often 3-5 cm) to graft the more proximal circumflex marginal in the most ideal site, and then construct a proximal end-to-side anastomosis. The inflow to the main graft can either be directly from the aorta, or from the LIMA (Fig 9b).

A similar technique can be used to the inferior LV. In this instance, the main aorto-coronary RA graft would go to the PDA, and an additional 4-5 cm RA segment runs from a more distant left ventricular branch (LVbr) or distal inferior circumflex, back to the main RA graft.

Extension graft

The RA can be used to extend a RITA graft, end-to-end in order to sequentially graft the PDA and LV branch of the RCA in anaortic off pump surgery (10% of cases). The end-to-end anastomosis can be constructed directly using widely spatulated reciprocating ends. An end-to-side RITA to RA anastomosis is easier, and the "blind" superior pouch of the RA can be excluded and a smooth laminar inflow created by the angled placement of a vascular clip.

Occasionally an intended aortocoronary RA or SV graft may be unintentionally short. The best management is to extend this end-to-end with a segment of RA (or SVG) if any has been left over. Often only a 3-4 cm segment is all that is required.



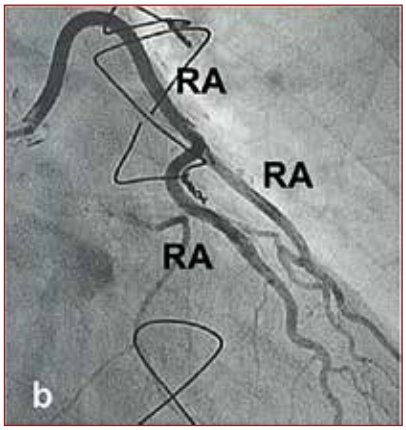


Figure 9:

a. Aorto-coronary radial artery sequential graft to an intermediate, and circumflex marginal artery.

b. Aorto-coronary "baby y" radial artery configuration to the intermediate, and first circumflex marginal. These vessels were separately stenosed, but the anatomy was such that sequential grafting would have been difficult. This anatomic situation was addressed by a "baby y" graft. The main aorto-coronary graft is to the first circumflex marginal. A short segment of radial artery graft runs to the intermediate.

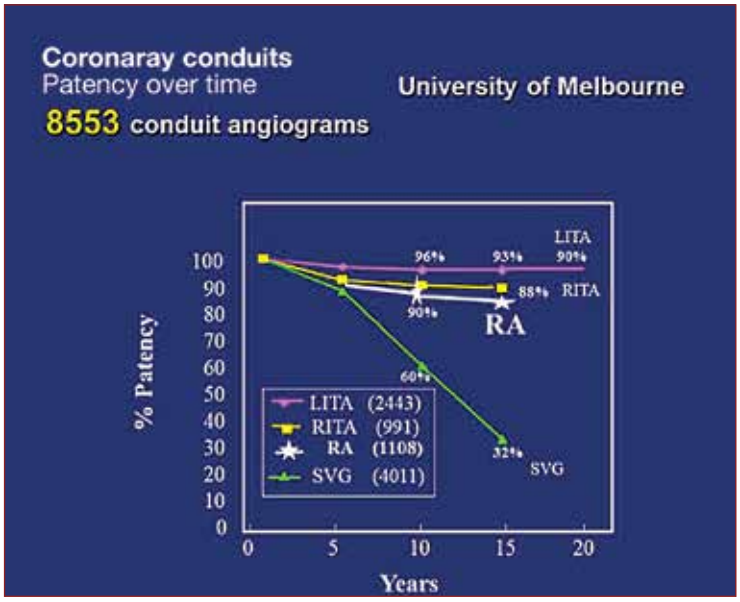


Figure 10: Graph showing patencies of coronary bypass grafts in 8553 consecutive symptom directed graft angiograms (University of Melbourne). The radial artery (RA) and right internal thoracic artery (RITA) are both 90% at 10 years, and 88% at 15 years. Far superior to saphenous vein graft (SVG) patency of 32% at 15 years. LIMA = left internal mammary artery

Inverted T graft

This is another alternative when left-sided vessels do not align for an ideal sequential graft - an aortocoronary segment (SVG or RA) is connected end-to-side to the central portion of an RA conduit, with flow passing superiorly to an intermediate or high marginal artery, and inferiorly to a large second diagonal [14].

Patency

Observational Studies

Observational studies of 10 years and beyond describe excellent RA patencies, with reports of 89% patency at 10 years [3, 15], and 86% at 20 years [16]. Moreover, RA angiograms in these late phases show the patent RAs to be smooth, and completely free of any atheroma. These patency results are far superior to any reported with SVG (Fig 10). The excellent RA patencies correlate with better long-term clinical results when multiple arterial grafts (including RA) are performed as opposed to where the majority of bypass grafts are SVG [3,17].

Randomised Control Trials (RCTs)

Three major RCTs all showed superior RA patencies by comparison to SVG:

1. The Radial Artery versus Saphenous Vein Patency (RVSP) study showed a 92% RA patency by comparison to 78% for SVG at 5 years [18].
2. The Radial Artery Patency Study (RAPS) also showed superior RA patency at 1 year and again at 7 years follow up [19].
3. The Radial Artery Patency and Clinical Outcomes (RAPCO) study again showed superior patency for the RA over SVG at 5 and again at 10 years. The RAPCO studies are particularly relevant in that the RA or SVG was randomised to the next best vessel, performed by a Consultant Cardiac Surgeon, and the SVG was the best on offer, usually harvested from the leg, with uniform diameter, normal wall and often with no branches

and no valves. The SVG was grafted to the next best available stenosed vessel after the LAD. Hence the milieu for SVG patency was the best possible [20, 21]. Additional / other SVGs would be of a lesser quality (branches, valves, thicker walls, larger lumen) and placed to smaller, less important, and often more diffusely diseased vessels.

Patency determines clinical outcomes. The comparisons between RA, RIMA, and SVG as the second graft after the LIMA are considered separately below. Contemporary randomised Trials that have included non–symptom directed angiography of SVG have shown early failure to be as high as 12% within 1 week. In the Prevent IV trial where over 4000 SV grafts were studied as part of the protocol, SV grafts showed a failure of 26% at 12 months. SVG failure was higher in off-pump surgery, and with endo harvesting of SVG, which is now performed in over 80% of cases [22].

In an observational study of over 4000 SVGs, patency at 10 years was 50%, and 13 years 32% and many of the patent SVGs in the late phases, though patent, were atheromatous [23]. Once RA grafts are in position and are patent (i.e. no technical, nor competitive flow issues), then they remain free of atheroma and remain patent in the long-term. By contrast SVGs are affected by sub-intimal proliferation (2-5 years post-operatively) and then from progressive atherothrombosis and eventually occlusion in the long-term (5-15 years) [3, 11, 16, 23, 24].

Clinical Results

The overall survival for patients having CABG, which include a RA graft will vary depending on age, co-morbidities, and number of arterial grafts (or conversely venous grafts). All reports show better long-term survival and fewer Major Adverse Cardiac Events (MACE), particularly greater freedom from recurrent angina, reoperation, myocardial infarction (MI), and repeat revascularisation, in patients who have had multiple arterial grafts (MAG) which include RA. Average survivals are 85-90% at 5 years, 70-80% at 10 years and 55-60% at 15 years [3, 10, 17, 25-27]. Broadly, for every 100 patients operated on, 10 more will be alive 10 years post-operatively if they had multiple arterial grafts (including RA) by comparison to an ITA and SVG [10, 26]. Specific sub groups will be considered below.

RA versus saphenous vein as the second graft

The clinical outcomes parallel conduit patencies. It takes at least 10 years for the difference in clinical outcomes to appear as the survival curves progressively diverge from the 7th year onwards. This was also seen when bilateral IMA was compared to LIMA plus SVG. Many groups have published long term (10 years plus) results for patients with LIMA plus RA versus LIMA plus SVG. All have shown significant benefit for the former [10, 11, 16, 17, 26]. Typical 10-year survival for LIMA plus RA is 85% - 90% versus 75% - 80% for LIMA plus SVG. In addition, patients with SVG have a higher incidence of recurrent angina, MI, repeat revascularisation and leg wound infection. Infection in the RA harvest site is extremely rare. Recent modifications of SVG use (LIMA/SVG Graft, external “splinting”) and harvest are showing more promising medium term SVG patencies [28-30].

RA versus RIMA as the second graft after LIMA

Clinical outcomes at 10 years and beyond are similar when either RA or RIMA is used as a second graft to the second most important stenosed coronary artery. Some reports show an advantage for the RA and others for the RIMA [25, 31–34]. These differences may be due to

incorporation of the earlier experiences with the RIMA and/or RA in the long-term follow-up of these patients, and hence encompass the learning curves, evolutional experience, elucidating the best ways of using these arterial conduits, and the delayed appreciation and subsequent management of the importance of spasm prophylaxis and avoidance of competitive flow.

In general, the 10-year survival is 85% - 90%. Bilateral IMA (BIMA) configurations have been associated with higher rates of sternal infection and dehiscence but now this is largely overcome by using skeletonized IMA grafts, which not only protect the vascularity of the sternum, but also result in longer, more versatile grafts [35]. In addition, the RIMA grafts are less affected by competitive flow [36]. Conversely RA grafts are longer, more versatile, associated with fewer sternal problems, can be harvested more expeditiously concurrently with the LIMA and have a significant place in CABG in diabetics, those with chronic obstructive pulmonary disease (COPD), the elderly and the extremely obese [3, 6, 25,33, 34].

Clinical Outcomes – Specific Sub-groups

Diabetes

The RA is well suited to diabetic patients, as it can potentially avoid the requirement for bilateral IMA harvest, and extends the reach of arterial grafts. LIMA + RA for diabetics can be performed with a hospital mortality of less than 1%, similar for that with BIMA or LIMA + SVG, an 80-85% 10-year survival, which is better than LIMA + SVG, and similar to BIMA +/- SVG [37-39].

Fremes and co-workers, in their RAPS trial, found a RA graft patency of 95% versus 75% for SVG at 7.7 years post-operatively ($p=0.004$) This difference was similar in both diabetic and non-diabetic patients, and strongly reinforces the use of the RA in diabetic patients undergoing CABG especially with high-grade target vessel stenosis [39].

Chronic obstructive pulmonary disease (COPD)

Very little information exists for this specific sub-group, however severe COPD is a well described contraindication for BIMA, because of a high incidence of sternal instability, malunion, and infection. Hence to achieve multiple or total arterial grafting, the use of one or both radial arteries should strongly be considered [6].

Gender

A detailed propensity-matched study of 567 female matched pairs, and 1416 male matched pairs found 10-year survival for females was 76% versus 66% for LIMA + RA versus LIMA + SVG respectively ($p<0.001$), and for males 83% versus 73% ($p<0.001$) with the advantage for LIMA + RA [40]. This again underscores the recurrent finding that 10 more patients who have multiple arterial grafts (as opposed to LIMA +SVG) will be alive 10 years post-operatively, for every 100 patients operated on.

Elderly Patients

Older patients, even octogenarians, benefit from multiple arterial grafting - the main form tends to be LIMA + RA. Ten-year survivals in septuagenarians of 70% versus 52% favour LIMA + RA over LIMA + SVG ($p < 0.001$), and similarly in octogenarians, 60% versus 40% ($p = 0.03$) [41].

The Melbourne group reported similar findings. In 507 matched elderly pairs (mean age 71 years), 10 years survivals of 68% versus 52% favoured LIMA + RA over LIMA + SVG (p= 0.008) [42]. These findings are important, as human life span increases. In most western countries. a 70-year-old has a life expectancy of 18 years.

Obesity

Morbidly obese patients are known to have higher rates of sternal infection if BIMA is used and may result in mediastinitis which can be catastrophic, not to mention the prolonged and laborious and multi-interventional post-operative course to remedy sternal wound breakdown. There are no major studies comparing BIMA versus LIMA + RA in this sub-group. Intuitively, use of the radial artery markedly decreases sternal wound infection whilst preserving the benefits of multiple arterial grafting and the additional avoidance of leg or thigh donor site complications for SVG [3, 6].

Renal Dysfunction

There are no specific data in this sub-group. Some workers have reported better long-term survival with similar peri-operative mortality and morbidity with BIMA in patients with severe renal dysfunction and even on permanent dialysis. LIMA + RA can be performed more efficiently, with shorter operative and anaesthetic times, whilst achieving similar patencies, and long-term results similar to BIMA. Hence this more efficient surgery may be appropriate for patients with renal dysfunction, particularly those that may be tipped into requiring long-term renal dialysis by longer surgery.

Conversely if patients requiring CABG are close to requiring long-term haemodialysis, use of a RA may be relatively contraindicated if a forearm arterio-venous fistula is to be constructed. This potential problem may be overcome by creation of a brachial artery-to-vein fistula if the RA has been previously harvested.

CABG Re-Operations

Although specific CABG reoperations are not as frequent due to the greater use of arterial grafts, PCI management of stenosed SVG, antiplatelet drugs, and statins, nevertheless they still represent an important component of CABG surgery. The RA is ideally suited in this environment, as often the best saphenous vein grafts have already been taken (often all the available vein may have been used) resulting in conduit shortage. It makes sense to use the RAs, which are now proven over the past 20 years rather than the worst possible remnants of SVG. In addition, usually two RAs are available, and extensive revascularisation, can be performed, often resulting in total arterial revascularisation (intact LIMA plus new RAs). The results of reoperation with RAs are excellent [43,44].

When re-entry via the sternum is either not required, or contraindicated (past mediastinitis, intact bilateral IMAs) and a new bypass graft is required to an important circumflex, posterior lateral or posterior descending coronary artery, then a RA can be used via a left thoracotomy, from the descending thoracic aorta below the left pulmonary hilum (after dividing the pulmonary ligament) to the appropriate lateral or inferior wall vessel, using beating heart off-pump techniques. The proximal anastomosis is constructed first either using a partial occlusion clamp or an anastomotic device. This way the correct length of the RA can be measured. Often only a short length is required (8-10cm) [6,43].

Left Ventricular Dysfunction (EF < 40%)

CABG with multiple arterial grafts including RA can be performed in this group with excellent perioperative outcomes, but with superior long-term results by comparison to LIMA plus SVG. All forms of CABG provide better long-term outcomes in patients with severe left ventricular dysfunction or heart failure by comparison to PCI with drug eluting stents (DES) and even more so with MAG and total arterial revascularisation [45].

Conduit Shortage / Avoidance of Leg Incisions

Prior SVG harvest, severe varicose veins, severe peripheral oedema, leg ulcers, prior lower limb venous thrombosis and severe peripheral vascular disease are all contra-indications for lower limb surgery. In these instances, usually both RAs are available, can be readily harvested, and are usually of excellent quality and allow extensive myocardial revascularisation that would otherwise not have been possible [3, 6, 11, 43].

Skeletonised Radial Artery

The RA can be used in a skeletonised fashion. It can be harvested in this way, particularly with a harmonic scalpel by pushing the accompanying veins away from the RA prior to sealing the individual branches. Alternatively, the RA can be harvested as pedicle together with its two accompanying veins, removed from the forearm and then the accompanying veins can be dissected off ex-vivo prior to use. This technique results in potential maximal dilatation of the RA, and an additional 2-3 cm in length [46].

The Radial Artery as a 3rd Arterial Conduit

There is mounting evidence that the higher the number of arterial grafts, the better the long-term outcomes (beyond 10 years), without compromising the currently established excellent perioperative results. Total arterial revascularisation achieved with BIMA and RA results in superior survival [10, 26, 47, 48]. A recent meta- analysis of 8 propensity score matched series of over 10,000 patients showed that 3 arterial grafts (the majority of third conduits being RA) showed a survival benefit for 3 arterial grafts over 2, of 24% over 6.5 years, hazard ratio 0.8, $p<0.001$ [49].

The instrumented Radial Artery

There is increasing use of the RA, particularly the right, for routine angiography and PCI. Fortunately, the left radial is much more commonly used for CABG. Nevertheless, the instrumented RA is usually significantly damaged in its most distal 3-5cms where a sheath has been inserted, and there is intimal damage within the rest of the vessel by the catheters. Some authors have recommended not to use the RA within 3 months of PCI. We avoid the instrumented RA unless use is absolutely necessary because of conduit shortage, and then we would avoid using the distal 3-5cms [50].

Conclusion

The radial artery is an important though under-used conduit in coronary surgery. It should be part of every coronary surgeon's skill set. It is extremely versatile – long, robust, an excellent size match for the coronaries, facile to handle, easy to harvest and lends itself to aorto-coronary and sequential grafting. It can be harvested and used exactly as a saphenous vein graft but has far greater long-term patency, and it is associated with superior long-term

survival as opposed to SVG. Bilateral RA use further extends possibilities of total arterial revascularisation in those where bilateral IMAs are contraindicated, in morbidly obese diabetic patients and those with COPD, and is extremely useful in repeat coronary surgery where traditional conduits may not be available. Anti-spasm prophylaxis must be used and competitive flow avoided.

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The Right Internal Mammary Artery as the Second Arterial Conduit

Umberto Benedetto, David P Taggart

"Audiatur et altera pars"

Introduction

The choice of conduit for coronary artery bypass graft (CABG) is widely debated by cardiac surgeons [1]. Since the seminal papers published by the Cleveland Clinic group on the use of bilateral internal mammary artery (BIMA) grafts for coronary bypass surgery (CABG) [1,2], it has traditionally been accepted that the use of BIMA at the time of CABG leads to a significant survival advantage especially over the longer term [3,4]. The current United States and European Guidelines encourage the use of arterial grafts including BIMA grafts in patients with long-life expectancy [5,6,7].

The evidence of the survival benefits of right IMA usage is extensive but based mostly on observational series. The Arterial Revascularisation Trial (ART) is the only large randomized controlled trial (RCT) comparing the clinical outcomes of CABG patients receiving single internal mammary artery (SIMA) vs. BIMA grafts [8]. The 5-year interim results of the trial did not show any difference in terms of survival or event-free survival between patients randomised to receive SIMA or BIMA grafts. However, a longer follow-up is needed to draw final conclusions from the ART trial. In addition, as with every RCT, ART has its own intrinsic strengths and limitations. We herein critically review the current evidence on the use of BIMA grafts for CABG and discuss the apparent contradiction between the results of ART and the previous literature.

Angiographic Outcome of BIMA Grafts and Venous Grafts

The patency rate of BIMA has been shown to be excellent and significantly superior to that of saphenous vein grafts (SVGs). Tatoulis and associates [9] reported 15-year BIMA patency rates of >90%. The patency of SVGs is considerably lower. The Project of Ex Vivo Vein Graft Engineering via Transfection IV trial (PREVENT IV) reported a 12-18 months SVG patency of only 75% [10]. SVG patency at 5 and 10 years is usually reported between 75-86% and 55-60% respectively [11-13]. The attrition rate of SVGs is 1-2%/year between 1 to 6 years and 4%/year between 6 to 10 years [14].

In a previous network meta-analysis of 9 angiographic RCTs we showed a significantly increased risk of late SVG graft occlusion when compared with the right IMA (odds ratio (OR):4.07; 95% confidence interval (CI):1.28-20.88) and radial artery (RA) (OR:2.94; CI:1.36-9.00) [15].

Clinical Outcomes of BIMA Grafts

Since 2001, five systematic reviews and 1 meta-analysis compared the clinical outcome of CABG patients receiving single LIMA vs. bilateral IMAs (BIMA). All of them reported a statistically significant survival advantage for the BIMA group. In the most recent of those, Takagi and coauthors performed a systematic review of the adjusted studies that compared LIMA vs. BIMA with at least 100 patients in each group and a minimum follow-up of 4 years [16]. The authors identified 20 publications totaling 70,897 patients. Overall, the use of BIMA was associated with a significant reduction in long-term mortality (hazards ratio (HR):0.80, CI 0.77-0.84). Five studies (11,159 patients) had a follow-up < 5 years. Of these, only one reported a significant survival benefit for the BIMA group.

In a meta-analysis of controlled observational studies with a mean follow up time > 9 years and more than 100 patients in each group, Yi and co-authors pooled data from 9 studies including over 15,000 patients. They reported a statistically significant 21% risk reduction in mortality for BIMA patients (OR:0.79; CI:0.75-0.84) [4]. Only three published studies have failed to demonstrate the superiority of BIMA (Joo 2012, Dalen 2014 and Gansera 2016), however, these were all limited to mid-term (5-7 years) follow-up.

Risk of Sternal Wound Complications

The most important downside of BIMA use is a slightly increased risk of sternal complications. A meta-analysis of observational studies, including 173,000 patients, reported a 38% increase in deep sternal wound infection when a second IMA is used (1.6% LIMA vs. 2.05 BIMA, RR: 1.38; CI:1.29-1.45) [17]. The ART reported an absolute increase in sternal wound reconstruction from 0.6% in the SIMA group to 1.9% in the BIMA group, i.e. an absolute difference of 1.3% or number needed to harm of 78 patients. However, if patients with both diabetes and obesity were excluded, there was very little difference between the groups [8]. The risk increases in patients with diabetes, chronic pulmonary disease, and morbid obesity. Deep sternal wound infection increases the operative mortality by 10-fold, has very high complication rates, and increases hospital costs [18]. The risk of sternal complications can be reduced with skeletonization of the IMAs. Sá and colleagues, in a meta-analysis of 22 observational studies involving 4817 patients, found that the risk of deep sternal wound infection was reduced by 55% with skeletonized IMA (OR:0.44, CI:0.32-0.61) (19). A post-hoc analysis of the ART trial showed that skeletonization almost eliminated the increased risk of deep sternal wound infection associated with BIMA (OR:1.00, CI:0.65-1.53 compared to LIMA) [20]. Alternatively, patients at risk of deep sternal wound infection might benefit from RA grafting. Diabetics are at higher risk of sternal complications and observational studies have shown a survival advantage using the RA vs. the right IMA in these patients [21]. In a sub-analysis of the Radial Artery Patency Study looking at diabetics, RAs outperformed SVGs in long-term angiographic patency (95.2% vs 74.7%) [22].

The Choice Between BIMA vs. RA Grafts

Whether BIMA is superior to SIMA plus the RA is uncertain. In a meta-analysis of 8 propensity score matched studies including 15,374 patients, BIMA compared to the RA was associated with a reduction in late death (HR:0.75, C l 0.58-0.97), and repeat revascularisation (HR:0.37, CI 0.16-0.85) [23]. In the quoted angiographic network meta-analysis and in two RCTs, RIMA and RA patency were similar and/or superior to SVG [17,23,26]. Recently presented results of the 10-year outcomes from the RAPCO trial (n=374) demonstrated similar

patency and better overall survival when using the RA compared to the RIMA (p=0.19 and 0.03 respectively). The RA has patency rates comparable to BIMA grafts when the RA is anastomosed to a target vessel with ≥90% stenosis [24]. The severity of the target vessel stenosis is probably more important for the RA than for the RIMA [25] making the latter better for revascularising targets with moderate lesions. On the other hand, the RA should be preferred over BIMA grafts in patients at significant risk for sternal wound complications.

Effect of BIMA Grafts on Disease Progression in the Native Coronary Circulation

Growing evidence suggests that the conduits used at the time of CABG have the potential to influence the native circulation after surgery. Grafting with SVG accelerates the progression of native coronary stenosis to total occlusion, whereas grafting with arterial grafts is associated with a reduced incidence of progression to occlusion [26]. In the Coronary Artery Surgery Study, a significant increase in the left anterior descending coronary artery territory disease progression was found in patients who received a SVG instead of a LIMA graft [27]. In the RAPCO trial, the use of arterial grafts instead of SVGs was an independent predictor of disease regression in the native vessel at 6-year follow-up [28].

Zhang and associates compared the 5-year progression rate of distal disease in the left anterior descending coronary artery in patients who received percutaneous coronary intervention (PCI) with bare metal stents or drug-eluting stents vs. CABG using the IMA [29]. Patients treated with IMA had a significantly lower risk of downstream disease progression (HR:0.34, CI 0.20-0.59 and HR:0.39, CI 0.20-0.79, respectively). The mechanisms of this protective effect are speculative, but it seems likely that the same vascular mediators that protect arterial grafts from atherosclerosis can elicit their action on the native downstream coronary bed after CABG.

Right / Left Choice with BIMA Grafts

While the use of BIMAs to graft the left coronary system has been consistently reported to be associated with excellent patency rates [30] and improved outcomes [31], the role of a second IMA for revascularisation of the right coronary system remains controversial [32]. Angiographic follow-up studies have demonstrated a hierarchy of right IMA patency; best for the left anterior descending artery (LAD), then the circumflex, and lowest to the right coronary artery (RCA) [33]. Although, a similar hierarchy of patency has also been observed for SVG, it has been shown that the patency of the right IMA is significantly affected by the stenosis of the recipient RCA [30], most likely as a result of competitive flow or poor runoff [34]. The variability of right IMA-RCA graft patency rate according to the severity of the RCA stenosis might partially account for conflicting findings reported on survival benefit from the use of right IMA instead of SVG. Schmidt et al. observed long-term survival of 93% when the right IMA was used to bypass left-sided coronary arteries but only 70% when grafted to the RCA system after a mean follow-up of 9.2 years (p=0.02) [35]. In contrast, Kurlansky et al. found similar survival after a mean follow-up of 12 years [36]. In their series, in situ grafting was used in the majority of cases (approximately 98% of arteries grafted) and when the right IMA was used to graft the RCA, efforts were made to graft severely stenosed vessels and distal branches rather than the main RCA. In this context, Sabik at al. documented equivalent long-term results with the use of the right IMA, whether applied to the left or right coronary artery systems, and this was attributed to careful patient selection [37]. There were 2 important factors: (1) RCA stenosis of 70% to 90% with viable myocardium in its

distribution; and (2) freedom from distal stenosis. In the present cohort, the right IMA was used only in case of native vessel stenosis >75% and this can partially explain the observed survival benefit over SVGs. We recently demonstrated that when compared to vein grafts, the use of right IMA for revascularisation of the RCA system was associated with improved late survival [38]. The beneficial impact on survival with use of the right IMA was delayed by as much as 9 to 10 years and persisted beyond that period. These findings support the hypothesis that the SVG failure rate increases significantly after 5 years and longer follow-up is needed to demonstrate a survival benefit from the use of right IMA regardless of the coronary artery system treated.

The ART Trial

The ART trial is the largest RCT designed to compare BIMA vs. SIMA, with a sample size of 3102 patients [8]. The trial included 28 centers in 7 countries and the enrolment phase lasted from June 2004 through December 2007. The study was powered to detect a 20% difference in mortality at 10 years (the primary outcome), mostly on the basis of a meta-analysis that analyzed the literature existing prior to the year 2000 [3].

At the planned 5-year interim analysis, survival was 91.3% in the BIMA group and 91.6% in the SIMA group without significant difference between the two groups (HR:1.04, CI 0.81-1.32) [8]. It is probably important to note that this survival rate exceeds by 5-10 % those reported in the majority of the studies published in the 1980's and 1990's. The rate of sternal wound complication was 3.5% in the BIMA versus 1.9% in the LIMA group (p = 0.005), and the rate of sternal reconstruction was 1.9% versus 0.6% (P = 0.002).

While the interim analysis of the ART potentially represents a step back for BIMA grafting, alternative explanations need to be considered. First, the attrition rate of SVGs is known to increase exponentially after the 4th-5th post-operative year [16]. It is possible that at 5 years, the SVG failure rate may not be high enough to have an obvious adverse effect on outcomes especially in the era of optimal medical therapy. In the ART trial, extremely high compliance with optimal medical therapy was noted (almost 90% of patients on aspirin, statins and beta-blockers at 5 years). Indeed, in Takagi's meta-analysis, 4 of the 5 studies with a follow up < 5 years did not show a survival benefit for BIMA [16].

There was a sizeable proportion of patients in the SIMA group that received a RA graft as a second arterial conduit (23%). This is another major potential confounder as the RA shows better patency rates and clinical outcomes compared to vein grafts at 5 years and this aspect may have further narrowed any potential differences in clinical outcome between the SIMA and BIMA groups along with a substantial rate of crossover in the BIMA group (16.4%). In addition, the four-fold higher crossover rate in the BIMA arm probably expresses the lack of complete confidence with the systematic use of BIMA grafting. Using BIMA is a more complex operation than the traditional CABG using SIMA and, although surgeons could participate in the trial only if their experience included 50 or more BIMA operations, this number does not seem high enough to guarantee absolute confidence. If this is indeed the case, technical errors (likely more frequent in the BIMA series) could have played a role in determining ART results. It is also noteworthy that in the absence of imaging data it is not possible to quantify the incidence and pathophysiology of graft failure in both groups.

Moreover, almost 25% of ART patients were 70 years or older. The use of BIMA is controversial in older patients [39] and in ART the treatment age interaction approached statistical significance (p=0.08). Finally, the higher incidence of sternal complication in

the BIMA group must be noted because, in ART, the IMA harvesting technique was not standardized and 48.9 % of the BIMA patients received pedicled arteries. As discussed above, a post-hoc analysis of the trial showed that skeletonization almost completely eliminated the increase in the risk of sternal wound complications [29].

Conclusions

BIMA grafts have better patency rate than SVGs at long-term follow-up. They also appear to exert a protective effect on the native coronary circulation. Whether the increased patency rates and the reduction in the progression of native coronary atherosclerosis translates into clinical benefits in the majority of patients submitted to CABG remains to be definitely proven.

To date, a large amount of observational evidence suggests a survival benefit for the use of BIMA grafts. However, these data will need to be confirmed as the final results of the ART trial become available. For the moment, BIMA grafts should be considered in patients with reasonable life expectancy and where the use of BIMA confers no additional risk. In addition, operator and centre experience remain key to achieving excellence in clinical outcomes.

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Chapter 2

Coronary Artery Surgery:

Intra-operative Assessment of Graft Flow in Coronary Artery Bypass Grafting

Rune Haaverstad, Havard B Nordgaard and Nicola Vitale.

"Fructu non foliis arborem aestima"

Introduction

Coronary artery bypass graft (CABG) surgery is an established treatment for angina pectoris of ischaemic origin and can increase both quality of life and improve survival as well as reduce ischaemic complications [1]. The long-term results depend on graft patency.

Angiography is still the gold standard for intraoperative graft assessment, but it is rarely carried out routinely because of logistics and lack of time. Besides angiography, other techniques of intraoperative graft assessment have been introduced into clinical practice, namely transit time flow measurement (TTFM), *epicardial ultrasound scanning of coronary anastomoses* and *fluorescence imaging* [2].

Transit-time flow measurement has been in clinical use for more than a decade and it is the most frequently utilised technique for intraoperative assessment of CABG. In 2016, the National Institute for Health and Care Excellence in the United Kingdom (NICE) suggested that intra-operative TTFM is effective in detecting imperfections that may be corrected by graft revision; this may reduce the incidence of graft occlusion and may therefore reduce perioperative morbidity and mortality. They concluded that the application of TTFM is associated with an estimated cost saving of £115 per patient compared with clinical assessment, when it is used routinely for assessing coronary artery bypass grafts during surgery [3]. The guidelines on myocardial revascularisation, issued jointly by the European Society of Cardiology (ESC) and the European Association for Cardio-thoracic Surgery (EACTS) in 2014, recommended that routine intraoperative graft flow measurement should be considered (Class IIa, Level C) [4].

This chapter will focus mostly on the principles and clinical applications of TTFM for intraoperative assessment of grafts in coronary artery bypass surgery.

Principles of Transit-time Flowmetry

The transit-time flowmeter measures the time difference between an upstream and downstream ultrasonic pulse when transmitted and received by two spatially separated transducers in the flow probe. The time-delay difference can be converted to flow volume, which is displayed on-screen as a digitized signal. The flow is recorded as analogue signals that are initially sampled at a sufficiently high frequency according to the Nyquist-Shannon sampling theorem [5] (Figure 1).

Transit-time flowmetry in the operating room is easy to perform. The timing of TTFMs during the operation is dependent on the CABG technique employed:

(1) On-pump CABG - the measurements are usually done after discontinuation of cardiopulmonary bypass. Measuring the LIMA-LAD flow is also recommended before removal of the aortic clamp because this time point has no competitive flow and it is ideal to assure a patent LIMA anastomosis. Some cardiac surgery units register graft flow both before and after application of diluted papaverine, particularly within vein grafts. Some surgeons recommend repeated flow measurements when the sternal edges are approximated during chest closure in order to assure correct graft position and absence of kinking.

(2) Off-pump CABG - the arterial grafts are usually assessed both immediately after they have been constructed and before chest closure. For vein grafts, the assessment may be performed as with on-pump surgery.

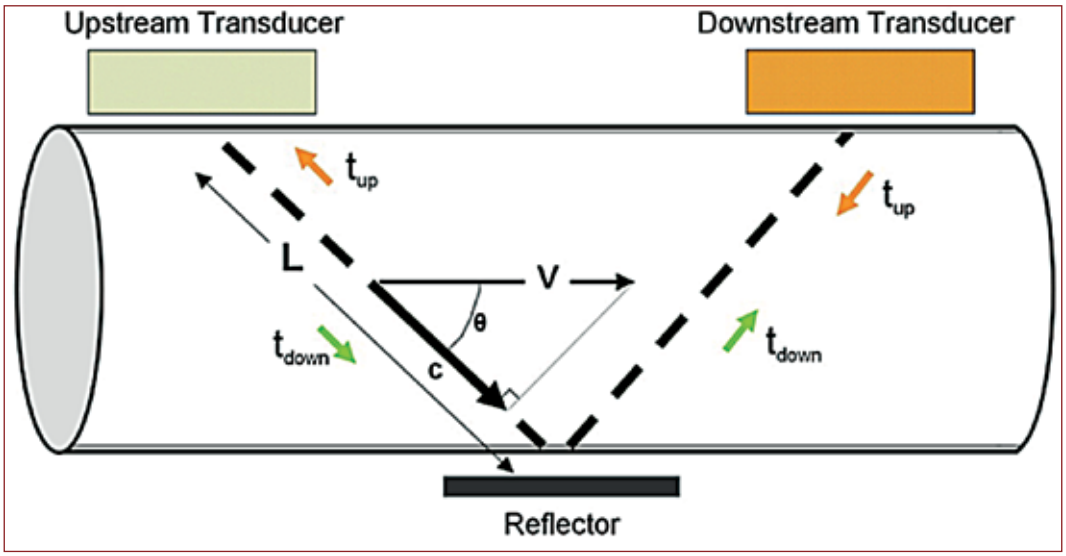

Figure 1: : The transit time flow principle. The perivascular transit-time flow probes used in coronary surgery are composed of two transducers placed at a specific angle with a metal reflector on the opposite side of the vessel. The two transducers act as the transmitter and the receiver for the ultrasound beams. The ultrasound beam transmitted through the vessel is wide enough to cover the entire flow diameter (or the vessel). When the beams are transmitted through the blood, there is a difference between the upstream and downstream transit-time (time of flight or time difference), which is proportional to flow velocity. The average cross-sectional flow velocity is calculated and presented as mean, diastolic and systolic flow at the flowmeter display. Larger time differences are correlated with higher flow velocities.

t_{up} t_{down} = the up and downstream transit time, respectively; L = distance between the transducer and the reflector; V = velocity of the blood flow; c = ultrasound or phase velocity; θ = angle between the flow direction and the line formed by the transducers.

The final measurements should be carried out under stable haemodynamic conditions, as flow in the graft is also pressure dependent. The hook of the flow probe connected to the flowmeter is placed around the bypass graft. The graft should fit within the flow probe because the ultrasound beam must illuminate the entire graft. A 4-mm probe is applicable in most situations; alternatively, a 3-mm probe may be used for IMA grafts (Figure 2).

When assessing a pedicled LIMA graft, a short segment of the graft should be skeletonised to fit the probe hook. By measuring the graft both before and after application of papaverine into the vein graft, the flow reserve for the individual graft is also measured. For the LIMA graft, papaverine is usually applied only externally, which is not as efficient as when it is given intraluminally. In order to obtain a correct interpretation of the blood flow patterns, an ECG recording should be combined with flowmetry to differentiate systole from diastole.

During assessment of grafts, transit-time flow meters automatically generate the following measurements:

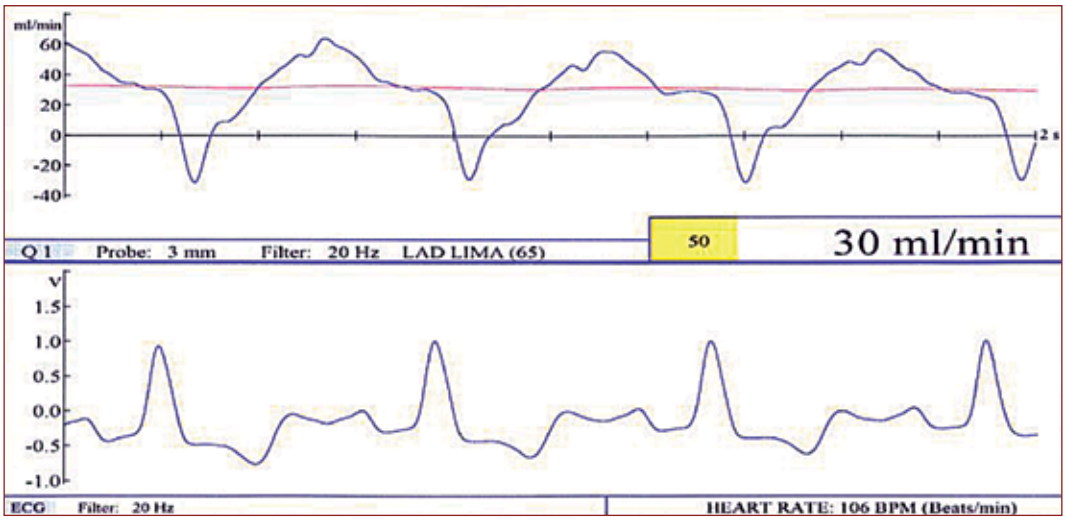

Figure 2: Transit time flow measurement of LIMA-to-LAD graft.

1) Mean graft flow (MGF) (ml/min) = antegrade – retrograde flow (or Q) in ml/min.

Graft flow will depend on graft quality and diameter, target vessel quality and distal run-off of the coronary artery. It also depends on arterial blood pressure, although it is not taken into consideration for calculation.

2) Pulsatility index (PI) = (maximum peak flow – minimum peak flow)/mean flow.

The PI is a dimensionless positive number that is considered a non-invasive method for the assessment of peripheral vascular resistance of coronary arteries. In other words, PI provides information on the resistance in the graft and, therefore, the distal target vessel run-off. It was first introduced by Gosling and King, and was originally defined as the peak-to-peak height of the waveform divided by the mean height during a single cardiac cycle, as assessed by Doppler ultrasound [5].

The flowmeter typically uses a low-pass filter to smooth the signal and attenuate the noise. Since the level of filter settings in a flowmeter may influence the waveform, different maximum and minimum peak flows may be registered and influence the PI values. Filter settings are usually at 20 Hz and 10 Hz, as in the flowmeters manufactured by MediStim ASA (Oslo, Norway) and Transonic Systems Inc. (Ithaca, NY, USA). The authors, in a previous study, demonstrated that lower filter settings produce lower PI values [5]. On clinical grounds, the difference in waveforms due to different filter settings may have important repercussions. The shape of the flow curve is an element that comes into play when assessing grafts that are difficult to interpret (low flows and high PI). In cases involving a failed anastomosis or a graft directed to coronary arteries with high peripheral vascular resistance, the waveform will present multiple spikes that will be higher than expected. On one hand, a device equipped with a higher filter setting will produce very spiky flow curves, making it difficult to evaluate the graft flow. On the other hand, a device with low filter setting will smooth out most of the spikes, making the graft assessment appear to be better than it actually is. Figure 3 shows PI values of eight different grafts calculated under various filter setting [5]. Therefore, the level of filter setting of the flowmeter, or at least the type of flowmeter, should always be reported when providing PI values of coronary grafts.

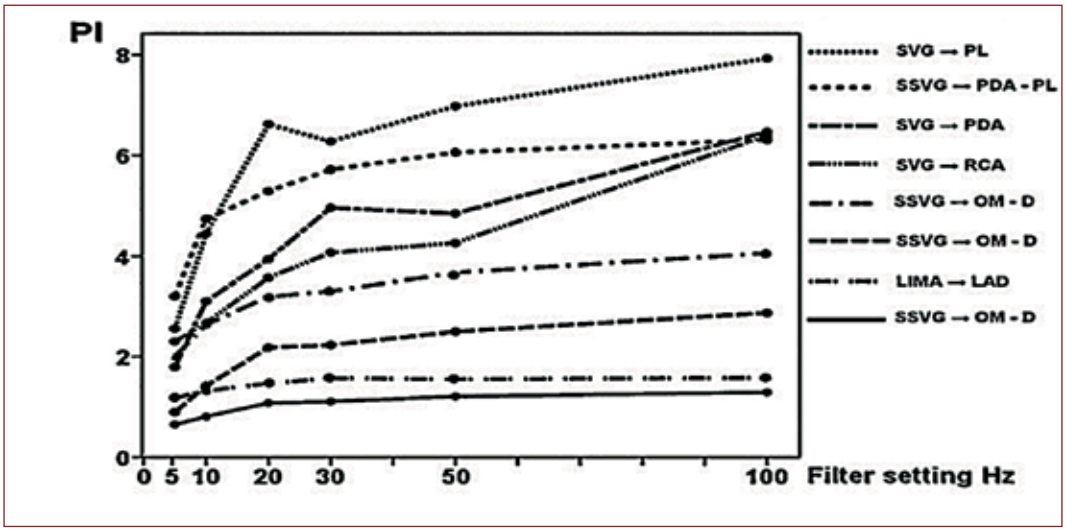

Figure 3: Pulsatility index values of eight different grafts measured under various filter settings.

3) Diastolic filling or diastolic flow fraction (DF) (%) = (diastolic flow/systolic + diastolic flow) ×100.

Diastolic filling is determined by connecting the TTFM console to an ECG, to calculate the percentage of the total flow during diastole. Diastolic filling should be higher than systolic flow, in particular for the left coronary system due to the higher transmyocardial pressure gradients of the left ventricle. A DF < 50% is suspicious of disturbed graft flow because it represents a systolic graft flow pattern [6]. Figure 4 overleaf shows transit-time parameters calculated before and after revision of a failed graft.

Some authors have introduced another parameter to detect graft failure by looking at the amount of retrograde flow within the graft. It is generally known as the systolic reverse flow (SRF), backward flow (BF) or insufficiency rate (IR), which corresponds to the percentage of the flow area below the zero line [7]. The accepted cut-off value for SRF is <5 % and it is calculated by the following formula:

SRF (%) = (retrograde flow/antegrade flow) ×100.

Clinical Application

Numerous reports have looked at TTFM, especially its reliability and its impact on the rate of graft failure at early and mid-term follow-up. Transit-time flowmetry has been carried out in an array of different clinical settings, target coronary arteries and graft types: the mammary arteries either single or as T or Y grafts, the radial artery, the gastroepiploic artery and saphenous vein grafts (SVG) either single or sequential [8-12].

Mean graft flow

Guidelines by the EACTS/ESC recommend a mean graft flow (MGF) of ≥ 20 ml/min as acceptable post-operative results for TTFM [4]. Some authors accept lower threshold values with a MGF of < 15 ml/min [1] and < 10 ml/min [4] before labelling TTFM abnormal. Our

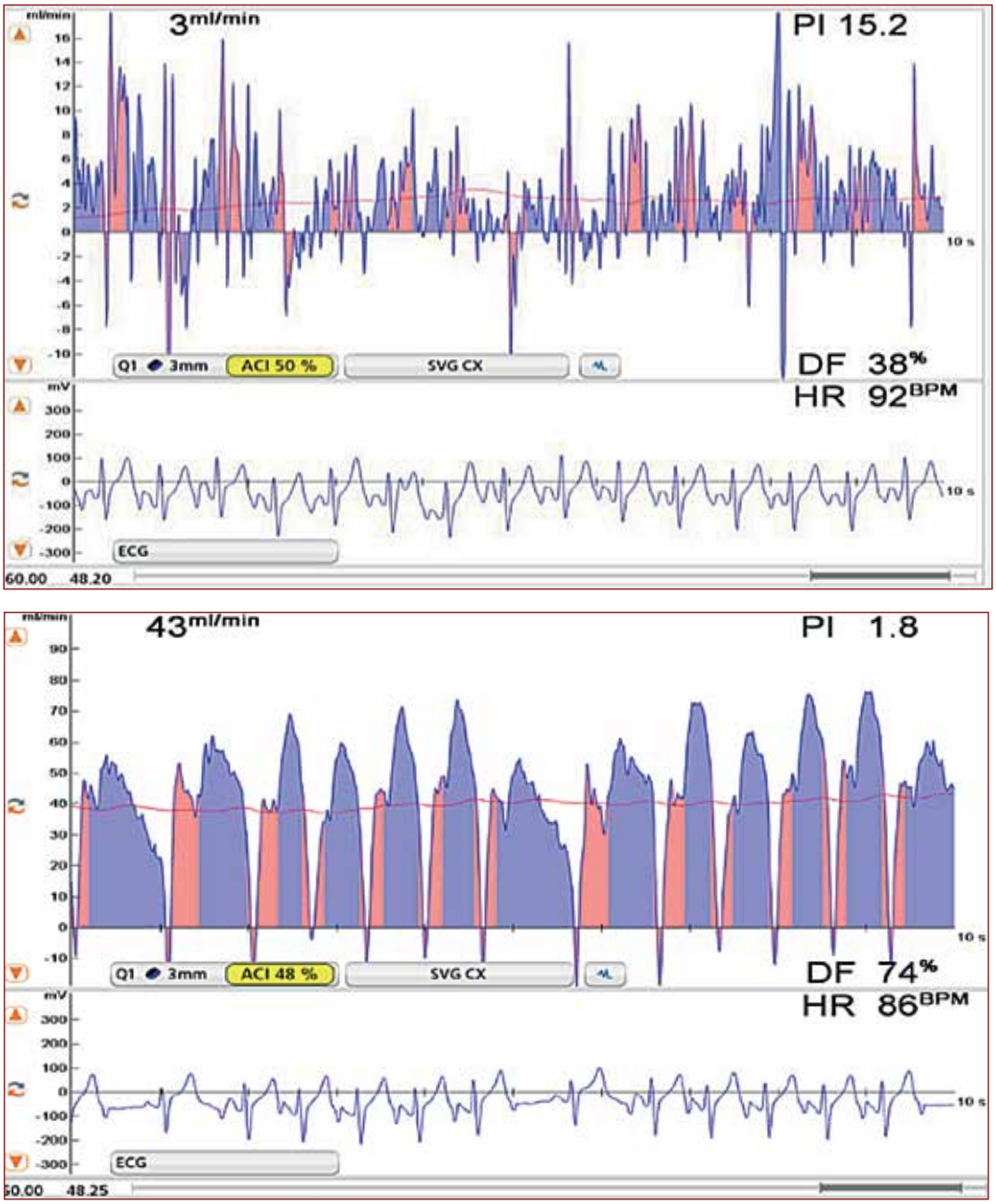

Figure 4: Transit time assessment of a SVG to obtuse marginal before and after revision. Unsatisfactory values of mean flow, PI and diastolic filling of a failed graft (top image). Satisfactory values after graft revision (bottom image).

study reported mean graft flows of LIMA-LAD in 386 male and 109 female consecutive patients, operated upon by the same surgeon (RH) of 34 ± 22 ml/min and 27 ± 15 ml/min, respectively [11] (Table 1). In a study enrolling 354 patients, the graft failure rate was 6.5% for single LIMA at 1-year follow-up [13]; MGF was directly correlated with the follow-up results, with an observed 4% decreased risk of graft failure for every 1 ml/min increase in MGF. This study confirms the current recommendation to achieve a minimum of 20 ml/min MGF for LIMA grafts [13].

The mean graft flow of the LIMA correlates well with the degree of coronary stenosis. Honda et al. evaluated the fractional flow reserve (FFR) of the LAD by dividing it into severe stenosis (FFR < 0.70), mild (FFR 0.70-0.74) and non-stenotic lesions (FFR ≥0.75). Corresponding rates of MGF were 24.7 ± 10.6, 19.2 ± 14 and 16 ± 9.7 ml/min, indicating higher bypass flow in cases of more severe LAD stenosis. String signs were observed in 4.2%, 21% and 50% of severe, mild, and non–stenotic lesions, respectively [7]. The authors agreed on a cut-off of 20 ml/min for LIMA grafts [7]. Walker found a significant difference in intra-operative MGF between LIMA-LAD grafts which were either patent or occluded at follow-up [14] with six LIMA-LAD grafts with a MGF of < 15 ml/min not patent at follow-up [15].

Kieser et al. in their series of arterial grafts reported median flows in the major single conduits (LIMA, RIMA and radial) of 39, 32, and 34 ml/min, respectively (average 35 ml/min) [8]. In sequential grafts (LIMA, RIMA and radial), the median flow was 43, 45.5 and 42 ml/min, respectively (average 43.5 ml/min), and composite grafts had the highest median flow (54 ml/min) [8]. Sequential grafts had greater flow than single conduits and when these in-between segments were in a technically easy accessible location to measure, the individual components were evaluated. Flow in the sequential grafts was 1.24 times higher, and flow in the composite grafts was 1.5 times higher than flow in single conduits [8]. In a study evaluating two different anastomotic techniques (standard running suture versus nitinol U clips) of free RIMA on LIMA, Bigdeli et al. measured a MGF at the common T graft of 93.7 ± 44 and 108 ± 68.4 ml/min, respectively, and an overall graft failure rate of 2% at follow-up [16].

Uehara et al. found no statistical differences in MGF values in occluded versus patent gastro-epiploic arteries to the right coronary artery [12]. Similarly, Lehnert et al. did not find any correlation between MGF and radial artery graft failure [13].

With regard to saphenous vein grafts, Lehnert et al. observed a rate of 16.9% graft failure for single vein grafts. Increased MGF was significantly associated with a better result (a 2% decreased risk of graft failure for every 1 ml/min increase in MGF) and an MGF of at least 40 ml/min was recommended for SVG [13]. In a study of post-operative antiplatelet treatment comparing aspirin to aspirin and clopidogrel, 169 (68%) out of 248 patients received a SVG with a graft failure rate was 8.4%. Predictors of SVG patency were dual anti-platelet therapy, a higher MGF and a lower PI [17]. Data from the GRIIP trial revealed that, in a subgroup of 65 SVG, a MGF < 31 ml/min was associated with 50% late graft occlusion [18].

In our study, analyzing TTFMs in single and sequential saphenous vein coronary artery bypass grafts, several findings were highlighted both for single and sequential vein grafts (Table 1 overleaf) [11]. Within the single SVG group, grafts directed to the diagonal branches exhibited significantly lower flows than those directed to other target vessels, and this held true both for men and women. The explanation is that diagonals may be vessels of smaller diameter and with less peripheral flow reserve, thus posing a higher coronary resistance. Overall, flows were significantly higher in men versus women because the former are

Table 1: Mean graft flow and Pulsatility Index values.

			Male			Female	
Graft	Target vessel	N (grafts)	Flow (ml/min)	PI	N (grafts) (ml/min)	Flow	PI
Single LIMA	LAD	386	34 ± 22	2.4 ± 0.9	109	27 ± 15	2.2 ± 0.8
Single SVG	Diagonal	60	36 ± 18	1.9 ± 0.8	15	32 ± 17	1.6 ± 0.3
	PDA	200	47 ± 26	2.5 ± 1.5	59	42 ± 28	2.2 ± 1.0
	OM	78	54 ± 29	2.1 ± 1.0	24	48 ± 26	2.0 ± 0.7
	RCA	37	56 ± 32	2.3 ± 1.6	19	49 ± 22	2.1 ± 1.1
	Posterolateral	12	54 ± 33	2.8 ± 1.7	0	/	/
	LAD	20	56 ± 25	2.1 ± 0.8	9	51 ± 23	1.9 ± 0.9
Double SSVG	PDA-posterolateral	33	62 ± 32	2.3 ± 1.0	8	50 ± 26	3.0 ± 1.5
	OM-OM	57	62 ± 33	2.1 ± 0.9	13	44 ± 20	1.9 ± 0.5
	Diagonal-diagonal	9	74 ± 42	1.9 ± 0.9	0	/	/
	OM-diagonal	153	73 ± 33	1.9 ± 0.9	43	56 ± 28	2.1 ± 1.2
Triple SSVG	Left coronary artery system	37	84 ± 44	2.1 ± 0.7	9	75 ± 19	2.0 ± 0.7

SSVG: sequential saphenous vein grafts
Data are mean values ± 1 standard deviation.

assumed to have coronary arteries of larger diameter than the latter as well as larger ventricular mass. Another finding was an increased blood flow in sequential SVG compared with single SVG. This observation was consistent both for male and female patients, with male patients exhibiting the highest flow (Figure 5). Specifically, male patients were predicted to have a graft flow of 8.7 ml/min higher than women of the same age and left ventricular ejection fraction. The blood flow increased according to the number of distal anastomoses: from a lower flow in single SVGs to a higher flow in double sequentials, up to the highest flow in triple sequentials. The trend was confirmed by the linear mixed model predicting that, in patients of the same age, sex, and left ventricular ejection fraction, a triple sequential graft had 13 and 39 ml/min flow higher than double sequential and single

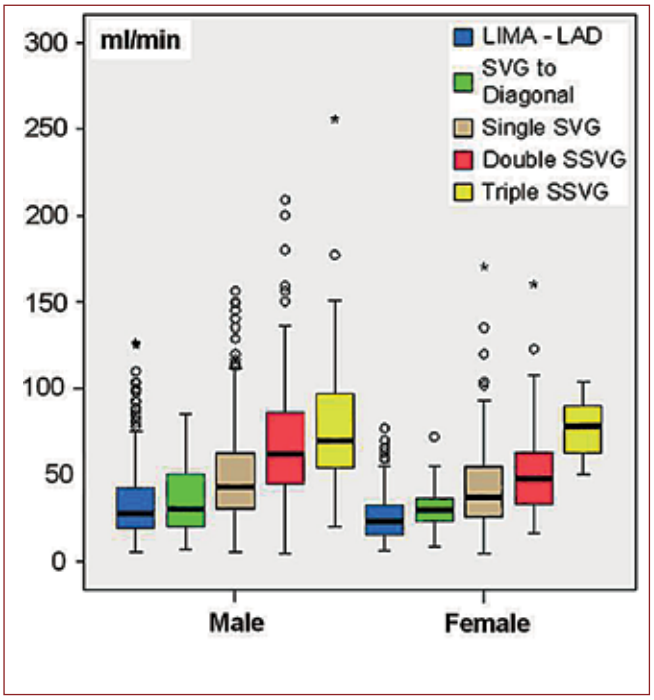

Figure 5: Transit time mean blood flows in LIMA, single and sequential SVG divided by sex.

SVG, respectively [11] This behaviour is recognized to be caused by decreased total resistance, better run-off, and minimized impedance difference. Although all the differences among the three flow values reached statistical significance, flows in double and triple SVGs were not twofold or threefold higher, respectively, compared with flows in single SVGs. A likely explanation may be the relation between the capacity of the graft, blood flow velocity in the graft, and the run-off of coronary vessels. Although a sequential SVG would be able to provide a blood supply two or three times larger than a single SVG, this will not occur because blood flow velocity should be similarly high. The native coronary blood velocity is relatively fixed because it is dependent on the cross-sectional area of the coronary lumen and regional left ventricular mass.

Pulsatility index

The pulsatility index (PI) provides information on peripheral vascular resistance of grafted coronary vessels. There is substantial evidence from several studies that a PI < 5 should be considered normal [4]. Increasing mean PIs of 2.4 ± 0.6 and 3.0 ± 1.1 in severe (FFR < 0.70) and mild (FFR 0.70-0.74) coronary lesions, and abnormal PI values (5.5 ± 8.2) in non-stenotic lesions (FFR ≥ 0.75) were associated with increased graft failure rates at follow-up due to the increased competitive native coronary blood flow [7]. In a series of 1000 consecutive arterial grafts (LIMA, RIMA, radial and gastro-epiploic), Kieser et al. underlined the substantial importance of PI assessment to predict outcomes, especially mortality [8]. In summary, 916 grafts out of 990 were considered satisfactory because the PIs were ≤ 5, whereas the remaining 74 grafts with PIs > 5 were deemed suboptimal.

No major differences of PI values were noted across the board for arterial graft types and construction. Moreover, during follow-up, PI values proved their predictability with regard to major adverse cardiac events (MACE) and death: MACE occurred in 10/59 (17%) of those

patients with at least one bypass graft with a PI > 5, and in 15/227 (5.4%) of those with a PI ≤ 5 for all bypasses (p = 0.005) [8]. Similarly, there were significantly more deaths in the high PI group: 5/54 (11%) compared to 5/250 (2%) patients in the low PI group (p= 0.02) [8]. The authors concluded that PI is a good indicator of graft function. For this purpose, they have introduced a flow chart based on PI values, as a guide to intraoperative conduct after CABG transit-time assessment [8].

Herman and associates, in their series of 985 patients, had abnormal flow defined as PI > 5 in 184 (19%); the remaining patients had a median PI of 2.9. The abnormal flow group had a higher incidence of peri-operative MI (0.7% vs 1.0 %; p=0.02), required more reoperation for graft occlusion (0% vs 0.5%; p = 0.04), and had more frequent low output syndrome post-operatively (10% vs 18%; p = 0.005) [9]. When a composite adverse event outcome was applied, it was more prevalent in the abnormal flow group (17% vs 31%; p<0.0001). After adjustment, abnormal flow was found to be an independent predictor of the in-hospital composite outcome with an odds ratio of 1.8 (1.1 – 2.7) [9].

In their prospective angiography-controlled study, Jokinen et al. found that the best predictor of early (<6 months) graft patency was the PI value: PI > 3 resulted in highest sensitivity (72%) and specificity (70%) in ROC analysis, and predicted reduced graft patency better than MGF or the insufficiency rate alone or in combination [19]. The average PI in the right coronary artery was statistically significantly higher than in the LAD artery (3.0; interquartile range 2.0 – 4.3 vs 1.9; interquartile range 1.7 – 3.2; p = 0.007) [19]. With regard to saphenous vein grafts, the authors found that, overall, the mean PI (± standard error of the mean) of SVG to the left or right coronary system were 2.0 ± 0.05 and 2.4 ± 0.06, respectively, with the difference being significant (p < 0.001) [11].

In our study, there were no significant differences between PI values for any type of grafts within the single and double SVG group to the left or right coronary system (P = 0.55) [11]. Moreover, PI values of single, versus double, versus triple SVGs within the left coronary system were not significantly different (p = 0.244). Similarly, PI values of single versus double SVGs to the right coronary system were also not significantly different (p = 0.126). Pulsatility index values were similar for men and women (p = 0.534) [11]. PI values of grafts directed to the left or right coronary circulation are shown in Figure 6. These findings are contrary to what one could expect as sequential grafts provide higher flows owing to a reduced peripheral vascular resistance. Thus, sequential grafts should theoretically provide lower PIs compared with single SVGs. Nonetheless, our data indicate that the increased blood flow from single to sequential SVGs is not associated with a decreased PI. The likely explanation is that the shape of the flow curves of the single and sequential grafts are similar, resulting in similar PI values. Thus PI, a dimensionless number derived from an equation taking into account the maximum and minimum peaks and mean flow measurements, will change concomitantly with marked changes in the flow curve. This is typically seen as a gross increase of resistance in the bypass grafts (i.e. technical failure of the anastomosis, graft kinking, or torsion) or coronary arteries (i.e. small diameter, poor run-off). This is in line with previous reports which showed a large increase of PI as a consequence of a progressive tightening of the LIMA-LAD graft in the pig causing a reduced mean flow [5, 20]. On the other hand, the right coronary system had significantly higher PI values compared with the left across all graft types because of a more spiky and systolic flow pattern, indicating higher vascular resistance in the right system. However, it is also known that blood flow to the right coronary artery takes place during systole as a result of minor compression of the epicardial vessels during right ventricular contraction.

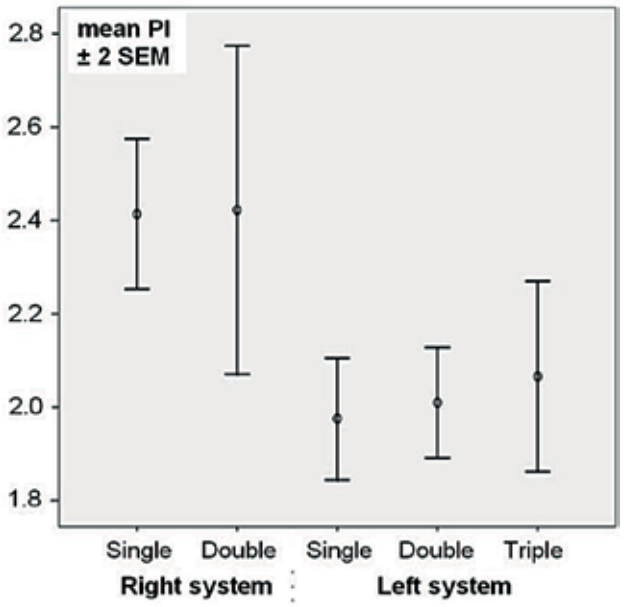

Figure 6: Mean pulsatility index (PI) values for single and sequential SVGs stratified by right and left coronary circulation [11].

Diastolic filling

Diastolic filling (DF) is rarely indicated, but may be useful. In an experimental animal model, Pagni et al. showed that competitive blood flow would have a greater impact (i.e. decreased blood flow rate) on LIMA than SVG, which is particularly evident during diastole [21].

Kieser et al. reported a median DF in the major single conduits (LIMA, RIMA and radial) of 72, 68, and 62%, respectively. In the sequential grafts (LIMA, RIMA and radial), the DF was 73, 64 and 67%, respectively. Although DF appears to be a significant predictor of MACE in their non-emergency group of patients, the authors are concerned this result may be incidental for several reasons: the significant p-value was achieved only when emergency patients were excluded, and DF is the least well-defined cut-off point of all three transit-time flowmeter parameters [8]. It is important to remember that a cut-off of DF ≥ 50% for a well-functioning graft was recommended by one of the flowmeter manufacturers; to the best of our knowledge, there are no research data to support this.

Systolic reverse flow or insufficiency index

Although this parameter may allow the identification of an oscillatory flow through the graft, it is not widely used because it is not generated automatically by the flowmeter. Tokuda and associates found that in a group of 104 grafts which have undergone coronary angiography at mid-term follow-up, systolic reverse flow (SRF) at the time of surgery was 3.08 ± 6.32 [10]. This group was subdivided into two groups: group A with graft stenosis and group B with fully patent grafts. Systolic reverse flow was 6.13 ± 9.47 and 2.30 ± 5.02 for group A and B, respectively ($p < 0.05$). In the univariate analysis, SRF was a predictor of midterm graft failure (odds ratio 1.08, $p < 0.05$) [10].

The SRF represents the amount of flow through the graft directed backward across the anastomosis, which reflects the amount of competitive flow through the native coronary arteries. It has been reported that greater competitive flow from the native coronary vessel observed at angiography is strongly associated with midterm graft failure [10]. A higher SRF represents greater competitive flow and lower downstream runoff, which can predispose a graft to functional failure.

Discussion

Mean blood flow and PI are the main parameters of TTFM applied in clinical practice. Although there is no consensus on the reference values for either measurement, the EACTS guidelines indicate that a MGF < 20 ml/min and a PI > 5 are indicative of a technically inadequate graft [4, 22].

Initially the MGF was the considered the most important measurement after grafting because of its immediate ease of interpretation [1], but experience and the literature have pointed out that other parameters, such as the PI, are relevant for a thorough assessment of grafts. This trend has been confirmed over the years to the point that several authors believe PI to be a better indicator of graft function, especially when the predictive value for outcome at follow-up is concerned [8].

Several studies have underlined the role of TTFM to predict mid-term results after CABG. In general, high MGF and low PI are predictive of satisfactory early and mid-term (i.e. within 12 months from surgery) graft patency, as assessed by coronary angiography [9, 10, 13, 14, 19]. In particular, the assessment of PI has been recognized as a valuable tool to identify grafts with competitive flow, which are vulnerable to early stenosis or occlusion. The PI is an indicator of graft quality that decreases with the severity of the coronary stenosis. Low values of this index indicate an adequate bypass; high values indicate technical failure and flow competition. Low values were observed in patients who have severe coronary stenosis; high values were observed in patients who had mild coronary stenosis [8].

Besides PI, the systolic reverse flow is another parameter that can demonstrate flow competition between native coronary and bypass graft flow [10]. Unfortunately, only a few clinical reports provide details on systolic reverse flow, most of them appearing recently [1,10]. The authors have shown, in a porcine experimental setting, that the LIMA graft flow was significantly reduced by the competitive flow of the native coronary: MGF and diastolic filling were at the lowest, whereas the PI value and systolic reverse flow were at the highest, when full competitive flow was present in the LAD. Moreover, MGF was not affected, as much as one would expect, by experimental stenosis of the anastomosis [23]. See Figure 7 and Table 2 overleaf.

All these findings bring to attention the impact of competitive flow from the native vessel on graft patency. There is also further experimental work, carried out by the authors, to support this statement [22]. Different degrees of competitive flow in the coronary arteries determine different wall shear stress (WSS) distributions in the LIMA-to-LAD anastomosis in the pig [23]. The WSS is the tangential frictional force on the endothelial surface and there is substantial evidence that this may result in impairment of endothelial function. Vessel areas with low and oscillatory (bidirectional) WSS, like the inner wall of curved segments and the outer wall of bifurcations, are considered non-optimal and more prone to endothelial dysfunction and vascular disease. The authors demonstrated that, high competitive flow, as may occur in the presence of non-significant coronary stenosis, resulted in the lowest WSS in the LIMA graft and the anastomosis. Partial competitive flow, as may occur in significant

stenosis, produced a WSS distribution comparable to the ideal situation of non-competitive flow [23]. On clinical grounds, this means that the coronary graft can tolerate a modest degree of competitive flow without major alterations in WSS distribution. On the contrary, major competitive flow triggers a decrease of WSS that may impair graft patency in the long term.

In line with these findings, TTFM results were linked to pre-operative fractional flow reserve of coronary arteries [7, 8, 10], because non-stenotic lesions are responsible for competitive flow [7, 8, 10]. Transit-time flow measurements are significantly higher in grafts constructed on coronary vessels exhibiting a FFR < 0.75 – this percentage being the expression of severe stenosis [7, 8, 10]. Furthermore, results from several studies are all concordant that the rate of graft patency is significantly higher, at follow-up, in those grafts to coronary arteries with a pre-operative FFR < 0.75. The results of TTFM assessment, as well as graft patency, became gradually and significantly worse in grafts directed to coronaries exhibiting mild stenosis (0.70 ≤ FFR < 0.75) and functionally non-stenotic lesions (FFR ≥ 0.75) [7, 8, 10]. The proven relationship between FFR and TTFM is an indirect confirmation of the key role of TTFM, as a very suitable method of graft assessment. The take home message is that, in the face of coronary lesions of uncertain severity, FFR should always be calculated, with the knowledge that grafting a coronary vessel with low FFR (as an expression of mild stenosis) will result in poor patency rates.

According to current evidence, the predictive power of TTFM measurements is limited to early and mid-term follow-up. Progressive stenosis after one year may be an ongoing process, principally affecting venous grafts, and may be due to factors other than surgical skill. Ongoing atherosclerosis or intimal fibrosis of the arterialized venous conduits may be the main mechanisms [1]. Internal mammary arteries remain, in general, free of atherosclerosis and failure is usually due to "technical" problems [1].

Improvements of intra-operative evaluation of coronary artery bypass grafts may be achieved with the concomitant use of TTFM and epicardial ultrasound scanning of coronary anastomoses [24-26]. The two techniques applied together can provide useful information regarding the physiology of the graft conduit (i.e. flow rate, competitive flow, peripheral vascular resistance) and morphology of the anastomosis [24-26] (Figure 8). As shown previously, technical failures of the anastomosis may produce mixed TTFM results that are difficult to interpret, whereas ultrasound scanning can readily visualize any technical failure.

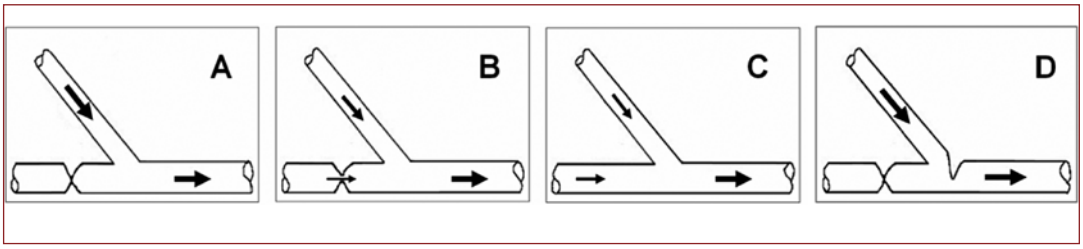

Figure 7: Four different experimental flow conditions [23]. In an experimental porcine model of LIMA-to-LAD graft, the authors reproduced four clinical situations: A) baseline flow with proximal LAD totally occluded; B) partial competitive flow with 50% occlusion of the LAD; C) full competitive flow with no LAD snaring proximal to the anastomosis, and D) on-purpose stenotic anastomosis with no competitive flow. See Table 2 for mean flows, derived indexes, and comparisons.

Table 2: True values of mean flow and derived indexes of four different experimental flow conditions in LIMA-to-LAD graft. See also Fig 7 [23].

Parameter	Baseline (A)	Partial competitive flow (B)	Full competitive flow (C)	Stenosis of the anastomosis (D)	P
Mean flow (ml/min)	48 (35-50)	38 (18-52) *	29 (3-38) * °	41 (19-60)	0.001
Pulsatility index	3.3 (1.6-10.1)	4.0 (2.0-9.7)	5.8 (2.2-12.8) *	3.9 (1.5-10.1)	0.006
Diastolic filling (%)	67 (56-85)	56 (40-71) *	46 (31-58) * °	61 (46-75)	<0.001
Insufficiency (%)	2.3 (0-13.1)	5.1 (0-14.5)	9.4 (0.21-37.0) * °	2.0 (0-14.6)	0.002

Median and range (N = 9).
P refers to Friedman's test.
** P < 0.05 refers to comparison with baseline condition analyzed by the Post-hoc test.*
° P < 0.05 refers to comparison with a luminal LIMA-LAD stenosis of 75 ± 11 %, analyzed by the Post-hoc test.

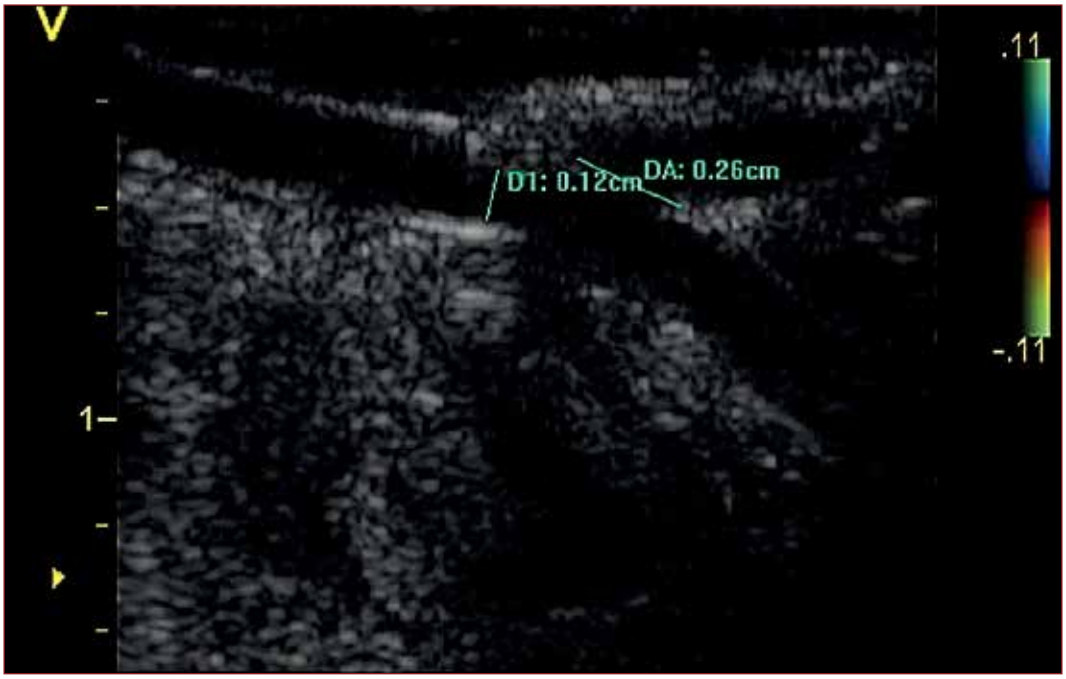

Figure 8: Ultrasound scanning of an on-purpose technically failed LIMA-to-LAD anastomosis in a porcine model. The stenosis of the anastomosis was created by placing a stitch at the toe. DA = diameter of LIMA, D1 = diameter of LAD.

Ultrasound scanning can be improved by the application of Doppler, especially blood flow imaging (BFI) techniques, which allow detailed identification of blood flow direction at the anastomotic site [24-26].

Conclusion

Transit-time blood flowmetry is a validated method of intra-operative assessment of grafts and anastomoses in coronary surgery. Several aspects of graft evaluation by TTFM remain to be clarified, but the widespread use of this technique, innovation from the industry and future research may enhance its reliability, for the benefit of the patients undergoing coronary revascularisation.

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Chapter 3

Mitral Valve Surgery:

Ischemic Mitral Regurgitation: Repair or Replace?

Arman Kilic & Michael Acker

"Felix qui potuit cognoscere causas rerum"

Introduction

Ischaemic heart disease remains the leading cause of death globally. Approximately 10-20% of patients with ischaemic heart disease have at least moderate ischaemic mitral regurgitation (IMR) [1]. IMR is grouped under the category of secondary mitral regurgitation (MR), defined as MR occurring in the setting of a structurally normal mitral valve. By contrast, primary MR entails structural disease of the mitral valve or its associated subvalvular apparatus.

The pathophysiological basis of IMR rests within the left ventricle. Indeed, IMR is often referred to as a "disease of the ventricle". Wall motion abnormalities arising from coronary disease result in migration and tethering of the papillary muscles. This, combined with adverse remodeling of the left ventricle and distortion of the mitral annulus leads to malcoaptation of the leaflets resulting in IMR.

IMR is graded on a similar scale echocardiographically as primary MR, from none to severe. There is a graded positive association between the presence and severity of IMR and heart failure or mortality [1]. It is unknown however whether this association is related to the IMR itself or if IMR is a surrogate for more advanced heart failure. Controversy exists as to the optimal management of IMR, particularly in the moderate or severe IMR settings. In moderate IMR, controversy exists as to whether any concomitant mitral valve surgery should be added to coronary artery bypass grafting (CABG) or not. In severe IMR, there is no question the mitral valve should be addressed, the debate, however, is whether the mitral valve should be repaired or replaced.

Indications and Techniques for Mitral Valve Surgery in Moderate Ischaemic Mitral Regurgitation

It is unclear whether performing mitral valve repair at the time of CABG for moderate IMR improves quality of life, relieves symptomatic burden, or improves survival. The 2014 American Heart Association and American College of Cardiology (AHA/ACC) guidelines provide a "could consider" IIb recommendation for mitral valve repair plus CABG for moderate IMR [2]. The 2012 European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines provide a stronger "should consider" IIa recommendation for CABG with concomitant mitral valve repair in moderate IMR [3].

There is a balance of reducing the severity of IMR by the addition of mitral valve repair to CABG in moderate IMR versus the additional cardiopulmonary and aortic cross-clamp time that accompanies the addition of concomitant procedures. In essence, to justify the addition of mitral valve repair in this setting, the long-term benefits of repair should be of enough significance to justify the increased operative mortality and morbidity risk incurred with the addition of a concomitant procedure. Advocates for coronary revascularisation alone argue that CABG will improve regional contractility and restore mitral valve function over time. Advocates for the addition of mitral valve repair suggest that CABG alone may not be sufficient and that reducing the degree of IMR will hinder adverse remodeling and the development or worsening of heart failure.

There are 3 randomized trials that have helped address this debate in moderate IMR. In the first of these trials, which was published in 2009, Fattouch and colleagues randomized patients with moderate IMR to CABG alone (n=54) or CABG with mitral valve repair (n=48) [4]. Survival was similar at 5 years at 89% for CABG alone versus 94% for CABG plus

mitral valve repair. There were significant improvements in other outcomes, however, for the CABG plus mitral valve repair group, including greater reduction in New York Heart Association class, left ventricular end-diastolic and end-systolic dimensions, systolic pulmonary artery pressure, grade of MR, and left atrial size.

The second trial named the Randomised Ischaemic Mitral Evaluation, or RIME trial, randomized patients with moderate IMR and a left ventricular ejection fraction >30% to CABG alone (n=39) or CABG plus mitral valve repair (n=34) [5]. The results of this study favored the addition of mitral valve repair. Moreover, the CABG plus mitral valve repair cohort had greater improvement in peak oxygen consumption, left ventricular end-systolic volume index, and plasma B-type natriuretic peptide levels with less MR than the CABG alone group. Similar to the Fattouch trial, mortality was similar between the groups. At 1-year, mortality was 5% in the CABG alone group and 9% in the CABG plus mitral valve repair group.

The third and most recent trial was published in 2016 by Michler and colleagues [6]. This trial, sponsored by the Cardiothoracic Surgical Trials Network (CTSN), was the largest of the 3 studies, randomizing patients with moderate IMR to CABG alone (n=151) or CABG plus mitral valve repair (n=151). At 2-year follow-up, there were no differences between the groups in measures of reverse remodeling, namely decrease in left ventricular end systolic volume index. There was a nearly threefold increase in the rate of at least moderate MR at 2 years in the CABG alone group (32% versus 11%). Mortality, major adverse event, and readmission rates were comparable between the groups.

When the collective results of these 3 trials are reviewed in detail, there is not a unanimous and clear recommendation in favor of one strategy versus the other for all patients with moderate IMR. Rather, we recommend the addition of mitral valve repair in certain subsets of moderate IMR where patients are similar to those in the Fattouch and RIME trials where a benefit to repair was demonstrated. This would include patients with moderate IMR with a large ventricle as measured by a left ventricular end-diastolic dimension >55mm or left ventricular end systolic volume index >70 ml/ m2. It would also include patients with left ventricular ejection fraction of 35% or less, in those with poor coronary bypass targets in the posterior descending or circumflex territories, when there is inferolateral ventricular wall scarring, a basal aneurysm, or dyskinesia. In contradistinction, if a patient has similar characteristics to those in the CTSN trial, where no benefit to mitral repair was demonstrated, CABG alone will likely be sufficient. Such characteristics included having a mildly reduced left ventricular ejection fraction of around 40%, not having a large ventricle, and having reversible ischaemia. In these cases, moderate IMR is relieved in nearly 70% with the remaining 30% having only moderate persistent MR that is well tolerated clinically. In a study of 135 patients with moderate IMR, CABG alone resulted in an improvement in MR in those with a large extent of viable myocardium and the absence of dyssynchrony between the anterolateral and posteromedial papillary muscles [7].

Mitral valve repair for moderate IMR should entail a restrictive annuloplasty. This is performed by undersizing the ring by at least one size below the standard measurement. Small rigid and complete rings are preferred for treating IMR. A zone of coaptation of at least 8mm and the absence of MR or mitral stenosis on intraoperative echocardiography following weaning from cardiopulmonary bypass mark a successful mitral valve restrictive annuloplasty.

Indications and Techniques for Mitral Valve Surgery in Severe Ischaemic Mitral Regurgitation

In patients with chronic severe IMR who are undergoing CABG, the 2014 AHA/ACC guidelines provide a IIa "should consider" recommendation for the addition of mitral valve surgery [2]. The ESC/EACTS guidelines provide a class I recommendation for mitral valve surgery concomitant with CABG in severe IMR where the left ventricular ejection fraction is greater than 30% and in symptomatic patients with a left ventricular ejection fraction of less than 30% who have evidence of viability and suitable bypass targets [3]. In the authors' opinion, the mitral valve should be addressed at the time of CABG in the setting of severe IMR. The controversy lies more in whether repair or replacement should be performed.

The balance between repair versus replacement lies in the fact that mitral valve repair is associated with lower operative morbidity and mortality. However, recurrence of MR is greater in these patients. Although mitral valve replacement provides a more durable correction of MR, there is greater operative risk as well as greater risk of thromboembolism, structural prosthetic valve deterioration, and infective endocarditis.

The best evidence regarding this controversy comes from another CTSN sponsored trial in the setting of severe IMR. Acker and colleagues randomly assigned 251 patients with severe IMR to mitral valve repair or chordal-sparing replacement [8]. At 1 year, there was no difference in the left ventricular end-systolic volume index between groups. Furthermore, mortality rates were similar between the repair (14%) and replacement (18%) cohorts. Data regarding quality of life, functional status, and adverse events were also comparable. However, the most provocative finding was that rates of recurrent moderate or severe MR at 1 year were substantially higher in the repair group at 33% versus 2%.

A 2-year follow-up to this CTSN trial in severe IMR was conducted [9]. The major findings from the 1-year trial were mirrored in the 2-year trial. Moreover, there were comparable decreases in left ventricular end-systolic volume index between the groups. Mortality at 2 years was also comparable: 19% for repair and 23% for replacement. The rate of recurrent moderate or severe MR was again much higher in the repair group at 59% versus 4%. This difference one could argue was even more pronounced than in the 1-year trial. In addition to higher rates of recurrent moderate or severe MR, those patients undergoing repair had a higher rate of major adverse events related to heart failure and more cardiovascular readmissions. Collectively, the results from both the 1-year and 2-year CTSN trial advocate for mitral replacement in the setting of severe IMR.

Although not supported by the randomized data discussed above, if mitral valve repair is selected in the setting of severe IMR, a similar technique of using a small rigid complete ring that is undersized for a restrictive annuloplasty is utilized. In the case of replacement, a complete choral sparing technique should be used. This results in more favorable maintenance of the mitral axis and left ventricular function. Indeed, a randomized trial compared complete versus partial chordal sparing mitral valve replacement and demonstrated the beneficial effects of complete sparing on left ventricular performance [10]. Complete chordal sparing can be achieved by bisecting the anterior leaflet and rotating the leaflet tissue to the left and to the right with placement of annular sutures through the leading edge of the rotated leaflet tissue, thus "tacking" it to the annulus. The posterior leaflet tissue can be sutured in continuity with the posterior annular sutures by bringing the needle through the leaflet edge, thus tucking the tissue behind the annulus of the prosthetic valve.

Conclusions and Future Direction

The mitral space has witnessed an exponential increase in transcatheter therapies similar to what has occurred in aortic valve disease. This is particularly attractive in that many patients with moderate or severe IMR are high surgical risk patients. There are several transcatheter devices that are currently used for degenerative mitral disease that may have potential utility in IMR. The MitraClip (Abbott Vascular, Santa Clara, California, USA) device uses an edge-to-edge repair technique that is similar to the Alfieri stitch to create a double orifice and reduce MR. Other devices are implanted within the coronary sinus to push the posterior leaflet anteriorly and thus reduce the anterior-posterior dimension of the mitral annulus. The coronary sinus lies 6-12 mm away from the annulus and therefore the effectiveness of this approach is unclear, particularly when there is mitral annular calcification.

The number of patients with IMR will likely climb in coming years due to the aging population and concomitant increase in the number of heart failure patients. The role of such percutaneous devices is currently being evaluated and will undoubtedly evolve over the next several years for not only IMR but for mitral valve disease in general. The central controversies of adding mitral valve repair to CABG in moderate IMR and in selecting mitral valve repair versus replacement in severe IMR have been addressed by several randomized trials. As further data accumulates, this will hopefully be met with continually improving outcomes for this patient population.

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Chapter 4

Mitral Valve Surgery:
Subvalvular Repair Techniques for Functional Mitral Regurgitation

Peter Chen, Subhasis Chatterjee, Ahmed Alnajar & Joseph Lamelas

"Tempora mutantur, nos et mutamur in illis"

Functional Mitral Regurgitation

Functional mitral regurgitation (FMR) is mitral regurgitation (MR) occurring in the absence of intrinsic structural damage to the leaflets, chordae, and papillary muscles with variable degrees of left ventricular (LV) dysfunction. Also known as secondary mitral regurgitation, FMR can occur in the setting of either dilated, ischaemic, or idiopathic cardiomyopathy. Most commonly, FMR occurs in association with coronary artery disease and previous myocardial infarction (MI) and is termed chronic ischaemic MR (IMR) [1]. The development of chronic IMR has been associated with worse prognosis after myocardial infarction despite subsequent percutaneous or surgical revascularisation. The degree of IMR is directly related to diminished long-term survival [2,3].

The pathophysiology of FMR can be attributed to a combination of anatomical and physiological changes that occur in response to chronic ischaemic disease: annular flattening and dilation, papillary muscle displacement, mitral leaflet tethering, and diffuse left ventricular dysfunction with global LV dilatation. With myocardial infarction, the papillary muscles and LV remodel resulting in a thin, dilated LV with reduced LV closing force. This ultimately leads to the development of posterolateral papillary muscle displacement and stretching of the chordae tendinae increasing the tethering forces on the mitral valve (MV) leaflets. As a result, leaflet coaptation occurs in a more apical direction with restricted leaflet closure leading to MR [4,5]. Due to the posterolateral location of the papillary muscles, infarction in the right and left circumflex coronary territories results in a greater incidence of MR. Moreover, LV dyssynchrony may play a role in the setting of left bundle branch block exacerbating MR. Fundamentally understanding the pathophysiology of the disease process provides the framework for the surgeon to be able to provide the patient with durable surgical treatment. As the LV continues to dilate due to the severity of MR, mitral annular dilation worsens resulting in further retraction of the mitral leaflets leading to even less complete closure of the MV. "Mitral regurgitation begets more mitral regurgitation" as the dictum says.

Within the Carpentier classification, MR due to ischaemic disease is associated with papillary muscle displacement and chordae tethering and is classified as Type IIIb. This aetiology of MR differs from isolated annular dilatation with normal leaflet motion (Type I). The pre-operative echocardiographic evaluation of a patient and the intra-operative three-dimensional visualization of the valve should help identify whether a Type IIIb vs. Type I is responsible for the MR. If Type IIIb MR predominates, it stands to reason that a simple annular repair method is less likely to be durable than with a Type I dysfunction. In contrast to organic mitral regurgitation from degenerative or rheumatic aetiologies, functional MR is fundamentally a ventricular problem first and a valvular problem second.

The American Heart Association/American College of Cardiology (AHA/ACC) Guidelines were revised in 2017 restoring the echocardiographic criteria for chronic secondary MR to be the same as primary MR, specifically an effective regurgitant orifice area (EROA) ≥ 0.4 cm^2, regurgitant volume ≥ 60 mL, and regurgitant fraction ≥ 50% [6]. These revisions were a reversal from the changes made in the 2014 guidelines with regards to EROA and regurgitant fraction in defining severe secondary MR since changes were felt to be less specific for severe MR [7,8]. The European guidelines outlined in 2017 by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery issued similar recommendations [9]. For patients with secondary MR undergoing CABG and LVEF>30% concomitant MV surgery was a Class I recommendation and for patients with LVEF<30%, it was considered a Class IIA recommendation. However, both the AHA/ACC and ESC/EACTS

guidelines continue to caution against the use of these criteria alone in the assessment and treatment of chronic secondary MR, in the absence of a clear survival benefit. It is recommended to integrate the clinical, exercise, and echocardiographic findings together to prevent unnecessary operations when the MR may not be as severe as documented on echocardiography.

Surgical Management with a Restrictive Mitral Annuloplasty Repair

Initial surgical management with MV repair for FMR was popularised in the 1990s, and most commonly consists of restrictive mitral annuloplasty (RMA) repair during myocardial revascularisation as advocated by Bolling [10]. Physiologically, the purpose of a RMA is to force the posterior leaflet to coapt to the anterior leaflet through the mechanism of septo-lateral cinching [11]. Given its relative ease of placement during myocardial revascularisation and reproducible technique, the RMA has been adopted worldwide for the surgical management of FMR. To date, however, there has not been a prospective randomised trial of mitral valve surgery (repair or replacement) compared with goal-directed medical therapy in patients with FMR and heart failure demonstrating a survival benefit to surgery [1]. Thus, it is with appropriate humility that surgeons approach this condition.

While the best method of RMA remains debatable with regards to whether a partial versus complete, or flexible vs. rigid/semi-rigid ring is needed, there is a consensus that suture annuloplasty alone does not achieve durable and adequate septo-lateral cinching for reliable long-term results [12]. Complete rigid annuloplasty rings have been associated with reduced rates of recurrent FMR by addressing the anterior annular dilation that occurs along the inter-trigonal distance not achieved by incomplete rings [11,13]. Stringent downsizing of the mitral annulus has been advocated by some due to favorable clinical outcomes and reverse left atrial and LV remodeling at 18-month follow-up [14]. In IMR the annulus loses its dynamic ability in systole to deepen its saddle shape to improve leaflet coaptation. The recent introduction of three-dimensional physiological annuloplasty rings with a saddle-shape can restore the physiological non-planarity and 3D leaflet curvature across the entire mitral valve surface [15] with good early results and significant reductions in mitral annular diameter, mitral tethering area, and tenting height [16]. This is the senior author's favoured annuloplasty ring.

Early studies assessing the benefits of RMA during myocardial revascularization demonstrated excellent results in terms of survival, clinical status, LV reverse remodeling, cardiac output, and preserved systolic function [10]. However, the reported recurrence rates of MR after RMA during the follow-up period generally ranged between 15 and 30 % within 6 months and later recurrence rates as high as 66 % with the Peri-guard annuloplasty repair [17]. It is important to intervene with a RMA before the LV has dilated beyond "the point of no return." Dion and colleagues identified a pre-operative left ventricular end diastolic dimension (LVEDD) of 65mm was the threshold measurement for adverse results [18]. Specifically, in patients with a LVEDD of 65 mm or less, actuarial survival rates at 1, 3, and 5 years were 93%, 87%, and 80%, respectively, whereas for LVEDD greater than 65 mm these rates were 71%, 61%, and 49%, respectively ($p = 0.002$). Additionally, in the group with a LVEDD of 65 mm or less, all late survivors showed a sustained significant reduction of LVEDD at intermediate follow-up, with a further decrease at late follow-up. On the other hand, only 25% of the group with a LVEDD greater than 65 mm demonstrated reduction. Despite these encouraging results, there are conflicting results regarding the

long-term survival benefit with the addition of a RMA to myocardial revascularisation in FMR patients with moderate to severe MR [19-21]. Furthermore, a RMA does not address the ventricular mechanism that leads to the development of FMR. This has led to increased focus on the development of complementary subvalvular techniques for FMR.

Mitral Valve Repair versus Replacement for Surgical Management of FMR

While there remains significant debate regarding the optimal surgical strategy for patients with severe FMR, there has been speculation about the traditional role of MV replacement compared to repair. Earlier meta-analyses investigating mitral valve repair versus replacement in patients with ischaemic FMR favoured mitral valve repair, which was associated with better short-term and long-term survival compared to mitral valve replacement [22]. However, the marked patient heterogeneity made it difficult to generalize these results. Additionally, the studies included within these meta-analyses applied sub-optimal replacement techniques, specifically inconsistent chordal preservation leading to disruption of valvular-ventricular continuity, a lack of LV remodeling, and resultant LV dysfunction [14,23,24]. In identifying echocardiographic findings predictive of recurrent MR after mitral valve repair for FMR, several factors were associated with poor outcomes: mitral valve tenting height > 10 mm, posterior leaflet angle > 45°, tenting area ≥ 2.5 cm^2, systolic interpapillary muscle distance ≥ 20 mm, systolic sphericity index ≥ 0.7, end-systolic volume ≥ 145 ml and wall motion score ≥ 1.5 [25]. The discrepancy in these studies highlighted the need for a randomised control trial to identify if one strategy was optimal in this patient population.

In 2014, the Cardiothoracic Surgical Trials Network (CTSN) conducted a multicenter, randomised trial to evaluate the relative benefits and risks of repair versus replacement, with or without coronary revascularisation, in patients with severe IMR with follow-up for 12 months with a primary endpoint of LV reverse remodeling as determined by the LV End Systolic Volume Index (LVESVI). A total of 251 patients (126 in the repair group, and 125 in the replacement group), with an average age of 68 years, LVEF 41%, and EROA of 0.4 cm^2 were enrolled. There were no significant differences in LV reverse remodeling or survival between the MV repair or replacement groups. Additionally, no significant differences in major adverse cardiac or cerebrovascular events, functional status, or in quality of life were noted. What received the most attention was that the recurrence rate of moderate or severe MR was significantly higher in the repair group than in the replacement group (32.6% vs. 2.3%, respectively; $p < .0001$). Similar findings were identified at the 2-year follow-up of the trial, with no significant between-group differences in the rate of a composite of major adverse cardiac or cerebrovascular events, LV reverse remodeling or survival. An even larger discrepancy, however, was identified with regards to the recurrence rate of moderate or severe mitral regurgitation in the repair group versus the replacement group (58.8% vs. 3.8%, respectively; $p < 0.0001$) [26]. Additionally, patients in the repair group had more serious adverse events related to heart failure and cardiovascular readmissions. Although the trial was not powered for a survival difference, it should be noted that despite a < 4% rate of recurrent MR compared to the almost 60% seen in the repair group, there was no evidence of a survival benefit within two years in the replacement group, underscoring the lack of survival difference even with less recurrent MR. It remains to be seen if at longer follow-up (5 years) a survival difference becomes apparent. It should be noted, however, that the 2-year mortality rate of 19% in the repair group and 23% in the replacement group

(p=0.39) is still considerable. In response to the findings of the CTSNet trial, the ACC/AHA 2017 guidelines were revised and currently favour MV replacement as a IIA recommendation over repair in secondary or FMR [6].

It should be noted that post hoc analysis of this trial demonstrated that recurrent MR after MVA alone was greatest in patients with a postero-basal aneurysm leading to apical tethering of the posterior leaflet [27].

Despite the large difference in recurrent MR in the CTSN trial, advocates of mitral repair for FMR point out that only 12% of patients in this study received a concomitant subvalvular procedure for their mitral repair. While there has been no study to date comparing chordal-sparing mitral valve replacement versus mitral repair with RMA and a concomitant subvalvular procedure, the initial results from the addition of a sub-mitral technique have been promising, as we will outline. These initial studies have led to increased efforts to identify patient populations who would benefit the most from a mitral repair utilizing a subvalvular procedure which potentially restores the anatomy of the papillary muscles at the time of RMA allowing for LV remodeling and reducing the rate of recurrent MR. In the senior author's practice, patients who receive a mitral repair for FMR beyond simple Carpentier Type I annular dilatation will receive a subvalvular procedure with MV annuloplasty given the results of RMA alone. Certain criteria, on the other hand, make mitral valve replacement more advantageous including advanced age (>75 years), the need for concomitant procedures at the time of surgery that may significantly increase the cross-clamp and cardiopulmonary bypass times, additional complex MV leaflet pathology increasing the repair difficulty, or previous attempt at MV repair. Elderly patients, in particular, benefit from a minimally invasive chordal-sparing bioprosthetic MVR with excellent operative outcomes [28].

Subvalvular Techniques of Mitral Valve Repair for Ischaemic Mitral Regurgitation

Chordal Cutting

A variety of different subvalvular techniques have been developed (Table 1). The technique of chordal cutting, first introduced by Messas et al. [29] in 2001 in an ovine model of ischaemic MR, focuses on anterior mitral leaflet tethering in FMR resulting from the attachment of basal chordae to the basal and mid body of the anterior mitral leaflet. This attachment can lead to an abnormal bend in the anterior mitral leaflet described as a "seagull wing" by Professor Alain Carpentier [4]. In theory, second-order chordal cutting should reduce the degree of leaflet tethering and increase leaflet mobility and coaptation height limiting the degree of mitral regurgitation. Chordal cutting is typically performed by dividing secondary chords to the anterior leaflet, posterior leaflet, and the commissure that arise from the papillary muscle or muscles affected by the infarcted myocardium [30]. This procedure is performed prior to placement of the annuloplasty band to optimize visibility during chordal cutting to prevent inadvertent injury to primary chords.

The first large clinical study utilizing chordal cutting techniques in the surgical management of ischaemic MR was published by Borger et al. comparing patients who underwent chordal cutting mitral valve repair versus conventional RMA mitral valve repair for IMR [30]. The mean age was 64 years with the majority in both groups presenting with an MR grade >3+ (71% in the control group and 57% in the chordal cutting group). Pre-operatively, patients in

Table 1: Case series of subvalvular mitral repair techniques - table continues overleaf

Author	Year	Ref	Institution	# Patients	Technique	Major study findings
Borger	2007	30	University of Toronto; Toronto, Canada	92 total (43 = chordal cutting)	Chordal-cutting (CC)	No difference in mortality. Reduction in tent height, greater mobility of the anterior leaflet in CC. More recurrent 2+ MR in control group. No effect of CC on postoperative LVEF
Calafiore	2014	33	Prince Sultan Cardiac Center, Riyadh, Saudi Arabia	52 total (propensity-matched)	Chordal-cutting (CC)	In selected patients, with a bending angle < 145 and coaptation depth <10 mm, CC led to less MR, improved EF, and more symptom relief.
Kron	2002	33	University of Virginia; Charlottesville, VA. USA	18 total	PM relocation	No mortalities, at 2 months follow-up all with none-trace MR
Langer	2007	36	University Hospital Homburg, Homburg, Germany	12 total	Ring + String	At mean 1 year follow-up, valve function has remained stable, with mitral regurgitation < class II in all patients
Fattouch	2014	38	Maria Eleonora Hospital, Palermo, Italy	115 total	PM relocation	Five-year freedom from cardiac-related death was 91%. 3% rate of > moderate recurrent MR. Reversal in LV remodeling was observed (P<.05). There was considerable decrease in tenting area and coaptation depth.
Hvass	2003	39	Bichat Hospital, Paris, France	10 total	PM sling	Regurgitation is none to trivial in 9 patients (90%), and mild in 1 patient. The posterior LV wall between the PMs is shortened as a result of surgical remodeling.
Santana, Lamelas	2014	41	Mount Sinai Heart Institute, Miami Beach, Fla. USA	19 total	PM sling	30-day mortality was 0. A follow-up echocardiogram, obtained at a median of 3 (IQR, 1-7.5) months, demonstrated none to trivial MR in all patients

Author	Year	Ref	Institution	# Patients	Technique	Major study findings
Hvass	2010	42	Bichat Hospital, Paris, France	30 total	PM sling	Mean follow-up at 55 months shows MR is none to trivial in 31 and mild to moderate in 4. Follow-up beyond 1 year shows improvements in ventricular diameters, EF, volume, and sphericity index
Mihos (Lamelas)	2016	43	Mount Sinai Heart Institute, Miami Beach, Fla. USA	58 total	PM sling	At 10 months follow-up, a Ring+Sling repair significantly improved MV tenting height ($p = 0.005$), MV tenting area, and interpapillary muscle distance; a smaller posterior leaflet tethering angle; and a greater leaflet coaptation length, when compared with Ring only. Recurrence of moderate or greater MR occurred significantly less in the Ring+Sling group (14.7%), as compared with Ring only (35.3%) ($p < 0.001$). Finally, actuarial survival at three years was 87% for Ring+Sling, and 82% for Ring only ($p = 0.49$).
Rama	2008	44	Pitie-Salpétrière Hospital, Paris, France	8 total	PM approximation	None of the patients had residual mitral valve regurgitation
Nappi	2016, 2017	45, 46	Università Campus Bio-Medico di Roma, Rome, Italy	96 total (48 in each group)	PM approximation (PMA)	No difference in mortality at 5 years, but freedom from MACCE favored PMA in the last year of follow-up. PMA significantly reduced tenting height, tenting area, and interpapillary distance soon after surgery and for the long-term, and significantly lowered moderate-to-severe MR recurrence. Preoperative symmetric and asymmetric tethering and isolated inferior wall dyskinesia are an indication for subvalvular apparatus surgery in IMR.
Mandegar	2011	47	Day General Hospital, Tehran, Iran.	30 total (15 with PMA)	Left ventriculoplasty +/- PMA	Postoperative echocardiography revealed significant changes in the concavity area, EF, and sphericity index in the PMA group

the chordal cutting group had a significantly lower LVEF than patients in the control group (33% versus 43%, respectively; $p < 0.001$). Patients who underwent a chordal cutting mitral repair experienced greater reductions in tenting area as well as greater mobility of the anterior leaflet, as measured by a reduction in the distance between the free edge of the anterior mitral valve leaflet and the posterior left ventricular wall without compromising post-operative left ventricular ejection fraction. This led the authors to conclude that chordal cutting improved mitral valve leaflet mobility and reduced mitral regurgitation recurrence in patients with ischaemic mitral regurgitation, without any obvious deleterious effects on left ventricular function. What is less clear is whether the same benefit would be expected in the group of patients with better preserved LVEFs? Would "prophylactic" chord cutting prevent later leaflet tethering and provide a more durable repair or at least delay the onset of recurrence of MR?

Song et al. reported their findings in 38 consecutive patients with dilated or ischaemic cardiomyopathy who were candidates for cardiac transplantation by analyzing the impact basal chordae insertion site had on the development of secondary MR [31]. Wide variations in basal chordae insertion sites on the anterior leaflet dictated the severity of secondary MR in patients with LV dysfunction secondary to severe dilatation. Ultimately the authors concluded that basal chordal cutting would reduce the tenting angle and increase the bending angle of the anterior MV leaflet, thereby reducing the MV tenting area. However, if selective partial basal chordal cutting is needed to preserve LV systolic function, it may be best to cut the outer two basal chordae to reduce mitral valve tenting and MR severity. Calafiore et al. published their results from a propensity-matched analysis of 52 patients to determine the optimal surgical treatment of ischaemic mitral regurgitation (MR) utilizing a chordal cutting technique. [32] Patients were equally divided between chordal cutting (CC) and no chordal cutting (noCC) with a mean age of 62 years, EF of 30%, and LVEDD of 57mm. With a mean follow-up of 33 months, they found that in patients with a bending angle $< 145°$ and a coaptation depth ≤ 10 mm, chordal cutting led to less residual or persistent MR, improved EF, and lowered New York Heart Association class (Figure 1).

Papillary Muscle Relocation

In the early-mid 2000s, significant efforts were made primarily by Irving Kron and Frank Langer to develop surgical papillary muscle relocation techniques to address restrictive leaflet motion associated with severe leaflet tethering and displacement of the coaptation point seen in ischaemic MR. Kron et al. reported their technique of surgical relocation of the posterior papillary muscle using a 3-0 polypropylene suture placed through the posterior papillary muscle fibrous tip and then passed through the adjacent mitral annulus just posterior to the right fibrous trigone [33]. Subsequently the mitral annuloplasty is performed using a partially, flexible ring. After placement of the annuloplasty ring and saline testing, if there is evidence of leaflet tethering with inadequate leaflet coaptation and resultant MR typically located in the P3 segment, a single throw is placed in the posterior papillary muscle relocation suture and brought up to the annulus, drawing the posterior papillary muscle tip closer to the annulus. The final position of the posterior papillary muscle tip is then estimated by determining the point at which leaflet coaptation occurs in the plane of the mitral annulus.

Building upon the work of Kron, and in conjunction with the work by Tibayan et al. [34] which determined that the distance between the mid-septal fibrous annulus and the posterior papillary muscle plays a key role in the pathogenesis of IMR, Langer and colleagues developed a new posterior papillary muscle repositioning "ring plus string"

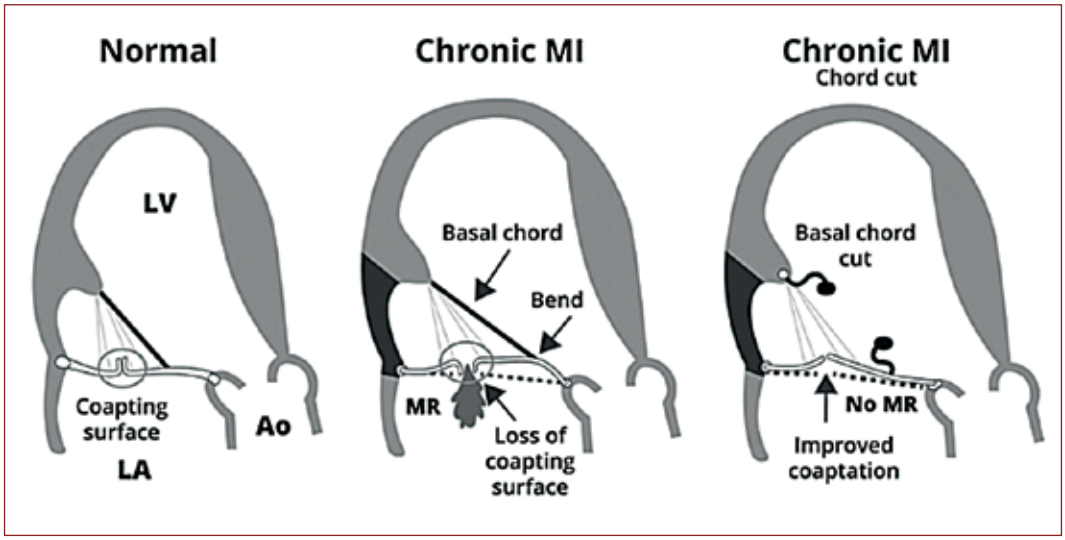

Figure 1: Chordal cutting technique in the surgical management of ischaemic MR

repair technique that could be adjusted under TEE guidance on the beating heart [35,36]. This technique is performed by anchoring a Teflon-pledgetted suture in the head of the posterior papillary muscle, then passed through the fibrosa (midseptal annular saddle horn) under direct vision and exteriorized through the aortic wall underneath the commissure between the non-coronary and left coronary aortic cusps. The suture is then tied under echocardiographic guidance in the loaded beating heart to reposition the displaced posterior papillary muscle toward the fibrosa. This technique has since been refined to allow for further reduction of the septal–lateral diameter after implantation in the loaded beating heart with their DYANA nitinol-based dynamic annuloplasty device that can be deformed by activation with radiofrequency [37].

Fattouch et al. reported their midterm results on the surgical management of severe, ischaemic MR in 115 patients who underwent a papillary muscle relocation plus non-restrictive mitral annuloplasty and coronary artery bypass grafting [38]. In their cohort, the five-year freedom from cardiac-related death and events was 91.3% and 84%, respectively, and the incidence of more than moderate recurrent MR occurred in only 3 patients (2.7%). Additionally, reversal in left ventricular remodeling, as measured by a change in the end-diastolic and systolic diameter was observed. Based on their findings, the authors concluded that in patients with ischaemic MR, papillary muscle relocation with a CV-4 Gore-Tex suture plus non-restrictive mitral annuloplasty promotes a significant reversal in left ventricular remodeling, a decrease in tenting area and coaptation depth, and less recurrent MR. What remains to be seen is if restrictive MVA compared to non-restrictive MVA would have led to better results. This study brings up the question of the relative contribution of the annuloplasty technique vs. the subvalvular repair in the success of MV repair for FMR.

Papillary Muscle Approximation

The technique of papillary muscle approximation (PMA) with a papillary muscle sling technique was first introduced in 2003 by Hvass et al. to treat patients with ischaemic LV

dysfunction and FMR [39]. By restoring a more normal alignment between the mitral annulus and the laterally displaced papillary muscles, this technique could relieve the excess tethering on the mitral leaflets, and significantly restore leaflet mobility. This method is performed by placing a 4 mm Gore-Tex (W.L. Gore & Assoc. Newark, DE, USA) tube graft around the base of the posterior and anterior papillary muscles (Figure 2). The loop is then progressively tightened until there is no residual graft between the bases of the two papillary muscles. Placement of an annuloplasty ring that is "true sized" to the anterior leaflet is then placed and the procedure has been termed the "sling and ring" repair.

This technique has since been modified and performed safely in a minimally invasive fashion via a mini-right thoracotomy by Lamelas [40,41]. Briefly, after standard femoral artery and vein cannulation, a 5-6 cm incision is made in the right 4th or 5th intercostal space lateral to the anterior axillary line. A rib spreader is inserted and the pericardium opened anterior to the phrenic nerve. A single dose of antegrade del Nido cardioplegia is infused and then repeated after 90 minutes if needed. A left lateral atriotomy is performed through Waterston's groove to enter the left atrium. An atrial lift retractor and atrial exposure blade are used to visualize the mitral valve. A specially designed papillary exposure instrument is used to evaluate the subvalvular apparatus. A long curved clamp is used to encircle all sets of papillary muscles with great care to make sure that the clamp is as close to the base as feasible. A 4mm polytetrafluoroethylene graft (Gore-Tex. WL Gore & Associates. Newark, DE) is placed around the base of the papillary muscles with attention to ensuring that the graft has an anchoring muscle to prevent upward migration (Figure 3). The edges of the sling are approximated as tightly as possible and then sutured together with a 4-0 Prolene suture (Ethicon, Inc. Somerville, NJ) (Figures 3). At this point, the "sling" portion is completed and attention is directed to the annuloplasty ring. Using the anterior leaflet height to size the ring, a rigid saddle ring is placed without under-sizing (Figure 4). The remainder of the operation proceeds in a standard fashion. In patients with previous coronary bypass grafting, the procedure is performed with moderate to deep hypothermia (24-26°C) under fibrillatory arrest. In patients with concomitant tricuspid regurgitation, both cavae are snared after the single femoral venous cannula is withdrawn into the inferior venae cava. The right atrium is opened and a sump suction, as opposed to a separate

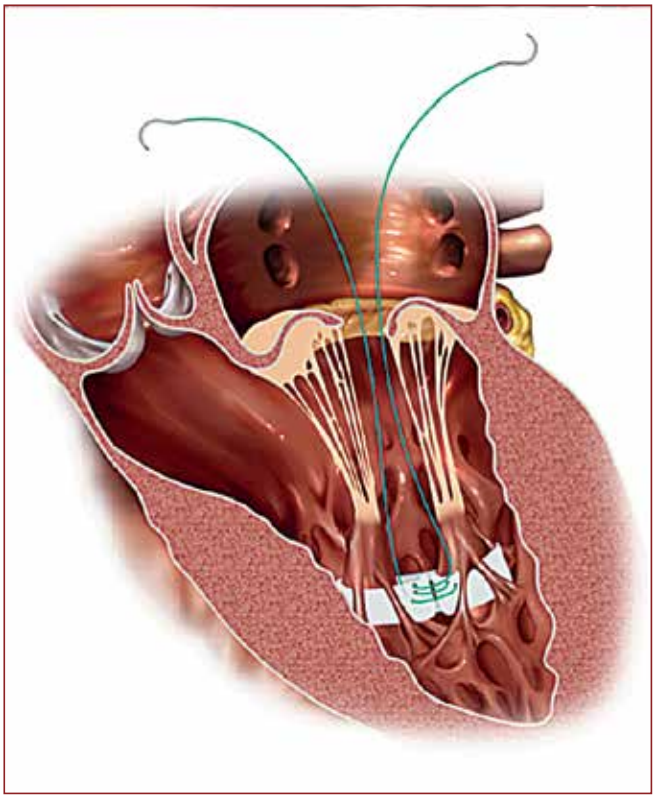

Figure 2: Papillary Muscle Approximation

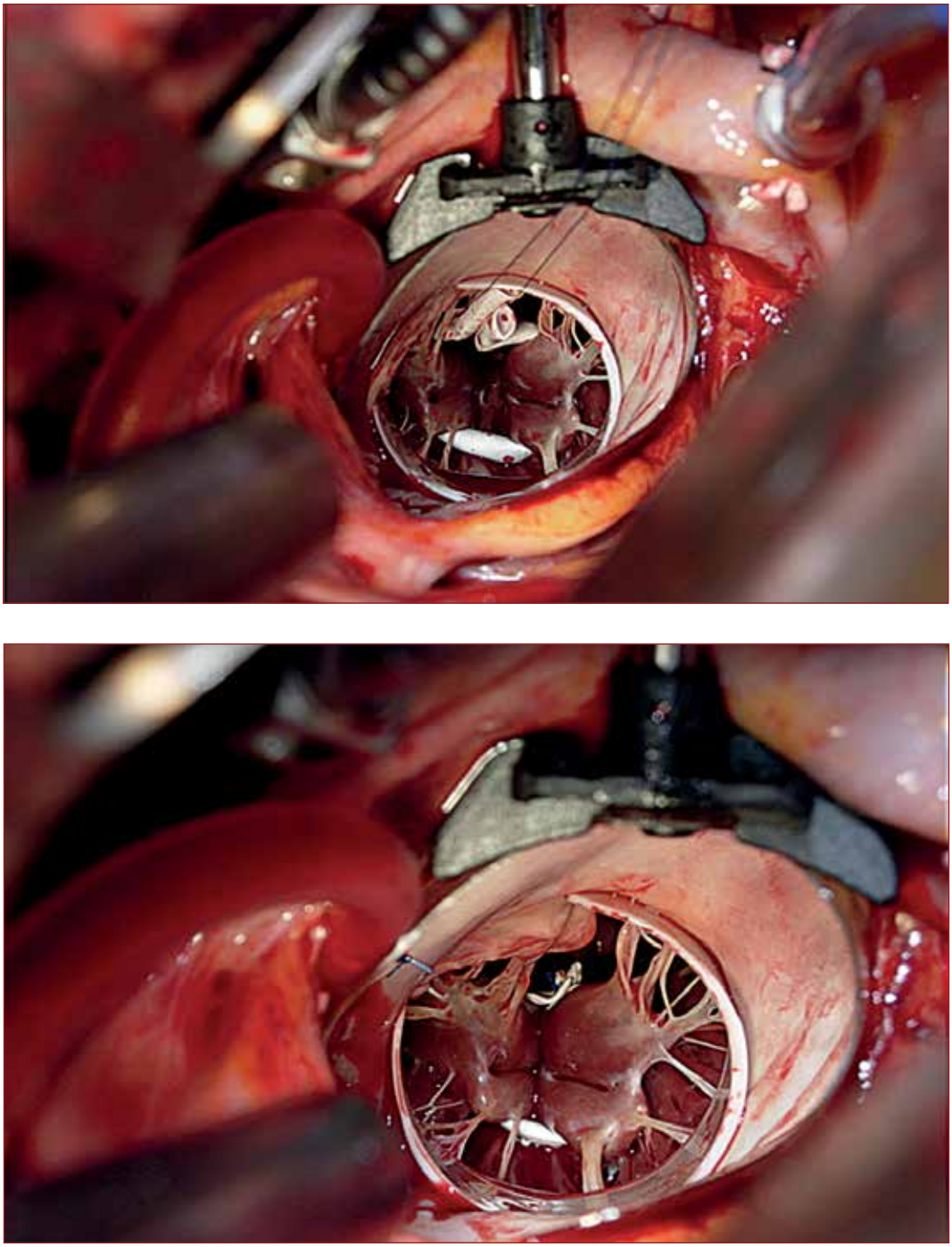

Figure 3: Top: papillary muscle sling encircling base of papillary muscles. Bottom: complete approximation of papillary muscles with tightened sling

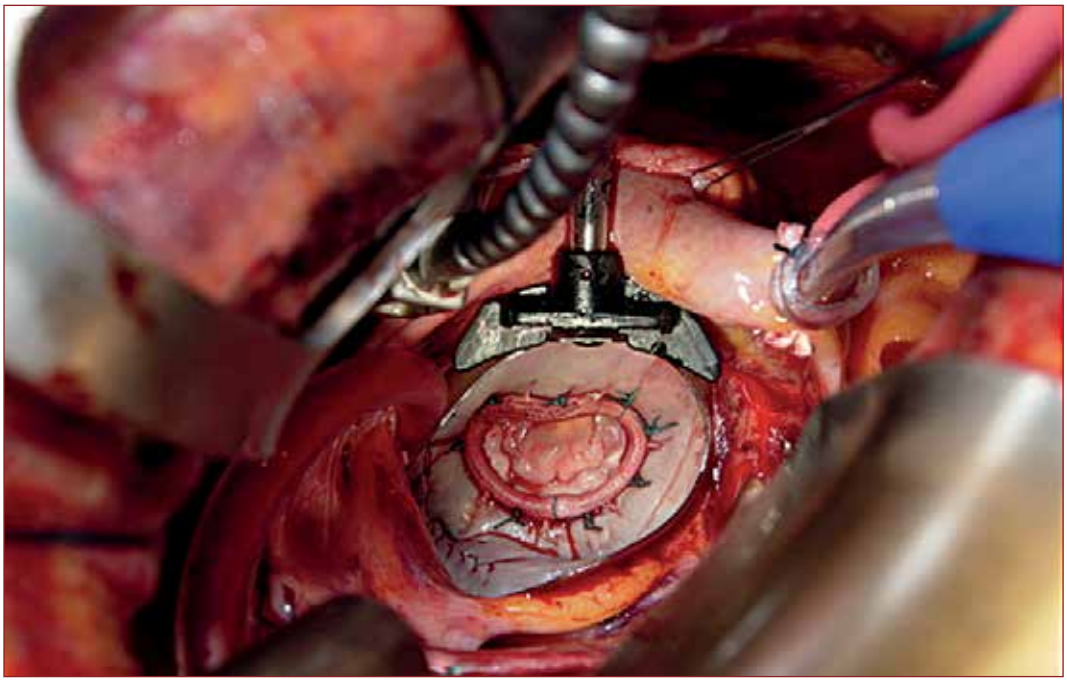

Figure 4: True sized complete rigid annuloplasty ring

superior vena cava cannula, provides adequate drainage for the procedure. In patients with atrial fibrillation, after the MV is immediately opened, the left atrial ablation is performed followed by closure of the left atrial appendage. Attention is then directed towards the mitral valve procedure.

Outcomes utilizing a "sling and ring" repair have shown promise with regards to improvement in LV remodeling and leaflet mobility. Hvass. et al. reported an immediate effect on mitral leaflet mobility by suppressing the tethering resulting from displacement of the papillary muscles [42]. This anatomical correction led to improvements in ventricular diameter, ejection fraction, volume, and sphericity index. Similar positive results have been seen when comparing papillary muscle sling plus RMA to annuloplasty ring alone. In the senior author's experience, the papillary muscle sling plus a true sized mitral annuloplasty ring was associated with a lower MV tenting height, MV tenting area, inter-papillary muscle distance, as well as a smaller posterior leaflet tethering angle and a greater leaflet coaptation length when compared with RMA alone [43]. Additionally, recurrent moderate or greater MR occurred significantly less in the sling and ring group, as compared with RMA only (15.7% vs. 35.3% respectively, $p < 0.001$) with a mean follow-up of 11 months.

In 2008, Rama et al. described a similar subvalvular approach of papillary muscle approximation (PMA) where a single U-shaped stitch, reinforced by two patches of autologous pericardium and passed through the bodies of posterior and anterior papillary muscles, repositions the papillary muscles to the midline [44]. This method of PMA is believed to correct papillary muscle displacement with a more anatomic papillary muscle-to-mitral annulus alignment. Nappi et al. conducted the PMA trial – a randomised controlled trial designed to determine the benefits of papillary muscle surgery on long-term clinical outcomes of patients with ischaemic MR [45]. A total of 96 patients were

enrolled in this study divided equally into groups with each receiving CABG and RMA and one group undergoing additional PMA. At 5-year follow-up, the PMA group was noted to have significant improvement in ventricular remodeling with reduction in mean LVEDD and improvement in mean LVEF. While there was no statistically significant difference in mortality at 5 years, the freedom from MACCE favored PMA. Additionally, PMA significantly reduced tenting height, tenting area, and inter-papillary distance both immediately and at late follow-up with significantly lowered recurrent moderate-to-severe MR. A sub-analysis by the same group determined that patients with pre-operative symmetric and asymmetric tethering and isolated inferior wall dyskinesia benefit most from concomitant subvalvular surgery [46]. This is consistent with the CTSNetwork trial that demonstrated more complex tethering may benefit from additional subvalvular procedures.

Surgical Ventricular Reconstruction

In certain populations, the addition of left ventriculoplasty to mitral valve repair for FMR has been found to be associated with more effective control of MR and further improvement of LVEF than RMA alone [47]. Surgical ventricular reconstruction (SVR) was first popularized for the management of heart failure with LV remodeling caused by coronary artery disease, and was shown to reduce the left ventricular volume, increase the ejection fraction, and improve ventricular function [48,49]. In the STICH trial, despite a significantly greater reduction in LV volume with SVR than CABG alone, this improvement did not translate into a measurable survival benefit for patients [50]. However, as sub-mitral techniques for mitral valve repair have begun to gain favor in the treatment of FMR, the combination of left ventriculoplasty with a subvalvular procedure has been investigated.

Wakasa et al. reported on patients with severe mitral tethering and significantly enlarged LVs (LVEDD > 65 mm) who underwent concomitant PMA and left ventriculoplasty [51]. When compared with annuloplasty alone, or annuloplasty with PMA, the addition of left ventriculoplasty was associated with a significant improvement in LVEF. There was also a trend toward greater improvement in MR grade when a left ventriculoplasty was also performed; however, this finding was not statistically significant.

Mandegar and colleagues studied 30 patients with pre-operative EF < 30% who were candidates for CABG and left ventriculoplasty [47]. Some patients received PMA plus left ventriculoplasty, and this group experienced significant changes in the concavity area, ejection fraction, and sphericity index. These findings led the authors to conclude that PMA as an adjunct to CABG results in better left ventricular function and shape, even at long-term follow-up. While interesting, these patients with very severe LV dilation may be appropriately evaluated in conjunction with a multidisciplinary advanced heart failure team to determine if primary MV surgery with mechanical circulatory back-up, or durable left ventricular assist device, is the optimal treatment.

Conclusions

The surgical management of FMR continues to evolve with improvements in surgical techniques designed to address the pathological changes in the mitral valve apparatus and left ventricle associated with chronic, ischaemic heart disease. Current guidelines by the AHA/ACC and ESC/EACTS continue to recommend surgical management for severe, chronic secondary MR. Earlier attempts to surgically correct annular dilation and resultant MR secondary to chronic ischaemic heart disease utilized RMA; however, recent results

from the CTSN multicenter, randomised trial have demonstrated that these patients have a high rate of recurrent MR compared to mitral valve replacement at 1- and 2-year follow-up. The lack of long-term benefit from mitral repair alone in these studies appears to indicate the need for additional techniques to MVA alone. Based on these studies, the current AHA/ACC recommendation for treatment of severe, chronic MR is mitral valve replacement. There remains the potential for percutaneous intervention with the Mitraclip device in the treatment of FMR as the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Trial (Abbott Vascular, Abbott Park, IL. USA) is currently ongoing (NCT01626079).

Several new subvalvular surgical techniques for the mitral valve have been developed over the past decade to address the pathological changes associated with chronic FMR, specifically annular flattening and dilatation (RMA), papillary muscle displacement (PMA and PM relocation), mitral leaflet tethering (chordal cutting, PMA), and global LV dilation (left ventriculoplasty). Early results utilizing these techniques in the surgical management of FMR have demonstrated positive results with evidence of favorable LV remodeling seen on post-operative echocardiogram and less MR recurrence. There are continued efforts to identify subsets of patients who will benefit the most from subvalvular procedures in addition to an annuloplasty for chronic FMR, as performed by Nappi and colleagues with regards to PMA. Additionally, some patients may benefit from a combination of subvalvular techniques during MV repair to address all potential causes of FMR in this population. The senior author has demonstrated that any of these techniques can be reliably performed from a minimally invasive right thoracotomy platform.

As the role for individual subvalvular techniques continues to evolve in the surgical management of FMR, there will be an impetus to compare results with mitral valve replacement and percutaneous mitral intervention. A randomized control trial between subvalvular MV repair versus chordal-sparing mitral valve replacement would address current concerns regarding the durability of MV repair in this population. Furthermore, as percutaneous mitral techniques continue to improve and are determined to provide a durable, lesser invasive approach to this problem, they will also need to be compared against mitral annuloplasty and subvalvular mitral repair. A survival benefit to any form of FMR surgical correction has yet to be shown. Symptom relief may be the metric to determine outcomes. Newer minimally invasive approaches to valve surgery via a right mini-thoracotomy have demonstrated significant reductions in ICU and hospital stay, blood transfusions, and pain and narcotic use when compared even to a mini-sternotomy, and may further improve short and long-term morbidity [52].

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Chapter 5

Mitral Valve Surgery:

Mitral Valve Catheter-Based Interventions: An Update

Vinayak (Vinnie) Bapat & Oscar Millan Iturbe

"Argumentum ad judicium"

Introduction

Mitral valve disease is one of the most common valvular heart disorders, particularly in ageing populations, with a prevalence of more than 10% in people over 75 years of age [1]. Heart failure is one of the most frequent causes of functional mitral valve regurgitation (MR) [2]. Enriquez-Sarano and colleagues estimated that moderate to severe mitral regurgitation will double its prevalence by 2030 affecting more than 4 million people [1,3]. Interestingly, MR is the second most common valve disease requiring surgery in Europe. MR is divided into either primary (a structural or degenerative abnormality of the mitral valve apparatus) or secondary MR (a disease of the left ventricle (LV) which interferes with the function and integrity of the mitral valve apparatus). Mitral stenosis is usually due to rheumatic disease, often with heavy calcification of the mitral leaflets involving the subvalvular apparatus [1,4].

The most common cause of primary MR is degenerative mitral valve disease, in which there is myxomatous degeneration of the mitral valve leaflets and elongated and redundant chordal apparatus [5]. Thickened redundant leaflets will prolapse back into the left atrium causing malcoaptation of leaflet edges and subsequent regurgitation. Rupture of chordal structures is common in patients with MR, especially in older men, which will then cause a further increase in the severity of MR because of unsupported segments of the mitral valve leaflets. Other causes of primary MR include rheumatic disease, with rare causes being drug-induced mitral valve disease, healed infective endocarditis, and MR associated with systemic disease. Secondary MR is usually due to annular dilatation or leaflet tethering, both resulting in incomplete coaptation of the leaflets resulting in regurgitation.

Surgical mitral valve repair and replacement are the current treatment options. American and European guidelines support surgical repair of the mitral valve over valve replacement whenever possible [4,6]. However, in up to 50% of patients with severe MR, surgical treatment is not performed owing to increased risk related to comorbidities [7]. For these patients, the possibility of percutaneous solutions has generated increased interest in recent years. Catheter-based approaches have focused on replicating a surgical repair or replacement. Repair techniques usually focus on the leaflets, annulus, or chordae. The largest body of experience comes from the use of a leaflet based technique, the MitraClip® system [8]. MitraClip imitates the surgical technique of Alfieri (edge-to-edge) stitch and is associated with an improvement in mitral regurgitation in a high percentage of well-selected patients [9]. Other approaches, which are leaflet-, annulus- or chordae-based, are at various stages of development.

With the success of transcatheter aortic valve implantation (TAVI), technological developments in the field of catheter-based treatment of MR is advancing at a rapid pace, with treatment modalities aimed to treat both primary and secondary MR. However, compared to TAVI, technological development in this field faces multiple challenges owing to the more complex structure of the mitral valve with unique anatomy and physiology, heterogeneity in mitral pathology and engineering challenges to design and deliver a much larger size valve in cases of replacement [2,10].

Further, it is still unclear if reduction in MR rather than abolition of MR is essential for clinical benefit. Most percutaneous repair techniques achieve reduction rather than elimination of MR but are relatively low risk procedures [11]. However, it may be conceivable that following repair using one technique, a second procedure may be required in some patients thus increasing risk, complexity, and cost. On the other hand, independent of the pathology, transcatheter mitral valve replacement (TMVR) has a potential to abolish MR completely

but may be associated with higher risk. Mitral annular calcification (MAC) represents rather a unique problem as surgical treatment can be suboptimal and transcatheter repair or replacement techniques may also fall short. Interestingly, TAVI devices are being increasingly used to address this issue [12]. This chapter will focus on transcatheter repair and replacement techniques.

Mitral Valve Anatomy Relevant to Percutaneous Techniques

It is important to understand the mitral anatomy and its relationship with the surrounding structures relevant to percutaneous techniques. The mitral is a complex apparatus that includes the annulus, the leaflets, the chordae, and the papillary muscles (PM). As the PM originate from the LV, the mitral apparatus plays a fundamental role in the structural and functional integrity of the LV. Therefore, disruption of the mitral-ventricular geometry could result in maladaptive remodeling and impaired LV performance [13].

1. Mitral valve annulus:

The mitral annulus is an oval saddle shape structure, which provides the base for the leaflets. The anterior annulus (1/3rd of the total circumference) is fibrous but the posterior annulus (2/3rd of the circumference) is predominantly muscular and hence prone to dilatation (Figure 1A). The annulus also changes in size during different parts of the cardiac cycle with an estimated reduction of 25% of the diameter during systole [14]. The annulus location is variable in relation to adjacent vascular structures but can lie 1cm below the coronary sinus and 2cm below the circumflex artery. Furthermore, the length of contact between the coronary sinus and the posterior annulus varies and is relevant to therapies based on external annular compression. (Figure 1B). Proximity of the posterior annulus to the circumflex artery is important as variation in anatomy dictates the risk of injury to the circumflex artery.

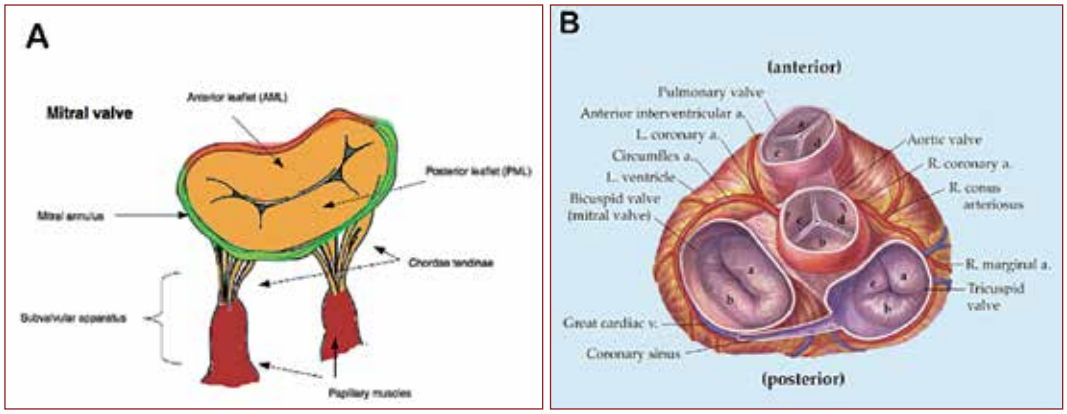


Figure 1: A. Mitral valve anatomy: The mitral valve is a complex structure composed of the annulus (anterior annulus shown in red and posterior annulus in green), two leaflets, chordae tendinae and papillary muscles. B. End on view of all four heart valves demonstrating external relationship between posterior mitral valve apparatus, coronary sinus and circumflex coronary artery.

2. Leaflet and subvalvular apparatus:

The mitral valve has two leaflets, a wider anterior mitral leaflet (AML) and a longer posterior mitral leaflet (PML). The leaflets are attached with their base to the mitral valve ring and they are attached with their free edges to the left ventricle via the subvalvular apparatus. Both leaflets receive chordae from both papillary muscles (Figure 1A) [15]. All TMVR devices interact with leaflets and subvalvular apparatus, and hence pathologies of these structures such as flail or tethered leaflet, calcification on the leaflet, fused subvalvular apparatus or abnormal papillary muscle morphology may pose a challenge for placement and secure deployment of TMVR devices. Usually there are two PMs: anterolateral and posteromedial. It must be recognized that these structures are dependent on adequate myocardial blood flow through the coronary arteries for optimal function. The anterolateral PM is often a single structure with dual blood supply from the left coronary artery, whereas the posteromedial PM is usually a multi-head structure with blood supply from only the right coronary artery (Figure 1A) [16].

3. Left ventricular morphology:

As the PM connect the LV wall with the mitral apparatus, any changes in the LV geometry can result in mitral valve dysfunction either due to leaflet tethering or annular dilatation. As most TMVR devices will project to varying degrees into the left ventricular cavity, any deformation of the LV geometry may affect device implantation and function. Because most of the ventricles with MR are dilated due to volume overload, TMVR device design must take LV dilatation into account. Furthermore, LV geometry can also influence the

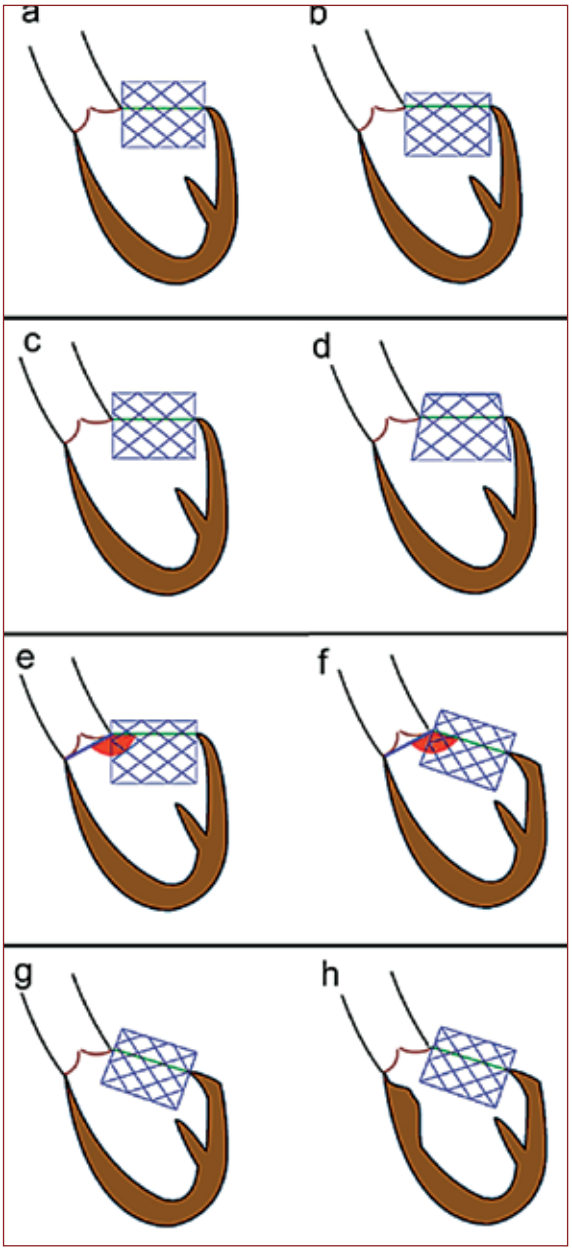


Figure 2: Anatomical factors that might be associated with the risk of left ventricular outflow tract (LVOT) obstruction in transcatheter mitral valve replacement: effect of depth of valve implant (a, b); effect of flaring of the device (c, d); aorto-mitral annular angle (AMAA; e, f); extent of septal bulge (g, h). Reproduced with permission Tang G et al [21]

optimum delivery angle and apical anchoring, both representing important components of TMVR implantation [17]. In addition, a septal bulge can also limit the suitability for a particular type of TMVR.

4. Left ventricular outflow tract (LVOT):

The AML is essentially a curtain, which divides blood flow between the LV inflow and outflow. During surgical mitral valve replacement, the AML is often removed or repositioned, which is not possible during transcatheter TMVR. Hence, the AML will be held open by the TMVR and essentially wraps the TMVR device similar to a covered stent. The wrapping could however result in LVOT obstruction (LVOTO) [18,19]. Various factors, such as size of the LV cavity, septal bulge, aorto-mitral annular angle, length and bulk of the AML and finally length of the TMVR device in the LV will determine the presence and degree of LVOTO (Figure 2) [19,20].

Transcatheter mitral valve repair technology

Mitral valve repair is currently the most widely used approach for transcatheter interventions for MR. Transcatheter mitral valve repair (TMVRep) options currently approved for medical use are Mitraclip [21] (leaflet approximation), NeoChord [22] (replacement of chordae), Carilion [23] (external annuloplasty) and Cardioband [24] (internal annuloplasty). Each of these techniques tends to address one component of the mitral complex, i.e. annulus, leaflets or chordae rather than the entire mitral valve complex; hence, the majority of these interventions may result in reduction rather that elimination of MR [21-24]. Furthermore, patient suitability for each technique may be limited due to the variable aetiology of MR [11]. We discuss briefly these techniques and also some of those novel techniques currently under development.

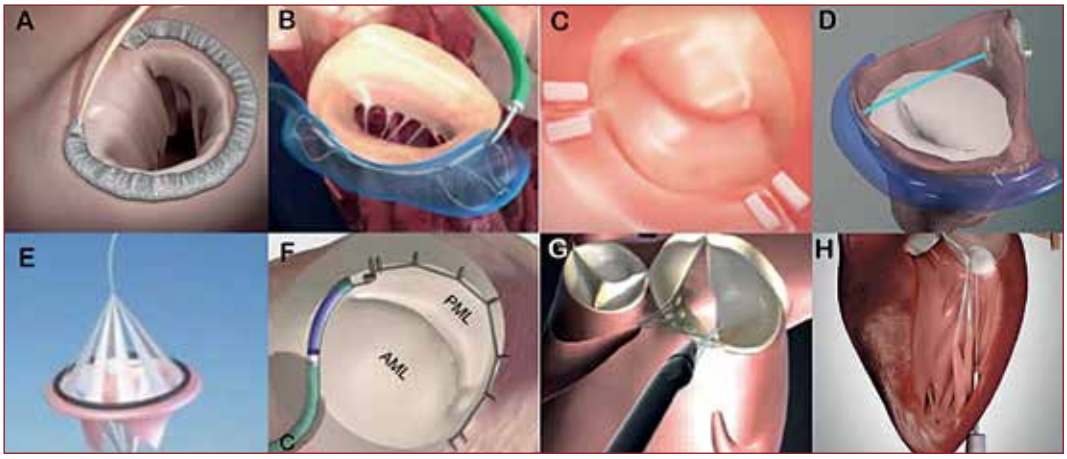
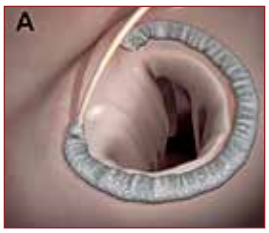


Figure 3: Percutaneous Mitral valve repair approaches: A: Cardioband, B: Carillon, C: Mitralign, D: MVRx, E: Intrepid, F: Accucinch, G: NeoChord, H: Harpoon

A) Annuloplasty techniques:

1. *CARDIOBAND TF (Valtech, Israel), Direct annuloplasty (Figure 3A)*



- Concept: An adjustable, sutureless posterior annuloplasty band.
- Approach: Transfemoral venous and trans-septal.
- Procedure: Anchors are screwed to attach the incomplete ring of the device along the posterior annulus, and then a cable is used to tighten the ring to accomplish reduction of the mitral annular circumference thus reducing MR [25]. The main reduction occurs in the septo-lateral annular diameter.
- Imaging guidance: 3D TEE and fluoroscopy.
- Clinical experience: Published data reported outcomes from 31 consecutively enrolled high-risk adult patients at five institutions in Europe with symptomatic secondary MR despite optimal medical therapy and cardiac resynchronisation therapy (CRT) where indicated. All patients received the full implant of a Cardioband. Adjustment of the Cardioband resulted in a significant reduction in the septolateral dimension in all but two patients experienced device failure. Excluding the two patients with device failure, MR was none or trace in six (21%), mild in 21 (72%), and moderate in two (7%). No patient had severe MR after adjustment. Procedural mortality was zero and in-hospital mortality was 6.5% (two of 31 patients). The two mortalities were not device-related. At 30 days, 88% of patients had MR ≤2+. The reduction of MR was stable at 12 months, with 90% of patients having MR ≤2+ on TTE at one year. The observed reduction of MR is associated with substantial and sustained improvement of quality of life and functional capacity[25].
- CE mark: for the treatment of functional MR was issued in September 2015

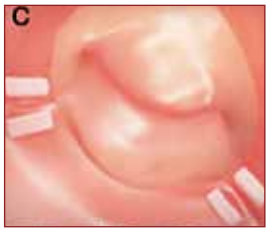
2. *CARILLON (Cardiac Dimensions, Kirkland, WA, USA) - Indirect Annuloplasty (Figure 3B)*

- Concept: This implantable mitral annular constraint device is percutaneously placed into the coronary sinus and great cardiac vein. Its working principle is based on the assumption that due to proximity of the coronary venous system to the posterior mitral annulus tightening of the shaping ribbon connecting the two anchors of the device will remodel and shorten the circumference of the mitral valve annulus. The device was specifically designed for heart failure patients with significant MR due to mitral annular dilatation.
- Approach: Transjugular venous.
- Procedure: Constructed of nitinol wire with distal and proximal anchors connected by an intervening cable. Shortening of the shaping ribbon results in cinching of the coronary sinus and thus remodeling of the posterior mitral annulus. The magnitude of beneficial effect appears to be similar to MitraClip [26]. A particular unusual feature of the response to a CARILLON device is a delayed response with progressive reductions in mitral annular dimensions.
- Imaging: 3D TEE, TTE and fluoroscopy.

Clinical experience: The Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) trial, which evaluated the clinical impact of the Carillon in heart failure subjects with significant functional MR, showed a significant reduction in functional MR grade with a reduction in LV diastolic and systolic volumes. Treated subjects were compared with a pseudo-control group consisting of subjects without implants. Functional and performance status significantly improved in the treated subjects. Late results showed that coronary sinus annuloplasty was associated with delayed reverse LV remodeling and clinical improvements up to 24 months even in subjects in whom an acute response was not observed [27]. The upcoming REDUCE (Safety and Efficacy of the CARILLON Mitral Contour System in Reducing Functional Mitral Regurgitation Associated with Heart Failure) randomized trial will compare the Carillon device to optimal medical therapy in 120 heart failure subjects with FMR. The first subject was enrolled in June 2015.

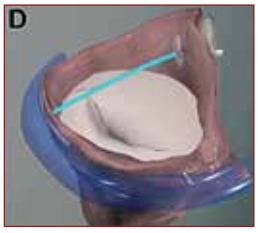
CE mark: CE mark approval (Model XE2) 2011. Not approved outside Europe and the Middle East.

3. *MITRALIGN Direct annuloplasty (Figure 3C)*



- Concept: Direct reduction of the annulus resulting in reduction of both anterior-posterior and septal-lateral dimensions of the mitral annulus, accompanied by decreased MV tenting area and an increase in MV coaptation depth [28].
- Approach: Transfemoral arterial retrograde (14F).
- Procedure: Plication of the mitral annulus is achieved by placing two sets of pledgets, one in the anterior annulus and the other in the posterior annulus and then plicating them together. A deflectable guiding catheter is placed at the ventricular side of the mitral annulus and then with the use of radiofrequency, a wire is passed through the annulus into the left atrium. The pledgets are then delivered in the atrial and ventricular side. This is repeated for the posterior annulus. Over the sutures a dedicated plication lock device is advanced to one of the pledgets. Once the required plication is achieved, a stainless-steel lock is placed, maintaining the plication of the mitral annulus. As a final step, the sutures are cut approximately 4mm from the lock [28].
- Imaging: 2D/3D TEE and fluoroscopy.
- Clinical experience: The results of the CE Mark Trial have been recently reported in 51 high-risk subjects with functional MR. Thirty day mortality was 7.8%; survival at 6 months was 88% with an 80% freedom from valve intervention. Significant improvements in MR severity, reduction in annular dimensions, and significant LV remodeling were demonstrated at 6 months (Schofer J. Mitralign procedure and results of the CE Mark Trial. Presented at the TVT Conference. Chicago, June 4, 2015). Results from the study also confirmed that 2 pairs of pledgets were more effective in reducing MR than a single pair of pledgets. The procedure was also safe with no procedure-related events.
- CE mark: CE mark approval in February 2016.

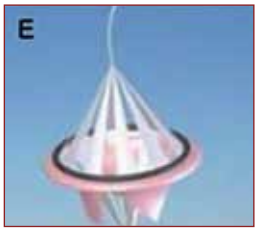
4. *PS3 (MVRx) ANNULOPLASTY (Figure 3D)*



- Concept: Direct leveraged trans-atrial shortening of the septo-lateral dimension of the mitral valve by providing two anchor points that are tensioned together [29].

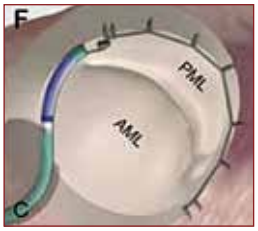
- Approach: Femoral or jugular trans septal.
- Procedure: Anchors a cord between the CS and the atrial septum, which is shortened to reduce mitral annular septo-lateral distance.
- Imaging: Fluoroscopy-guided. 2D/3D TEE and TTE only to assess MR.
- CE mark: CE mark trial underway.

5. MILLIPEDE RING (Millipede, LLC, Ann Arbor, MI, USA) (Figure 3E)



- Concept: Semirigid circumferential annular ring.
- Approach: Femoral retrograde or trans-septal.
- Procedure: Complete ring that is anchored into the mitral annulus using screws, and mechanical cinching to reduce the mitral annular circumference [30].
- Imaging: echo guidance.
- CE mark: Pre-clinical studies are underway.

6. GDS ACCUCINCH (Guided Delivery Systems, Santa Clara, Calif.) (Figure 3F)



- Concept: Catheter-based delivery of a subvalvular left ventricular reshaping (ventriculoplasty) system designed to reshape and resize the left ventricular base and to re-establish native mitral valve geometry while preserving native leaflet function and restoring leaflet coaptation.
- Approach: Femoral artery, retrogradely across the aortic valve with the guide tip shape chosen to sit in the anterior aspect of the sub-annular space.
- Procedure: Placement of a shaped guide catheter retrogradely across the aortic valve and into the sub-annular space, wiring of the sub-annular space, placement of a modular guide tunnel over the guidewire, deployment of 12-14 anchors with force distribution members between proximal and distal anchors, removal of the modular guide tunnel, cinching of the cinch cable and placement of a lock to maintain the applied tension within the system, and cutting of the cinch cable to leave the completed implant prior to removal of the guide catheter [31].
- Imaging: 2D/3D TEE and fluoroscopy.
- CE mark: International feasibility trial underway.

B) Chordae replacement

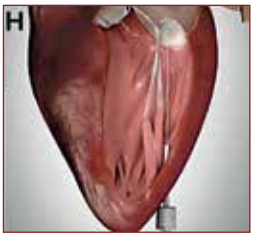
1. NEOCHORD (NeoChord DS1000) (Figure 3G)

- Concept: Placement of new chordae directly on to the leaflets.
- Approach: Transapical.
- Procedure: The LV apex is exposed via a left lateral minithoracotomy, and a sheath is advanced via the apex towards the MV leaflets. A catheter is used to grasp the leaflets and attach artificial chordae, which are then anchored to the LV apex. A fiber-optic monitoring device confirms that the leaflet has been adequately

captured. Once the NeoChord is attached, the operator can optimize real-time reduction in MR by varying chord tension and the extent of MV prolapse [32].

- Imaging: TEE and fluoroscopy.
- Clinical Experience: The Transapical Off-Pump Mitral Valve Intervention with Neochord Implantation (TOP-MINI) assessed early clinical outcomes. Forty-nine patients were treated. Acute procedure success (defined as successful placement of at least 3 neochords with reduction of residual MR to < 2+ was achieved in all patients. In-hospital mortality was 2%. At 30 days, major adverse events included one AMI (2%) successfully treated percutaneously and one sepsis (2%); no stroke or bleeding events occurred. At 3 months, overall survival was 98% and MR was absent in 16 patients (33.4%), grade 1+ in 15 (31.2%), and grade 2+ in 12 (25%). Five patients (10.4%) developed recurrent severe MR due to anterior native chordae rupture. Four of them were successfully re-operated. At 3-month follow-up, freedom from reoperation was 91.7 ± 4%. Early results with Neochord procedure indicate that it is feasible and safe. Efficacy is maintained up to 3-month follow-up with significant clinical benefit for the patients [32].
- CE mark: CE approval in December 2012 for minimally invasive mitral valve repair via surgical implantation of artificial chordae tendinae.

2. *HARPOON (Harpoon Medical) (Figure 3H)*



- Concept: Placement of pre-knotted chordae directly on leaflets.
- Approach: Trans-apical, beating heart, 14 F delivery system
- Procedure: A small anterolateral thoracotomy is performed in the fourth or fifth intercostal space. The introducer is inserted into the ventricle through a purse-string suture in a location that is 3 to 4 cm basal from the apex and lateral to the left anterior descending coronary artery. The Harpoon device is steered to the underside of the prolapsed leaflet at the targeted location, and once leaflet stabilization is achieved, the device is actuated, forming a double-helix knot on the atrial surface. Multiple expanded polytetrafluoroethylene (ePTFE) cords are anchored on the leaflet, the introducer is withdrawn, and the cords are titrated to maximize coaptation and to minimize mitral regurgitation. The cords are tied on a Teflon pledget on the epicardium at the insertion site [33].
- Imaging: Echo guided procedure.
- Clinical Experience: In the first-in-human experience, the Harpoon used for beating-heart image-guided MV repair demonstrates a significant reduction in MR with favorable left ventricular and left atrial reverse remodeling. Eleven patients with posterior leaflet prolapse and severe MR were treated with 100% procedural success. Immediate post-procedural mean MR grade was 'trace'. At 1 month, the mean MR grade was 'mild' with significant decreases in end-diastolic volume and left atrial volume [34].
- CE mark: Feasibility study

C) Leaflet based repair

1. *MITRACLIP (Abbott)*

- Concept: Based on the Alfieri stitch (Figure 4A).
- Approach: Trans-septal.

Figure 4: Mitraclip: device and procedure.

A: Trans-septal delivery system

B: Mitraclip close up

C: Trans-septal puncture

D: Leaflet grasping with the Mitraclip.

- Procedure: This is performed under general anaesthesia with TEE imaging. It is a trans-septal procedure. A dedicated system with multi-directional control is introduced through the femoral vein. Following a trans-septal puncture, the delivery system is introduced into the left atrium and steered towards the mitral valve. Once the system is aligned, the clip is opened and the edges of both leaflets are grasped at the desired location and secured by closing the clip. If necessary, additional clips are placed. It is important to ensure adequate tissue grasp to avoid early or delayed detachment. Similarly, before releasing the clip, it is important to assess the possibility of mitral stenosis and reduction in MR.
- CE mark and FDA approval: Mitraclip has the largest clinical experience with over 20,000 procedures performed worldwide. Mitraclip was the first product to receive CE mark in Europe for transcatheter mitral repair. The EVEREST trial in the USA led to a limited approval for degenerative MR only. The COAPT trial has not finished enrolling and will clarify its efficacy in primary MR.

2. MISTRAL (Mitralix)

- Concept: Leaflet gathering.
- Approach: Transseptal.
- Procedure: Delivered with12F catheter (3D nitinol spiral shaped atraumatic wire) for mitral valve repair via chord grasping. This is Mitralix's 1st product [35].
- International Status: Pre-clinical underway.

3. MITRA-SPACER-TRANSAPICAL (Cardiosolutions)

- Concept: Facilitate leaflet coaptation.
- Approach: Transapical.
- Procedure: Catheter-based mitral valve spacer to reduce MR improving leaflet coaptation [35].
- International Status: First-in-man study underway

Transcatheter mitral valve replacement (TMVR)

In some patients, mitral valve repair is not feasible or effective. TMVR has several advantages, compared with valve repair, as it can potentially eliminate MR irrespective of the underlying pathology. TMVR also preserves the chordae and leaflets and hence helps to preserve left ventricular function [36].

A) Device design

The 'Ten Commandments' of an ideal TMVR design would be:

1. Ease of implantability,
2. Reproducibility,
3. Results in complete elimination of MR,
4. No risk of left ventricular outflow tract (LVOT) obstruction,
5. No adverse effect on LV function,
6. Addresses a wide range of sizes,
7. Effective independent of the aetiology,
8. Long-term durability,
9. Non-thrombogenic,
10. Does not result in hemolysis.

First-in-man experience has now demonstrated feasibility and proof of principle for many devices but these early experiences have also revealed some challenges [37]. When designing a TMVR, there are numerous challenges. These can be grouped as follows:

1. Anatomical: large and saddle-shaped annulus, varying morphology of leaflets depending on the pathology, size of the left ventricle and proximity to left ventricular outflow tract (LVOT). A large valve requires a large device, which can accommodate dynamic changes in the annulus.
2. Physiological: Higher closing pressures influencing stability, effects on blood flow in the atrium and LVOT and thrombogenicity. Higher closing pressures also impact durability.
3. Challenges with device delivery: delivery systems and route of delivery.

Thus, the design of potential therapeutic devices is rather complex, particularly when compared with the development of TAVI devices.

B) Delivery system

The larger nature of the device and delivery routes influence the construction of the delivery system. Designing a suitable delivery system that allows a safe route of delivery is a key factor influencing outcome. As the majority of TMVR devices are manufactured from a nitinol stent frame, most delivery systems are self-contained i.e. the device is crimped within the delivery system. Some of the common features are:

1. A gradual, stepwise deployment of the device and, to a certain degree, retrieval of the device within the sheath if the result is not satisfactory.
2. Access route defines the orientation of the device within the delivery system. Thus, a TMVR device delivered through a transapical approach will have the atrial portion towards the distal end of the delivery system.
3. As the device size is relatively large, most delivery systems will be larger than the current TAVI delivery systems, i.e. > 30F outer diameter.

C) Approaches

The mitral valve can be accessed through multiple approaches i.e. transapical, transseptal or transatrial. The majority of TMVR implants to date have been performed through the

transapical approach, which reflects on the ease of access to the mitral valve, size and maneuverability of the delivery system.

1. *Transapical approach (Figure 5A):*

   This approach is similar to that of the transapical approach in TAVI, but with some important differences. In contrast to TAVI, the site of the puncture needs to be accurately determined, as angulation during TMVR deployment can result in technical difficulties and imperfect results. Thus, the puncture site is determined pre-operatively using 3D-reconsruction of the CT scan, which will allow a near perpendicular direction of the delivery system in relation to the mitral annulus. The size of the purse-string is large, reflecting the size of the current delivery systems. Difficulties can be encountered at the puncture site due to the thickness of the myocardium. The presence of an apical aneurysm, thrombus, or a thin, friable ventricle would be contraindications for this approach.

2. *Transseptal approach (Figure 5B):*

   Percutaneous access though the femoral vein has been used for balloon mitral valvuloplasty for several decades and more recently also for transcatheter procedures such as Mitraclip and valve-in-valve replacements in the mitral position. For most procedures, the tear/puncture of the inter-atrial septum can be left alone without any clinically relevant consequences. But, delivering a large TMVR device with a large delivery system will result in a much larger tear, which will need to be closed with a device [38]. Furthermore, the nature of the current delivery systems may not allow optimum manipulation for placement of the device in a perfect position, and can add to the complexity of an already complex procedure. This is supported by the fact that most valve-in-valve procedures in the mitral position are performed through a transapical approach [39]. It is, however, conceivable that with improvements in the device and delivery system technology, this approach will become viable in future.

3. Transatrial approach (Figure 5C):

   Delivery of a transcatheter mitral valve via transatrial access for a valve-in-valve or valve-in-ring device implantation has been described. Feasibility of this approach in the native mitral annulus has been only demonstrated in animal models [40]. Essentially,

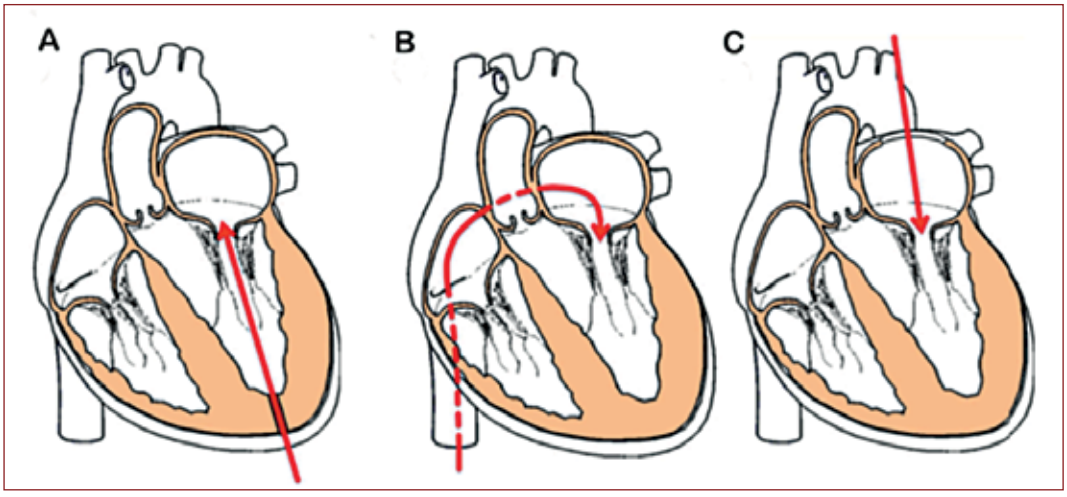


Figure 5: Approaches for TMVR. A: Transapical; B: Transseptal; C: Transatrial

a small thoracotomy is performed on the right side and left atrium or right superior pulmonary vein is accessed. After placing purse strings, a short delivery system is used to implant the valve in the mitral position. Although this approach may allow better control of the implant due to the proximity to the mitral valve and antegrade nature of delivery, it still remains an invasive surgical approach and coaxiality of the device is not always feasible. This approach is currently reserved only when transapical or transseptal approaches are not feasible.

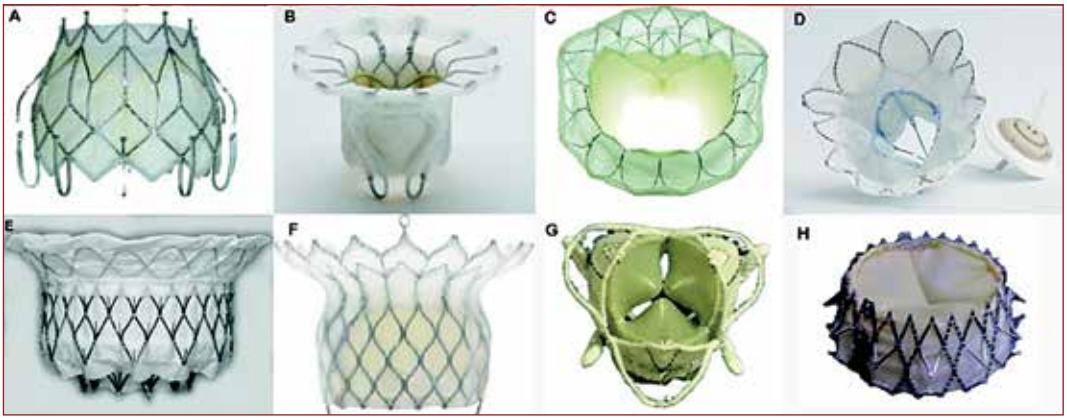


Figure 6: Transcatheter mitral valve replacement (TMVR) devices with successful clinical implants. A: CardiAQ valve system; B: FORTIS valve; C: Tiara™; D: Tendyne valve; E: Twelve; F: Highlife; G: Caisson; H: Navigate.

D) TMVR devices

We describe devices with first in man experience and highlight some of the unique features, advantages and disadvantages of these devices.

CardiAQ valve system (Edwards Lifesciences, Irvine, CA) (Figure 6A)

- Stent frame: self-expanding nitinol frame, circular.
- Leaflets: three leaflets made of bovine pericardium.
- Anchoring mechanism: two sets of opposing anchors, atrial and ventricular. Ventricular anchors, hook around the leaflets.
- Suitable for native annulus size: 36 to 39.5 mm.
- Delivery system: 33F.
- Approach: Transapical and transseptal.
- Effect on LVOT: Minimal, as the device sits relatively high in the atrium
- Sizes: Single 30 mm at the inflow and 40 mm at the annulus.
- Clinical experience to date: The first implant was performed in 2012 with the first generation CardiAQ porcine bioprosthesis through a transseptal approach.

From May 2014 to June 2015, the second generation of the CardiAQ bovine bioprosthesis was implanted in 10 patients. The transapical approach was used in 9 cases and the transseptal approach was used in one case [41]. The CardiaAQ valve has been implanted in ten patients in a compassionate use protocol. The outcomes of 3 patients who underwent TMVR through the apex were published. Successful implant was achieved in all subjects and 30-day mortality rate was 33.3% without late mortality. Of the 3 patients, 1 patient died in hospital as result of post-operative pneumonia [41,42]. The same group published the successful implant of the second generation of the CardiAQ valve through transfemoral-transseptal approach in 1 patient [43].

- Stage of development: Feasibility trial.

Fortis (Edwards Lifesciences) (Figure 6B)

- Stent frame: self-expanding nitinol frame, circular and cylindrical.
- Leaflets: three bovine pericardial leaflets symmetrical.
- Anchoring mechanism: the Fortis TMV uses paddles located in the outflow of the central valve body allowing capture of the mitral leaflets.
- Suitable for native annulus size: 30 to 44 mm.
- Delivery system: 42F.
- Approach: Transapical.
- Effect on LVOT: Contraindicated in a small left ventricle.
- Sizes: single - 29 mm.
- Clinical experience to date: Twenty patients have been treated with the Fortis TMV [41]. In the US, the results of only 13 patients performed outside trial protocol are available. Procedural success was obtained in 10 patients. Two patients required conversion to open surgery, one due to malposition and another due to chordal entanglement. One patient had partial migration of the valve and died on post-procedure day 4. In-hospital mortality rate was 30.8% (4/15). Excellent results in abolishing MR were seen on echocardiogram at the time of discharge. The 30-day mortality rate was 38.5%, as one patient died on day 15 post implant due to suspected valve thrombosis/endocarditis [44].
- Stage of development: On hold/withdrawn

Tiara (Neovasc) (Figure 6C)

- Stent frame: Self-expanding nitinol frame, D-shape.
- Leaflets: Three asymmetric leaflets made of bovine pericardium.
- Anchoring mechanism: 3 tabs, 2 anterior and 1 posterior. The tabs help to secure the device by anchoring it against the fibrous skeleton of the mitral valve.
- Suitable for native annulus size: The A-P diameter is 30-34 mm, and the lateral diameter is 35-40 mm.
- Delivery system: 32F.
- Approach: Transapical.
- Effect on LVOT: Minimal as it is a D-shaped device

- Sizes: multiple. Although the only size available for investigational use is 35 mm. The other sizes (40 mm and 45 mm sizes) are under development.
- Clinical experience to date: Nineteen patients have been treated with Tiara valve. These patients were considered high-risk for mitral valve surgery. Three patients were reported to have malposition with conversion to open surgery (16%). The remaining valves were successfully implanted and the 30-day echocardiogram evaluation showed no evidence of mitral regurgitation [45]. Mortality at 30 days was 16% (3 patients). There was one case of late mortality on day 69 post-implant despite successful implantation of the valve with abolishment of MR due to refractory end-stage heart failure [46].
- Stage of development: Feasibility trial; the TIARA-I study is currently actively enrolling.

Tendyne/Lutter TMVR (Tendyne) (Figure 6D)

- Stent frame: Two self-expanding nitinol stents. Outer stent is D-shaped.
- Leaflets: Three symmetric leaflets made of porcine pericardium.
- Anchoring mechanism: Atrial flange and left ventricular apical tethered system with apical pad.
- Suitable for native annulus size: 30 to 43 mm.
- Delivery system: 34F.
- Approach: Transapical and Transseptal (Feasibility study for transseptal access route underway).
- Sizes: Multiple.
- Clinical experience to date: The first two patients who underwent a successful temporary implant of a Tendyne valve were operated in Paraguay under the International Organisation for Standardisation regulations [47,48]. These two valves were explanted as per the protocol agreed and replaced with a surgical valve. A series of 30 patients was subsequently reported. All patients underwent a Tendyne valve implant via transapical approach. The majority of patients (76%) treated had secondary MR. In 89% (26 patients) the EF was >30%. Two patients required device retrieval, one because satisfactory position of the implant was not achieved, and the second due to LVOT obstruction. Mortality at 30 days was 0%, information on late mortality is not available. One patient had haemolysis requiring transfusions and one patient had valve thrombosis. Overall results were impressive with no apical complications, improvement in functional class and abolition of MR [47,48].
- Stage of development: Feasibility trial.

Intrepid (Medtronic) (Figure 6E)

- Stent frame: Self-expanding nitinol frame which has a unique dual structure design consisting of a circular inner stent to house the valve and a conformable outer fixation ring to engage the mitral annular anatomy.
- Leaflets: Trileaflet bovine pericardial valve.
- Anchoring mechanism: Unlike other devices, the Intrepid valve is retained due to its unique interaction with the mitral annulus. The “cork effect” produced at the level of the annulus due to the variable stiffness of the stent frame is the primary mechanism for fixation. Small cleats on the outer stent also help by

engaging with the mitral leaflets and promoting tissue ingrowth. The conformable outer stent engages the annulus, providing fixation, and sealing while isolating the inner stent from the dynamic anatomy. The circular inner stent houses a 27-mm tricuspid bovine pericardium valve. The flexible brim aids imaging during delivery and subsequent healing [49].

- Suitable for native annulus size: 30 to 42mm (96% of screened patients).
- Delivery system: 33F.
- Approach: Transapical.
- Effect on LVOT: Minimal, as the stent is short.
- Sizes: 43 mm, 46 mm, and 50 mm outer diameters.
- Clinical experience to date: The last data presented included 38 patients enrolled in the Intrepid TMVR Pilot with successful deployment in 36 out of 38 patients [49]. Mortality at 30 days was 7 out of 38 (18%), with the cause of death not related to the procedure in 3/7 and cause of death related to the procedure but not the device in the remaining 4. There was one additional mortality between 3-6 months, which was not related to the procedure. Abolition of MR and improvement in the functional class was seen in all patients.
- Stage of development: Feasibility trial.

HighLife Mitral Valve Replacement (HighLife) (Figure 6F)

- Stent frame: Nitinol.
- Leaflets: Glutaraldehyde cross-linked bovine pericardium.
- Anchoring mechanism: A ring-shaped sub-annular implant (SAI) placed around the native leaflets and a specifically designed stent with a groove placed inside the SAI. The SAI together with the native leaflets provide complete paravalvular sealing [50].
- Suitable for native annulus size: Not specified.
- Delivery system: First access is made to the femoral artery and an 18F introducer sheath is positioned.
- Approach: Transatrial and transfemoral approaches.
- Effect on LVOT: Not specified.
- Sizes: Not specified.
- Clinical experience to date: The single-centre early feasibility clinical trial started in Kiev (Ukraine). The first patient was treated successfully and discharged home at day seven [51].
- Stage of development: Preclinical trials underway.

Caisson TMVR (Caisson) (Figure 6G)

- Stent frame: Dacron panels for tissue in-growth, D-shaped sealing cuff.
- Leaflets: Porcine pericardium.
- Anchoring mechanism: Unique ‘feet’ on the outer stent frame provide anchoring by engaging with the sub-annular fibrous grove.

- Suitable for native annulus size: Not specified.
- Delivery system: Not specified.
- Approach: Transseptal.
- Effect on LVOT: Not specified.
- Sizes: Not specified.
- Clinical experience to date: First in human PRELUDE: US early feasibility study
- Stage of development: Preclinical trials underway.

Navigate TMVR (NCSI) (Figure 6H)

- Stent frame: Self-expanding nitinol stent.
- Leaflets: Trileaflet fabricated from bovine pericardium.
- Anchoring mechanism: Self-expandable 21mm height nitinol stent with a truncated cone configuration and annular winglets for anchoring the native mitral leaflets. Annular winglets are attached around the lower portion of the valve for secure anchoring [51].
- Suitable for native annulus size: Not specified.
- Delivery system: Not specified.
- Approach: Transatrial.
- Effect on LVOT: Not specified.
- Sizes: Not specified.
- Clinical experience to date: Successfully implanted in two patients via a transatrial approach. Both patients had excellent valve performance without residual mitral regurgitation or left ventricular outflow tract obstruction. The first patient showed significant improvement in functional class and freedom from hospitalization at 6 months, but the second patient died within a week of the implant due to advanced heart failure [51].
- Stage of development: Clinical implants have occurred.

Future Direction

The mitral valve is undoubtedly the next frontier after the success of TAVI. With reasonable intermediate results, data on long-term outcomes are needed. As with all new procedures, appropriate patient selection is key for optimal results. Thus, better understanding of the anatomical and physiological factors affecting the outcome, implantability of the device and the need for device specific anticoagulation will all be important to ensure good outcomes. Anticoagulation strategy is still unclear and may play an important role in the success of TMVR, as the devices are large, are covered with fabric and the majority patients are in atrial fibrillation. As in TAVI, for now the transapical approach will likely remain the commonest access site but developments in the delivery system and device profile will move this technology towards the less invasive transseptal approach. TMVR success will also depend on further improvements in mitral repair and replacement technologies.

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Chapter 6

Mitral Valve Surgery:
Transcatheter versus Conventional Mitral Valve Surgery
Which Questions Should Future Clinical Trials Seek to Answer?

Francis Wells

"Stare super vias antiquas"

Introduction

Perhaps the biggest challenge in modern cardiac surgery is the development of ever less interventional procedures to correct cardiac pathology without reducing safety and efficacy. This has been happening in most surgical specialties. The drivers for this have been improved patient experience and reduced length of hospital stay. To that end there has been an explosion in the development of transcatheter devices for remote correction of cardiac pathology. Over the last three and a half decades the path has been led by intra-luminal coronary interventions first introduced by Grunzig with balloon angioplasty. This was followed by the introduction of coronary artery 'smart' stenting with drug eluting materials, which has now reached a mature form of reliability with predictable outcomes. Interestingly although in the earliest years of the current millennium and in the absence of meaningful comparative surgical data, it appeared that this novel technique would completely supersede coronary artery surgery, this situation was averted. The near capitulation of surgery in the face of this interventionist cardiology onslaught was as a result of an almost surgical data free zone; all the fault of the surgical community which literally fell academically to sleep on the job. It took a major effort on the part of energised and committed research oriented members of the surgical community to restore the balance with good quality prospective data. A position of acceptable equipoise between the disciplines has now been achieved with cardiologists recognising the true value of modern surgical intervention in well-defined groups of patients with coronary atherosclerosis.

Similarly, we have seen the rise of percutaneous transcatheter techniques in the management of heart valve disease. Prompted by the early relative success of closed transthoracic and then open valvotomy in rheumatic mitral valve stenosis, percutaneous techniques using balloon dilatation developed. Early success was clouded by poor selection of patients with post-procedural regurgitation occurring in several patients and rapid restenosis in others. Once again refinement of patient groups has led to the appropriate but now restricted use of this technique to carefully selected patients. The same has been true for aortic stenosis, with early enthusiasm being tempered by poor patient selection.

The development of transcatheter implantation of an expandable tissue valve in the pulmonary position in the paediatric population led on to the now extremely widely adopted trans-arterial/apical valve insertion (TAVI) into the aortic position. Once again, this technique has grown extremely fast and expanded beyond the initial population of elderly patients with multiple co-morbidities (arguably precluding safe surgery) into an ever-younger population, once again in the absence of level 1 evidence of its superiority over the mid- to long-term. The surgical community has begun to challenge this with less aggressive surgical strategies (mini-sternotomy and sutureless valves for example) and better constructed prospective clinical trials. The out-turn of these studies are awaited.

All of this more scientific assessment of surgical vs. catheter laboratory based procedures is confounded by the continued introduction by industry of putatively 'improved devices', refuting any objections to the inferiority of prior devices in the face of good surgical results. This pseudo-academic warfare is a real challenge in the production of truth, which patients and their relatives can understand and use meaningfully in decisions about which way to proceed with treatment options.

We are now in the midst of another revolution, this time in the treatment of the mitral valve. Interestingly it was initially suggested that the mitral valve would be more accessible to transcatheter techniques than the aortic because of the problem of aortic valve annular

calcification. However, the reverse has been the case. Whereas, even the heavily calcified aortic valve has been manageable with dilatation and stenting, control of the regurgitant mitral valve has proved a much more difficult problem to address because of the pliability of the atrio-ventricular orifice and the lack of secure anchoring points for devices.

This realisation has led to the development of a number of technologies that set out to mimic accepted surgical techniques. These include attempts at annuloplasty either utilising the coronary sinus, or more directly with various forms of attachment to the mitral annulus, neo-chordal insertion via a left ventricular puncture and perhaps, most controversially so far the "Alfieri edge-to-edge" technique.

During his surgical practice, Professor Alfieri came across a Mitral valve in which the aortic and mural leaflets were fused in the mid-line. This observation fostered the concept of surgical repair that became known as the "Alfieri edge-to-edge" repair. This technique, particularly useful for severe bileaflet prolapse encountered by the more occasional mitral surgeon, involved the suturing of the aortic and mural leaflets together, usually in two layers at the level of the secondary chords at the point of maximal prolapse. Accompanied by an annuloplasty ring, to compensate for annular dilatation and to stabilise the annulus, this technique has been shown to give a good long-term stable result. This technique has been reproduced for a transcatheter approach in the form of the "MitraClip" which reproduces the surgical result but utilising cloth-covered clips introduced transvenously and applied transseptally. This device was first implanted in 2003 and was approved by the FDA in 2013 and has been the subject of a growing number of published studies including the important Everest II trial. There are now numerous other techniques under development (some of which have been mentioned above) which are at various stages of implementation, which along with the MitraClip technology need full evaluation in well-constructed trials particularly in comparison with the gold standard of well-conducted accepted surgical techniques carried out by expert mitral valve surgeons. As a caveat to the last remark, it is important to note that the majority of mitral valve reconstruction continues to be done by low volume mitral surgeons. An argument can therefore be made that a comparison also needs to be made between these newer transcatheter techniques with results achieved by the more infrequent mitral surgeon especially in the more challenging forms of mitral valve pathology as it is unlikely that all surgery will be concentrated in the hands of so-called experts. This would need to be the subject of second order studies once the new technologies have been validated as safe and reproducible with sustainable results over many years.

As always with surgical procedures there is more than one important end-point. First, the mortality and morbidity of the procedure has to be acceptably low. Second, the immediate success of the procedure is essential. Third, the mid-term results and finally the long-term outcome is paramount. After all, the intention is to correct the lesion once and for all. Each of these variables needs to be measured and reported preferably in prospective studies framed by intention to treat. As mentioned earlier it is difficult to envisage how this can be achieved in such a fast-moving world of development when technology is changing (and improving) quickly and studies such as these need years to complete.

Whilst interested specialist mitral valve surgeons have been refining their surgical techniques and decision-making, the technology companies have been developing ever more ingenious tools for percutaneous approaches. Squaring this particular circle in the modern era is more difficult than ever before.

Let us begin with the desirable outcome for surgical mitral valve repair/reconstruction. Experienced surgical practices should be achieving repair rates well in excess of 90% for degenerative mitral valve disease. Mortality rates ought to be less than 1% and for many units <0.5% is regularly achieved. With minimal access approaches shorter hospital length of stay are claimed although like for like prospective trials are lacking. Those practicing frequent (>150) mitral repairs per year through open sternotomy can claim similar lengths of stay both for ICU recovery and ward stay.

Data of this kind is readily easy to access, however once one moves into the area of outcome by intention to treat and both mid and long-term results we enter a very data sparse zone. There are some long-term longitudinal data from which differences in result between types of mitral valve lesion can be discerned. However, the vast majority of surgical repairs go unstudied once the patient has left hospital, only presenting for re-study with new onset of symptoms. Before the surgical community begins to criticise the interventional cardiology results we, in the surgical community, need to put our own house in order and capture more of these important data. The development of heart valve teams ought to engender much better long-term data collection. It would behove the NHS to demand longitudinal data collection to allow much better apportionment of funds in patient care.

We do know that in the hands of an experienced surgical team, posterior (mural) leaflet mitral valve repair can achieve a better than 90% functionally competent valve up to and beyond ten years. For anterior (aortic) leaflet repairs the results are less good but still achieve more than 80% competency at the same time reference point, with bileaflet prolapse in the same territory. Therefore, we have data for comparison with the newer transcatheter techniques as they evolve. The ideal scenario would be for these techniques to be studied in a randomised controlled prospective setting but, as pointed out earlier with the rapidly changing/maturing transcatheter technologies, this is not going to be possible until stable technological platforms have been achieved.

What, therefore, are the questions that need to be answered in future clinical trials?

First and foremost, we ought to know across the whole cardiac surgical community the real frequency of mitral valve repair by intention to treat. A “happy hunting ground” for valve interventionist cardiologists are the patients that, with degenerative mitral regurgitation, still have mitral valve replacement. Whilst this is not necessarily a bad option for some patients, especially in the hands of infrequent mitral surgeons, it does leave room for the transcatheter cardiologist/surgeon to claim these patients. This situation demands the wider distribution of heart valve teams so that patients can access optimal care. Data that we do not have is prospective data on valve replacement with full subvalvular preservation versus repair in the more advanced degrees of mitral regurgitation where the inexperienced surgeon might feel that repair/reconstruction was beyond their capacity to perform safely and reliably. Just as the more recent comparative trials in ischaemic mitral regurgitation have shown, mitral valve insertion with full subvalvular preservation can lead to satisfactory results with longer functioning valves than many with severe MR that are repaired. There is nothing that would predict that a similar situation would obtend in degenerative regurgitant valves. It is quite possible that patients treated in this way who were not in the position to have successful repair could still fare better than following transcatheter techniques as the prosthetic valve is unlikely to leak for many years.

Long-term outcome data such as these would be very powerful in the face of the onslaught of transcatheter techniques with historical data suggestively damming mitral valve replacement. So much of the existing data are retrospective trawls of surgical valve patients with no control over surgeon experience, procedure actually carried out and stage of disease for which the surgery was carried out. Just like the absence of coronary data, the absence of these data leave the surgical therapy arm open to serious criticism.

Long-term functionality of repaired valves is urgently needed to be held up as gold standards for comparison with the newer transcatheter technologies. At the moment, data is accumulating out to 5 years and in a smaller number of patients out to 7 years, but we know that for our surgical patients we are aspiring to life-long post-operative competency for the vast majority.

If for the most part transcatheter technologies continue to be employed for the more elderly with co-morbidities in whom lifespan of more than 5 years is less likely, then comparison with surgery becomes less urgent. However, if the goal for these technologies is to target younger and fitter patients, then 10–15-year data (and beyond) becomes much more important.

As the drive to develop, progress and disseminate these technologies is unstoppable, then excellent quality surgical outcome data becomes ever more important. These data can then stand as defined end-points for the interventionist cardiologist to aim at, and to stand as trusted comparators, for true informed consent when patients face decisions over which therapy to choose.

It is perhaps facile to demand prospective randomised trials for all new developments in the modern world with technology advancing quickly every year, therefore known surgical end-points would act as a buffer to the too rapid introduction and dissemination of transcatheter technologies.

Functional (Ischaemic) MR

There has been a move towards adopting the Mitraclip technology as a potential solution to patients with advanced ischaemic mitral regurgitation. It has been shown by Alfieri and colleagues that for satisfactory mid-term to long-term results with the Alfieri procedure an annuloplasty ring is an important adjunct to stabilise the repair and to prevent later basal ventricular dilatation. It is becoming possible to achieve this with transcatheter annuloplasty but whether this is essential or not is another potential study that will need to be done.

Synopsis of Questions that Need to be Answered

Primary outcome measures that need to be assessed:

1. Mid- to long-term function of both technological platforms (surgical and transcatheter). Minimum of 5 years and preferably 10 years.
2. Recurrence rate of the primary lesion.
3. Rate and timing and nature of any re-intervention.
4. Occurrence and frequency of additional lesions.

Who Should be Offered Transcatheter Mitral Valve Interventions?

1. The elderly and infirm or is it ready to be introduced into a younger population?
2. When should intervention occur?
3. Early / late
4. What are the real mid- to long-term outcomes?
5. Success
6. Morbidity / mortality
5. What options are there in failed procedures?
6. Cost

Chapter 7

Heart Failure Surgery:

Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) for Post-Cardiotomy Cardiogenic Shock

In favour: *Mike Charlesworth, Rajamiyer Venkateswaran*

Against: *Jorge Mascaro*

Editorial: *VA ECMO - A Solution for the UK*
Antonios Kourliouros, Steven Tsui

"Per angusta ad angusta"

In Favour: VA-ECMO for Post-Cardiotomy Cardiogenic Shock

"Technology is nothing. What's important is that you have a faith in people, that they're basically good and smart, and if you give them tools, they'll do wonderful things with them. It's not the tools that you have faith in - tools are just tools. They work, or they don't work. It's people you have faith in or not."

Steve Jobs, 1994

Introduction

For the majority of cardiac surgical procedures, separation from cardiopulmonary bypass (CPB) is uneventful with the patient subsequently able to support their own circulatory demands. For some, vasopressors, inotropes, and intra-aortic balloon pump (IABP) counterpulsation are required. Rarely (~0.7%) cardiac performance following surgery is refractory to this support and there is a need therefore to consider peripheral or central veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as a bridge to recovery, ventricular assist device (VAD) implantation or transplantation. Postcardiotomy cardiogenic shock (PCCS) describes the syndrome of refractory cardiac performance following cardiac surgery, yet there is no agreed consensus with regards how it should be defined or managed. This is further complicated by the wide range of devices available to treat PCCS, the availability of such interventions in different centres, variations in experience and expertise as a function of local VA-ECMO workload, and regional variations in the diagnosis and management of PCCS. This article considers the use of VA-ECMO to treat non-transplant PCCS through our own experiences at University Hospital South Manchester, UK.

History and Development

Despite a recent upsurge in clinical activity, ECMO is by no means a new technology having been developed in the 1950s primarily for CPB [1]. The desire to provide longer periods of mechanical circulatory support than can be offered with CPB gave rise to a simpler, closed circuit configuration, that we now recognise as ECMO. It was not until the 1970s however that the first clinical report of VV-ECMO for acute respiratory distress syndrome (ARDS) emerged in the literature [2]. Despite initial promise, interest faded following reports of high mortality for ARDS treated with VV-ECMO as compared to traditional medical management [3]. Thereafter, ECMO research and practice was confined to the fringes of paediatric practice until a recent upsurge in adult interest in the 1990s. It is likely that this second wave of adult ECMO practice was born out of technological improvements in catheters, circuits, pumps, and oxygenators in combination with general improvements in critical care medicine. Even more recently, the practice of VV-ECMO for respiratory failure has seen significant advances through acquired expertise and experience during the 2009 H1N1 influenza pandemic [4]. Concurrently, several randomised controlled trials (RCTs) and observational studies of VV-ECMO for respiratory failure in adults have reported good outcomes as compared to traditional medical management [5,6]. Despite this and notwithstanding continued

reporting of successes from across the world, it has not yet been possible to pool such data in a meta-analysis to provide an overall appraisal of VV-ECMO due to considerable data heterogeneity [7]. The efficacy of postcardiotomy VA-ECMO is even more difficult to prove through traditional research methods despite observational data suggesting that it provides a significant survival benefit for what is ordinarily a condition with an extremely high mortality [8].

Approaches and Techniques

When VA-ECMO is initiated in theatre following intrathoracic CPB, the 'central' configuration is usually selected, as cannulation sites are identical. The sternum is sometimes left open so as to allow frequent re-exploration for bleeding. Peripheral VA-ECMO may be selected for cases where extrathoracic CPB is used, for example repeat surgery, minimally invasive surgery and cases where there is disease of the great vessels such as a thoracic aortic dissection. Additionally, peripheral VA-ECMO or extracorporeal cardiopulmonary resuscitation (ECPR) may be initiated in the intensive care unit without the need for re-sternotomy. Combined central and peripheral venous drainage (VVA-ECMO) may also be employed to enhance the venous drainage capabilities of the circuit.

Despite their similarities, VA-ECMO has several advantages over CPB in the context of PCCS. Firstly, it allows mechanical circulatory support for days, weeks or months as compared to hours. It is a closed circuit with shorter tubing, no venous reservoir, and less stagnation of flow in the cardiac and pulmonary vasculature. It therefore requires lower doses of intravenous unfractionated heparin. Although there is always a risk of intrathoracic or intracerebral haemorrhage, this risk is lessened though the reduced need for systematic anticoagulation. In addition to allowing for closure of the sternum through the tunneling of tubing, VA-ECMO achieves a more physiological haematocrit and blood flow, more efficient delivery of oxygen to tissues and normothermia. It allows concurrent cardiac ejection and thus further reduces the risk of thrombus formation. Finally, patients receiving VA-ECMO can be cared for in the critical care environment whereas those undergoing CPB cannot.

Of course, whilst any comparison of CPB and VA-ECMO gives an insight into their technical differences, pragmatically, the clinical choice is in fact between VA-ECMO or no circulatory support beyond IABP counterpulsation and vasopressors/inotropes. Regardless of the underlying cause, PCCS without mechanical circulatory support has an extremely poor prognosis and most cases will not survive the immediate post-operative course. VA-ECMO allows the opportunity for the acutely shocked heart to recover without also having to meet the demands of the circulation.

Despite these advantages, VA-ECMO for PCCS is an expensive resource with an as yet unproven evidence base and with funding bodies such as the National Institute for Health and Care Excellence (NICE) uncertain with regards its safety profile [9]. Highly skilled staff are required at all stages of the process, from initiation in theatre or critical care to maintenance, weaning and rehabilitation thereafter. Individual hospitals providing ECMO absorb the financial cost of their VA service, as there is currently no central funding in the UK. Such centres are usually expected to participate in the decision-making process for postcardiotomy VA-ECMO initiation at non-ECMO centres and sometimes even retrieve patients from other centres. There are controversies around the use of VA-ECMO for PCCS in non-transplant or low volume-ECMO centres in the UK, as whilst it is possible to initiate VA-ECMO in such centres patients are arguably best cared for in high volume ECMO centres [10]. The financial and logistical arrangements for such patients are therefore

complex and decisions are taken on a case-by-case basis. Some typical initial targets are provided below for reference only, however most targets are also selected on a case-by-case basis.

- Flow of 60-80 mL/kg/min
- FiO2 of 100%
- SpO2 of 95-100%
- MAP of 60-90 mm Hg
- pH of 7.35-7.45
- Haematocrit of greater than 28%
- Functioning platelet count of greater than 80
- ACT 180-220 seconds

Anticoagulation practices vary between centres, clinicians and patients. The Extracorporeal Life Support Organization (ELSO) have attempted to standardise this through their guideline [11]. For PCCS VA-ECMO, patients may not require an initial dose of unfractionated heparin (UFH). In the absence of bleeding and when the ACT falls into the target range, a heparin infusion of 20-50 units/kg/hour can be used for maintenance. A reduced platelet count, increased urine output or concurrent renal replacement therapy may increase the need for UFH [12]. Heparin induced thrombocytopenia and heparin resistance lie outside the scope of this article.

Weaning from VA-ECMO can be as a bridge to recovery, VAD implantation or transplantation. Where recovery is anticipated, signs of ejection, pulsatility and contraction should be seen using transoesophageal echocardiography (TOE) in at least the first week. TOE should also rule out significant valvular pathology and estimate ventricular function. ECMO flow rates can be incrementally reduced concurrently with TOE examination. If appropriate, the ECMO circuit is clamped and a trial of recirculation is initiated for 1-4 hours. The cannulae are continuously flushed during this period with UFH/saline to avoid cannula thrombosis. Decannulation is considered if haemodynamic parameters allow. Where VA-ECMO is a bridge to VAD implantation, this is considered only following the resolution of end-organ dysfunction.

Indications and Patient Selection

The technical aspects of VA-ECMO for PCCS are arguably more explicit than the tacit subtleties of decision-making, timing and patient selection. Whilst two recent systematic reviews conclude a significant survival benefit of VA-ECMO over and above alternative strategies, the majority of included research is retrospective and observational, with no randomised controlled trials [13,14]. Retrospective observational studies provide a good means for centres to report their results, but those who wish to make predictions for future patients must interpret this with great caution. Most are in fact reporting a case series and are therefore inherently prone to selection and information biases, amongst others [8,14]. Due to these problems, the majority of postcardiotomy VA-ECMO research has been unable to implicate prognostic indicators that can be used by clinicians to make evidence-based decisions. At our institution therefore, VA-ECMO for PCCS can only be initiated on a case-by-case basis with the agreement of four consultants including two surgeons and two anaesthetists with adequate clinical ECMO experience. The indication for VA-ECMO for PCCS is simple – inadequate tissue perfusion as evidenced by hypotension and low

cardiac output despite adequate intravascular volume that is refractory to inotropes, vasopressors and IABP counterpulsation. In general, all planned operative procedures should be complete and the chances of successful recovery should be considered to be high. Deciding where VA-ECMO is contraindicated is more complex. Where cardiac failure is considered irreversible in combination with a patient that is not a candidate for VAD implantation or heart transplantation, VA-ECMO for PCCS is absolutely contraindicated. Relative contraindications include advanced age, chronic organ dysfunction, multiple co-morbidities, established multi-organ failure syndrome (MOFS), obesity and when it is not possible to administer anticoagulants.

There is a dissimilarity between heart transplant and non-heart transplant patients with regards this decision-making process. In our own experience, the threshold for postoperative VA-ECMO is somewhat lower following heart and/or lung transplantation as compared to non-transplant procedures. It is often used pre-emptively, but it may also be used for primary graft dysfunction, acute organ rejection or refractory cardiogenic shock. A discussion of postoperative VA-ECMO following heart and/or lung transplantation lies outside the scope of this article, but its increasing role for such cases is increasing VA-ECMO expertise at regional transplant centres.

Clinical Outcomes

The generic complications of VA-ECMO are accepted to be thrombosis (1-22%), haemorrhage (5-79%), limb ischaemia (13-25%), infection (17-49%) and irreversible neurological sequelae (10-33%) [15]. A summary of several key studies reporting outcomes for patients undergoing VA-ECMO for PCCS is provided below. This does not represent a systematic synthesis of all the relevant literature and studies are presented to provide a representative overview only.

As demonstrated by Table 1, the vast majority of results are single centre retrospective analyses where survival data (usually in the form of hospital discharge) and complication rates are reported. Many also report the cause of death or try to establish a relationship between survival and factors such as serum lactate, vasopressor use/dose, age, risk stratification scores (EuroSCORE), surgery type, urgency, duration of support and obesity. Pragmatically, it would be unwise to pool the above clinical studies with all other related studies due to considerable data heterogeneity. Retrospective non-randomised non-controlled data of this type is unlikely to reflect the true efficacy of VA-ECMO for PCCS or the true incidence of procedure-related complications. These limitations together with the possibility of high complication rates are a major barrier to funding at present.

Unfortunately, the answer is not to simply perform a randomised controlled trial (RCT) [8]. This would invoke the unethical randomisation of patients to a non-VA-ECMO arm that will most likely lead to death as compared to a treatment that is arguably beyond experimental and where outcomes such as hospital discharge and 2-year survival have been reported to be as high as 50% [27]. We argue that to statistically treat VA-ECMO as a binary intervention with an on/off switch, such as a pharmaceutical agent, is a gross oversimplification. It is a complex multi-variable technology applied to a heterogeneous patient population at the extremes of pathology and physiology. Practices also vary between clinicians and between centres. Even if several RCTs were to be conducted, there may still be considerable data heterogeneity that will preclude meta-analysis. Therefore, clinical decision-making is determined by consensus, debate, summing factors for and against, negotiation and wider contextual factors such as location and resources.

Table 1: Several key studies reporting outcomes for patients treated with VA-ECMO for PCCS. Our own results from South Manchester are at the bottom of the table.

Study	Patients	Design	PCCS Survival	Complications
Doll et al 2004 [16]	n = 219, 1997-02, all PCCS	Prospective case series	5-year 16.8%, to discharge 24%	Mediastinal bleeding 62%, CVVHF 56%, Sepsis 24%, lower limb ischaemia 13%, oxygenator change 22%, neurological complications 15.5%
Combes et al 2008 [17]	n = 81, 2003-06, 16 PCCS cases	Retrospective case series	To decannulation 69%, after weaning 50%, to discharge 44%	Overall major complications including haemorrhage, thrombosis, ischaemia, sepsis, CVVHF and stroke of 65%
Rastan et al 2010 [18]	n = 517, 1996-08, all PCCS, same centre as [16]	Retrospective case series	To decannulation 63%, to discharge 25%, 6-months 18%, 1 year 17%, 5 years 14%	Stroke 17%, ischaemic bowel 19%, CVVHF 65%.
Wu et al 2010 [19]	n = 110, 2003-09, all PCCS	Retrospective case series	To decannulation 61%, to discharge 42%	Neurological injury 6.3%, ischaemic limb 10%, CVVHF 42%, haemorrhage 7% and sepsis 25%
Elsharkawy et al 2010 [20]	n = 233, 1995-05, all PCCS	Retrospective case series	To discharge 36%	Not reported
Unosawa et al 2013 [21]	n = 47, 1992-07, all PCCS	Retrospective case series	To decannulation 62%, to discharge 30%	Leg ischaemia 26%, CVVHF 32%, pneumonia 13%, sepsis 17%
Saxena et al 2015 [22]	n = 45 aged 70 and over, 2003-13, all PCCS	Retrospective case series	To decannulation 53%, to discharge 11%	AKI 44%, pneumonia 27%, sepsis 24%.
Li et al 2015 [23]	n = 123, 2011-12, all PCCS	Retrospective case series	To decannulation 56%, to discharge 34%	Leg ischaemia 17%, sepsis 10%, stroke 4%, CVVHF 24%

Study	Patients	Design	PCCS Survival	Complications
Khorsandi et al 2016 [24]	n = 16, 1995-15, all PCCS, one VAD included	Retrospective case series	3-day 37.5%, to discharge 31.2%	63% suffered a major complication including haemorrhage, stroke, ischaemia, AKI and sepsis.
Whitman et al 2017 [25]	ELSO database analysis 2000-2016	Retrospective case series	Increase in use of ECMO for PCCS has been exponential, but an already poor survival appears to have only decreased.	N/A
Chen et al 2017 [26]	1141 ECMO vs. 5685 non-ECMO PCCS 2000-2011	Retrospective propensity matched study	Patients receiving ECMO for PCS had equal outcomes to those of a non-ECMO group after the first year of follow-up.	Acute renal failure and massive blood transfusion independent predictors of in-hospital mortality
Charlesworth et al 2017 [27]	n = 28, 2012-16, all PCCS	Retrospective case series	30-day 50%, 2-year 50%	One limb ischaemia and one stroke

AKI = Acute kidney injury, CVVHF = continuous venovenous haemofiltration.

Conclusion

The questions of who should provide VA-ECMO for PCCS or which patients are most likely to benefit from it have no easy answers. It is also unlikely that traditional research will provide a breakthrough solution to guide clinicians anytime soon [8]. What is known is that PCCS without VA-ECMO is fatal for the majority of cases. It is likely that transplant centres are more familiar with postcardiotomy VA-ECMO as it is commonly employed pre-emptively following heart and/or lung transplantation. Due to this familiarity, together with increased experience and expertise, it is also likely that such centres will be more proactive at an earlier stage and prior to an established MOFS. Outcomes are likely to be worse when initiated later in the PCCS course in the context of an intractable lactic/metabolic acidosis, a MOFS and a failing heart in the critical care unit. VA-ECMO should be seen as a bundle of care and as an adjunct to other resuscitative measures as opposed to a binary intervention. It is likely that other factors such as the quality of medical and nursing care contribute significantly despite our inability to measure these. As outcomes appear to be better at transplant centres, there are many difficult ethical questions with regards current arrangements for PCCS VA-ECMO in the UK. Based on our own experience together with emerging observational evidence from around the world, we argue that VA-ECMO for PCCS

is far beyond experimental and that it greatly enhances cardiac surgical patient safety. We must increase collaboration to bring uniformity to practices, strive to better understand patient selection and establish an optimal bundle of care for such patients.

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Against: VA-ECMO for Post-Cardiotomy Cardiogenic Shock

"Mens aequa in arduis"

Introduction

Cardiac surgery is a well-established treatment for patients requiring coronary artery bypass grafting (CABG), aortic and/or mitral valve repair/replacement and, although the postoperative results have improved, there are still 3-6% of patients that develop severe cardiac dysfunction postoperatively [1-8]. The treatment of this involves the use of inotropic support and intra-aortic balloon pump (IABP) counterpulsation but 25% to 30% of this group still develop an even more catastrophic cardiac dysfunction with refractory cardiogenic shock. The treatment of this condition will usually require the use of advanced mechanical circulatory support in the form of Extra Corporeal Membrane Oxygenation (ECMO). Although ECMO has gained popularity as cardiac surgeons, intensivists and cardiologists have become more familiar with the technique, there are still important issues with its management that need to be overcome.

Once ECMO support is established in this group of patients, some questions should be rapidly answered by the team: what is the aim of the support, how long should it be used for, and most importantly, what to do if treatment fails? The answer to the first question is to achieve satisfactory recovery of the patient but this is not quite as simple as we would like it to be. Recovery might never happen, or it might happen but at the expense of a prolonged period in the intensive care unit (ICU) as well as with increased morbidity. This will undoubtedly impact on the delay in treatment of other cases with associated loss of revenue. We know that the most common expected outcomes for ECMO in post-cardiotomy cardiogenic shock (PCCS) are: recovery, death of the patient, or bridging to a longer-term type of mechanical circulatory support or transplantation [2, 8]. The extent to which pursuing recovery or bridging is justifiable is the subject of this chapter.

Current data

Currently available data are based on single centre experiences and case reports. There are no randomised trials and it is unlikely that such a trial will ever be carried out. Historically, the first successful ECMO reported in the literature was by Hill and colleagues in 1972 [4]. Hill reported the successful treatment with VA-ECMO of a young man who developed acute respiratory distress syndrome (ARDS) following a car accident. A second successful case of VA-ECMO for ARDS was reported in 1975. Following on from this, the National Institute of Health (NIH) funded a randomised trial comparing VA-ECMO to standard mechanical ventilation but unfortunately the results were discouraging: the mortality was high in the two groups (90%) with the big disadvantage that ECMO proved to be very resource consuming [4]. It wasn't until the Influenza epidemic in 2007 to 2009 that VA-ECMO started again to show utility with survival rates for ARDS of 50 to 60%. Since then the use of respiratory VA-ECMO has shown an exponential increase (Figure 1). Interestingly a similar and parallel increase has been seen in the use of VA-ECMO for refractory and post-cardiotomy cardiogenic shock (PCCS).

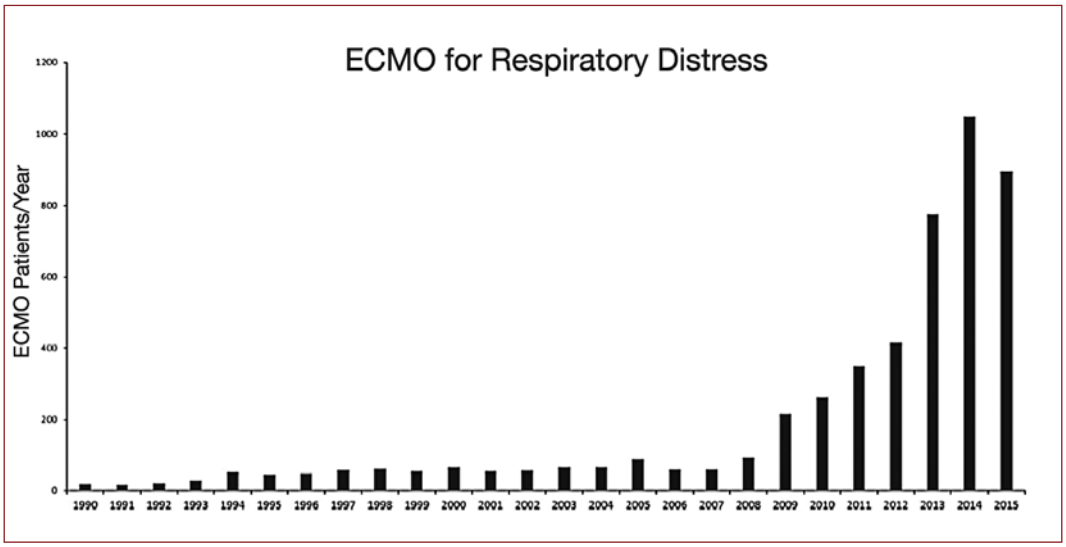

Figure 1: Taken from the US Extracorporeal Life Support registry, this graph shows the exponential increase in the use of extracorporeal membrane oxygenation (ECMO) for all respiratory diagnoses during the last 10 years. Reproduced with permission from The Journal of Thoracic and Cardiovascular Surgery, 53(1).

Interestingly a similar and parallel increase has been seen in the use of VA-ECMO for refractory cariogenic shock (Figure 2). The data is extracted from the ELSO database but this time for non-respiratory ECMO.

Clearly something positive has happened that has allowed VA-ECMO to experience such a growth. However, when the survival to discharge rate is studied, this growth is associated with a diminishing survival. Mortality and discharge from hospital remain poor despite the increase in activity. The interpretation of this data is difficult and requires a careful analysis. Currently, there is no available consensus or guideline to define PCCS, or to guide the selection of patients that will benefit from ECMO with PCCS or what the most appropriate escalation triggers are to follow until a decision can be made regarding the institution of advanced mechanical circulatory support (MCS). This lack of data makes the available literature difficult to compare.

The outcome data for ECMO for PCCS in the US between 2002 to 2012 was reviewed by McCarthy and colleagues [6]. Their findings reflect the poor outcome of ECMO for PCCS with a mortality rate of up to 60%, in keeping with the data reported by ELSO, but also the high incidence of morbidity. In one of the largest reviews available, Rastan et al. analysed more than 40,000 patients and found that the use of ECMO for PCCS was required in 1.2% of patients [7]. Most of these patients underwent CABG, valve replacement or a combination of the two, with 40% having ECMO instituted intraoperatively and 60% in the Intensive Care Unit (ICU), implying that a catastrophic event may have happened immediately post-operatively. As expected, morbidity was high with the major complications being bleeding, renal failure, reoperation, stroke, gastrointestinal complications, and leg ischemia [4,7]. Fukuhara at al. analysed the outcomes for all types of MCS strategies in the treatment of PCCS [5] reviewing 22 different publications between 1993 and 2015. The conclusions were, once again, discouraging. Mortality rates were high, ranging from 25% to 50% regardless of the type of mechanical support used (IABP, short-term ventricular assist device (VAD),

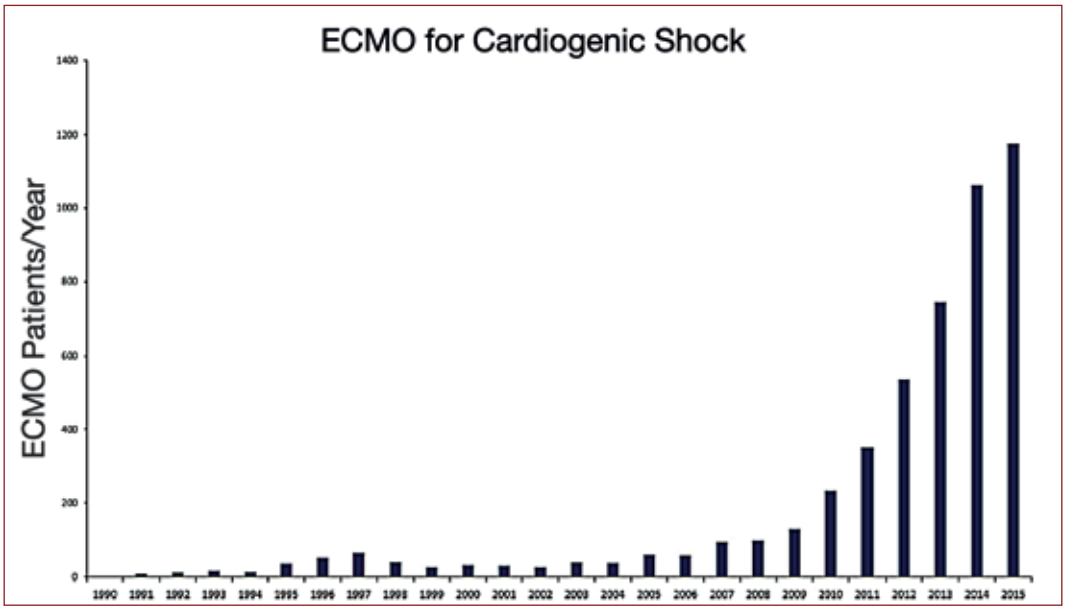

Figure 2: Taken from the US Extracorporeal Life Support registry, this graph, which parallels the respiratory experience, shows the increase in the use of extracorporeal membrane oxygenation (ECMO) for all cardiac diagnoses during the last 10 years. Reproduced with permission from The Journal of Thoracic and Cardiovascular Surgery, 53(1).

Surprisingly or not, the use of VA-ECMO for the rescue of post-cardiotomy cardiogenic shock shows a similar trend to the data already shown for respiratory ECMO (Figure 3).

VA-ECMO), and morbidity was high. Rastan et al. found that only 25-30% of patients were discharged from hospital [7]. It is of interest perhaps that there was no difference between ECMO support being instituted intraoperatively or post-operatively in the ICU. In keeping with the ELSO registry data, little progress has been made in improving outcome in patients undergoing ECMO for PCCS and perhaps there is even a trend to worse survival in recent years.

Shao-Wei et al. reported the Taiwanese experience where the Taiwan Health Care System fully funds ECMO in whichever centre it is instituted [3]. This, from a comparative point of view, is reassuring that patients have not been selected on the basis of funding as may happen in the UK where this service is not funded by the NHS. The authors looked at 12 years of experience of ECMO in patients developing PCCS using propensity matching of a similar population that underwent cardiac surgery to ensure more robust and solid conclusions. The incidence of PCCS requiring ECMO was similar to prior reports at 1.9% with mortality in the ECMO group remaining high at 62% against 6% in the non-ECMO group, and only 25% of patients being discharged from hospital following MCS. Looking at long-term data following discharge, they found that during the first year post-discharge, the ECMO group remained at higher risk of readmission and mortality, but following this there was no difference compared to the non-ECMO group. Costs were twice as high in patients requiring ECMO compared to those who did not. They also found that younger age, absence of preoperative heart failure, absence of renal dysfunction and absence of liver cirrhosis were associated with increased survival following ECMO in PCCS. These

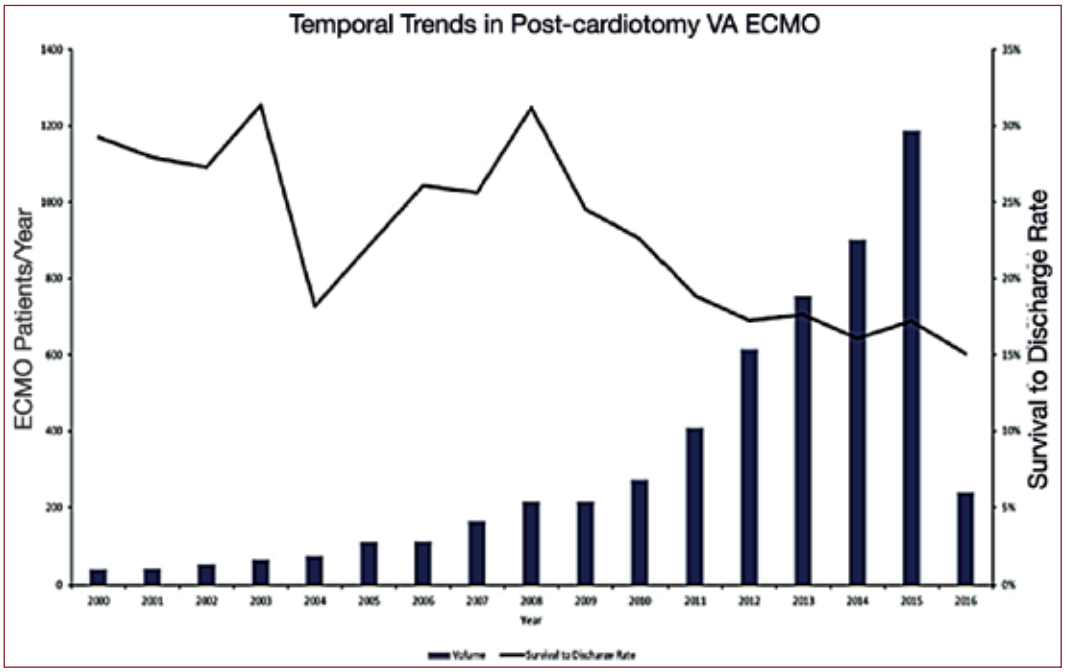

Figure 3: Data abstracted from the ELSO database show the exponential increase in venoarterial extracorporeal membrane oxygenation (VA-ECMO) for post-cardiotomy shock. This increase unfortunately appears to be associated with a diminishing survival. Reproduced with permission from The Journal of Thoracic and Cardiovascular Surgery, 53(1).

findings correspond with previous observations that patients with existing co-morbidities have worse outcomes than those without co-morbidities.

Khorsandi et al. recently published a meta-analysis of 24 studies which combined outcomes of almost 2000 cases of ECMO for PCCS [8]. The primary endpoint was survival and they also tried to identify Adverse Prognostic Indicators (APIs) as secondary endpoints. Age >70 years, impaired pre-operative left ventricular function, pre-operative renal dysfunction or development of renal dysfunction requiring renal replacement therapy, diabetes mellitus, gastrointestinal complications during ECMO, prolonged ECMO support and EuroSCORE were amongst the most commonly reported APIs associated with poor outcomes. EuroSCORE (logistic, additive and Euroscore II) was mentioned consistently in all the papers reviewed. The authors explained that although many of the papers used Euroscore, it was difficult to analyse this as there was no uniformity in how it was reported. When meta-analytical techniques were applied to the 1926 patients, 31% of patients were discharged from hospital which is consistent with data from other centres. The authors concluded that, although the cost of therapy was high, a significant number of patients were discharged from hospital, especially those without adverse prognostic indicators.

The cost of ECMO

A discussion of any new technology must review its financial implications as well as the impact of its use on the day-to-day activities of the cardiac surgical unit. The use of ECMO in patients developing PCCS will involve the use of costly equipment and the staff

to manage it as well as a prolonged length of stay and management of complications. Cancellation of other surgeries and loss of revenue will occur. The real cost of a patient on ECMO is difficult to determine and is very much dependent on the type of care model that the institution implements for the treatment of these patients. Assuming the cost of consumables is standard, the additional costs are driven by the type of personnel that are allocated to the care of the patient on ECMO. The lowest cost option is the use of a single ECMO-trained specialist nurse whereas a costlier alternative is a nurse with the added participation of a dedicated ECMO specialist, such as a perfusionist. Whitman et al. found costs of $10,000 to $20,000 (£7,500 to £15,000) for the TamdemHeart™ and the CentriMag devices [4]. The controller for the CentriMag added an additional $20,000 (£15,000). We then need to add the costs of ICU stay ($2,000 - $3,000 per day) when a single nurse is used, more if two nurses are needed. In a study of the NIS database between 1998 and 2009 looking at patients needing ECMO support, the estimated cost of ECMO for PCCS was $41,872±$4050 per day and $273,429±$31,361 total charges [9]. Whitman looked into their own activity at Johns Hopkins and found that the cost was very similar [4]. In 50 patients who underwent ECMO support for PCCS over a 2-year period, the survival rate was 37% with an average cost for survivors of $226,000 (range $110,000 to $460,000), and for non-survivors of $242,000 (range $42,000 to $1,028,000). These costs do not take account of the loss of activity every time a decision is made to use ECMO.

In the UK, Khorsandi et al. reviewed the cost of ECMO at University Hospital of South Manchester [2]. The cost of consumables of the CentriMag device was £3,542 and the total cost of a patient that underwent VAD implantation or ECMO was £15,669 and £8,616 per patient, respectively. The costs of the ICU stay may vary considerably and will depend on the duration of ECMO support, the number and type of complications arising as well as the potential added costs of more permanent mechanical devices that might be used as an exit strategy to ECMO. The cost of a long-term LVAD is in the region of the £80,000 for the device only.

In our institution, we have estimated the costs of establishing VA-ECMO as follows:

- Cost of consumables: approximately £5,000.
- Cost of ITU per day, with level 4 requirement of care (highly demanding work load) with 2 nurses assigned to the patient: approximately £4,000 per day.
- The cost of the console for the Levitronix Centrimag is £15,000 spread amongst the number of cases it is used for.

As mentioned previously, this does not take into account the financial implications of lost activity.

The Ethics of Advanced Mechanical Circulatory Support following PCCS

"I will use the treatments for the benefit of the ill in accordance with my ability and my judgement, but from what is to their harm and injustice I will keep them"

(From the Hippocratic Oath)

Written nearly 2,500 years ago, the Hippocratic Oath has been a fundamental guide for the way doctors in the Western world should apply and exercise their medical knowledge and relationship with their patients. The 2013 General Medical Council (GMC) Guide to Medical Practice states:

"You must use your judgement in applying the principles to the various situations you will face as a doctor, whether or not you hold a licence to practice, whatever field of medicine you work in, and whether or not you routinely see patients. You must be prepared to explain and justify your decisions and actions."

(4th paragraph, Chapter 1, 'Professionalism in action')

These two statements encourage doctors to treat their patients within a frame of capability and judgment based on solid knowledge that will allow them to justify and properly explain their actions. However, the above statements do not necessarily establish any limitations or boundaries as to how far any treatment should be extended.

Medicine has become a difficult and quite often challenging endeavour. Doctors have access to innumerable alternatives to treat patients, ranging from very conservative to very aggressive or invasive. Doctors are the gatekeepers of these treatments and they will make the decision on what, how, when and in whom certain therapeutic options will be used. The use of ECMO or any other form of advanced MCS in the treatment of PCCS is a good example of this challenge. In hospitals with access to this resource, it must not be forgotten that dying is part of our lives and that dying with dignity should be honoured as much as the efforts that we make to keep patients alive. Similar to dialysis where the kidneys are no longer necessary, it seems that with advanced MCS, life can be sustained without the need for a heart and/or lungs. The decision to establish ECMO is most of the time made after a long operation and between a tired operating surgeon and anaesthetist both of whom have been involved all day long with the patient. It seems that the aims of support, the realistic possibilities of recovery, the expected duration of support and future alternatives after support are generally not clearly explained to families and relatives. This creates a big problem as relatives often get a false and unrealistic expectation of what can be achieved following the institution of ECMO. The need for communication with the family on a regular basis has never been more important, not only to inform of progress or deterioration but also to hold their hands and guide them. Once support is instituted, the duration of it cannot be predicted in advance for any patient. It is however important to recognize that the elasticity of its duration should not be regarded as infinite and a clear time line should be given to the family to set out realistic hopes and expectations [4].

Final Comments

Post-cardiotomy cardiogenic shock is a rare entity which affects 1-3% of patients. The presentation is characterized by the inability to wean from CPB despite use of increasing doses of inotropes, vasoconstrictors and intra-aortic balloon counterpulsation. Without aggressive treatment, the outcome is usually fatal. Some centres advocate the use of advanced MCS mostly in the form of VA-ECMO for its treatment. This, as we have discussed above, demands specialised equipment, trained personnel and is very expensive. The institution of ECMO does not guarantee recovery and only 30-40% of patients leave hospital. This might seem encouraging when the alternative is almost certain death, but, in the greater context of a cardiac surgical unit, it is a rather 'onerous' way to save lives considering the associated morbidity, costs, length of stay and lost revenue due to postponed conventional activity. It is therefore not unreasonable to raise the question whether this service should be offered at all in a healthcare system with finite resources. Perhaps to be able to answer this question we should first ask ourselves what evidence supports its use. The available data comes from reports involving single centres, most of them retrospective with a limited number of patients. The more robust data is available from meta-analyses [8], reviews of large

series [7] or the review of a captive population [3]. It seems that patients >70 years old, patients with comorbidities, pre-existing heart failure and/or renal dysfunction are at increased risk of an adverse outcome. The absence of guidelines or consensus supporting this treatment is, in my opinion, indirect evidence of the weak support that the use of ECMO has in post-cardiotomy cardiogenic shock.

From an ethical point of view, the question of whether advanced MCS in PCCS is justified or not is as difficult to answer. Advanced MCS is rapidly available and can be used as soon as the need arises. However, is this availability of ECMO after PCCS enough reason to do so? There is the risk that it is not the patient who is being treated but the reticence of the doctors to accept that the patient has reached a point of no return. It must always be remembered that death should be honoured as much as the right to live. It has been advocated that the decision should be made by a team independent from the operating surgeon and anaesthetist. The guiding words of the Hippocratic Oath are most appropriate on these days where the boundaries of how far a treatment should be pursued become overlapped with what is rationally possible or what becomes a denial of failure. It is worth reading them again:

"I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of over treatment and therapeutic nihilism. I will remember that there is art to medicine as well as science, and that the warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemists drug"

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Editorial: Veno-Arterial Extracorporeal Membrane Oxygenation– A Solution for the UK?

"Acu rem tetigisti"

Introduction

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) offers mechanical circulatory and respiratory support and can be an invaluable tool in selected patients with refractory cardiogenic shock. Although the concept of ECMO dates back to the advent of cardiopulmonary bypass, its widespread adoption is relatively recent with an exponential growth in the use of VA ECMO during the last decade [1]. Patients with catastrophic cardiac failure refractory to medical therapy have an appalling prognosis. Veno-arterial ECMO can be used to buy time for recovery of the injured myocardium or as a bridge to cardiac replacement therapies such as durable left ventricular assist device (LVAD) implantation or cardiac transplantation. However, its injudicious application can exhaust the finite resources of healthcare systems with no improvement to patient survival or quality of life.

In this editorial, we aim to highlight the principle benefits and pitfalls of VA ECMO usage. We shall also provide a concise review of the current status of VA ECMO availability in the UK and discuss future perspectives in this field of practice.

Main indications and benefits of VA ECMO

Acute, most commonly ischaemic, and decompensated chronic cardiac failure are the main indications for VA ECMO (29% and 33%, respectively) [2]. Acute valvular heart disease, refractory arrhythmia, myocarditis, pulmonary embolism, sepsis, and hypothermia are other possible conditions where VA ECMO has a potential role in their management. VA ECMO is not a cure for the underlying cardiac disease process, but is used to provide temporary tissue oxygenation and perfusion while cardiac recovery is anticipated, when medical or surgical interventions are planned or as a bridge to decision regarding further therapies. This decision may be escalation to more durable mechanical circulatory support or optimisation for cardiac transplantation. In the absence of recovery or lack of suitability for durable LVAD or transplantation, ECMO withdrawal and patient palliation must be considered.

In the 2016 European Society of Cardiology (ESC) guidelines for the management of patients with acute heart failure, for those in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profiles I and II, short term mechanical circulatory support with VA-ECMO is included in the therapeutic algorithm [3]. In a meta-analysis of VA ECMO for post-acute coronary syndrome (ACS) cardiogenic shock or cardiac arrest, Pavasini et al. reported a short-term mortality rate of 58% [4]. However, due to the lack of randomised studies between VA ECMO and medical management in this high-risk group, it is difficult to conclude whether this short-term mortality is modestly favourable or prohibitively high. The same limitations apply to an observational study investigating patients in refractory cardiogenic shock complicating chronic cardiomyopathy whose 1-year survival was 42% after support with VA ECMO [5]. Finally, a recent meta-analysis demonstrated comparable

outcomes between the prompt establishment of ECMO as an adjunct to cardiopulmonary resuscitation (so called extracorporeal CPR or ECPR) versus conventional CPR in out of hospital cardiac arrest. In patients with in-hospital arrest (of cardiac origin), ECPR was associated with significantly higher survival rates [6].

Poorer outcomes have also been reported in patients transplanted directly from VA ECMO or requiring VA ECMO after heart transplantation [7]. The use of VA ECMO in the post-cardiotomy setting is also gaining attention from today's cardiac surgeons who are dealing with increasingly complex pathology in patients at extremes of age, often with multiple co-morbidities. In the largest meta-analysis incorporating almost 2,000 post-cardiotomy patients in refractory cardiogenic shock, 31% survival was achieved in those who were supported with VA ECMO [8]. Adverse prognostic indicators including advanced age, pre-ECMO intra-aortic balloon counterpulsation and protracted postoperative course on VA ECMO were associated with increased mortality.

In the absence of appropriately designed randomised controlled trials, the use of VA ECMO remains somewhat controversial. Patient selection, optimal timing of initiating mechanical support, what constitutes optimal medical management, who should provide this therapy and where the ECMO-supported patients are best managed are just a few of the uncertainties that hinder its wider application.

Pitfalls of VA ECMO utilisation

Patient selection is one of the most important determinants of outcome for temporary mechanical circulatory support. The realistic chances of survival of patients in cardiogenic shock must be weighed against the resource-heavy utilisation and opportunity cost of VA ECMO. Attempts have been made to predict survival following VA ECMO with risk stratification systems such as the Survival After Veno-arterial ECMO (SAVE)-score [2].

Although all cardiothoracic surgical teams are already familiar with the principles of cardiopulmonary bypass, VA ECMO entails specific knowledge and expertise that require specialist training for the surgeon, anaesthetist, perfusionist and intensive care medical and nursing teams. Being a closed-circuit and most commonly driven by centrifugal pumps, VA ECMO is preload dependent and afterload sensitive. Taps and connectors on the inflow side of the ECMO circuit should be kept to a minimum to reduce the risk of air entrainment. In peripheral VA ECMO whereby arterial return is via the femoral artery, poor lung function with inadequate oxygenation could result in hypoxia of the upper body, i.e. the Harlequin phenomenon. Other particular aspects of VA ECMO, such as ventricular distension, pulmonary venous hypertension and aortic regurgitation require specialist skills for recognition and management. The availability of a multi-disciplinary team with a wide skill set and comprehensive approach to these complex patients is fundamental to a successful outcome.

When a patient is placed onto VA ECMO in a specialist centre as an urgent case by trained personnel, all practice recommendations can take place resulting in a smooth and safe procedure. Conversely, when VA ECMO cannulation is attempted in the field, as part of CPR or as a salvage procedure, complications are more likely. Although the purpose of this review is not meant to be didactic, attention to the following areas must be paid during VA ECMO implantation and maintenance of mechanical circulatory support:

- Sizing and positioning of cannulae is pivotal to successful VA ECMO delivery. In the central VA ECMO configuration, standard sized cannulae commonly used for

cardiopulmonary bypass can be utilised. Attention to details such as putting the arterial cannula through a sleeve of Hemashield graft (Maquet, Getinge Group) can help reduce the risk of cannulation site bleeding. When peripheral VA ECMO is attempted, the size of the return (arterial) cannula must be such that it provides an acceptable pressure drop but with a diameter that does not completely obliterate antegrade flow to the distal limb. Antegrade limb perfusion with an additional reperfusion cannula in the superficial femoral artery or the use of an end-to-side Dacron graft on the common femoral artery is often required to mitigate distal limb malperfusion which remains common, and is one of the most morbid complications of peripheral VA ECMO.

- Bleeding is frequently encountered in VA ECMO affecting up to 60% of patients, with the ECMO cannulation site being the commonest culprit [9]. The fine balance between adequate anticoagulation for the prevention of thromboses must be weighed against bleeding diathesis such as intracranial haemorrhage or repeated re-explorations in the post-cardiotomy patient. Aubron and colleagues elegantly demonstrated the predictors and outcomes of bleeding complications of the VA ECMO patient [9]. In the absence of universally accepted criteria, tight aPTT control and meticulous haemostasis of all surgical sites, especially the VA ECMO cannula insertion site, are essential in reducing these complications.
- Availability and competency of trained personnel who can deal specifically with VA ECMO related problems, especially out of hours, is another area that warrants consideration. From relatively minor problems such as kinking of a line, to more complex ones such as an air lock or oxygenator failure, prompt and skillful response is essential for the survival of the patient. Although the management of complications is outside the scope of this editorial, staffing requirements and training are important considerations in the current UK environment which is facing unprecedented shortages in medical and nursing workforce in acute specialities [10].

Current status of VA ECMO use in the UK

There is currently no central registry for VA ECMO use in the UK but the number of cases is estimated to be in the region of 200 per annum with an increasing trend [11]. Data from the Extracorporeal Life Support Organization (ELSO) participating centres in the UK may underestimate its frequency as ELSO membership and data reporting is voluntary. A cost modeling study examining only the device cost, and without including costs for staffing, medication, and management of complications amongst others, estimated between £8,616 and £28,829 per patient. A United States-based study estimated ECMO-associated charges at $74,500 ± $61,400 per patient which only accounted for a relatively small proportion of the overall hospital charges for this patient group [12]. To date, a cost effectiveness comparison against optimal medical therapy in acute heart failure has not taken place. The specialised commissioning team from NHS England have not commissioned VA ECMO services in their recent review when taking into consideration the available clinical evidence and resource limitations within the NHS [11].

According to the list of ELSO participating centres, 16 hospitals in the UK offer a VA ECMO service. Six of these are also adult cardiothoracic transplant centres [13]. This has important implications as some VA ECMO patients are potential VAD and/or transplant candidates and are managed in non-transplanting cardiothoracic units. For patients with stable chronic heart failure, there is an established referral pathway between Cardiologists and transplant multidisciplinary teams. However, this may not always be the case when salvage

VA ECMO is established in emergency departments following ECPR, in intensive care units and immediate post-cardiotomy. The lack of central funding for VA ECMO also applies to transplant units, which are often faced with increased operational and ethical pressures to accept patients referred ad hoc for further management and/or escalation of treatment.

For hospitals with no ECMO capability referring to a VA ECMO centre, there is no formalised pathway. As a result, patients who could potentially benefit from this therapy may not be referred or may have to go through a labyrinthine process. A hub and spoke model of VA ECMO along the lines of successful programs in other countries has been proposed [14]. Higher volume centres with more than 30 cases per annum are known to provide better outcomes, further supporting the establishment of specialist VA ECMO hubs within the UK [15].

Challenges and future perspectives

In the current climate of significant financial pressures, resource intensive therapies without strong evidence base of cost effectiveness will not be considered by health care commissioners. Establishing specialised VA ECMO hubs in the UK cannot happen without formal funding. Individual hospitals are therefore left in a dilemma between focusing their resources on proven and cost-effective therapies with a high success rate such as coronary artery bypass surgery [16] and diverting their limited resource to acute heart failure patients with uncertain outcomes. In order to justify and maintain a sustainable VA ECMO service in the UK, judicious patient selection is paramount. In the first instance, this can be achieved through a multidisciplinary team approach to decision making, referencing published risk scoring systems and for the less experienced centres to liaise closely with their regional advanced mechanical circulatory support and transplant units so that appropriate communication and escalation of treatment may occur.

It must be emphasised that the lack of evidence from well-conducted and healthcare system-specific randomised controlled trials hinders the rationalisation of this treatment and, particularly for the NHS, poses a big hurdle for service commissioning. With one RCT currently underway in the Czech Republic, there is a need for a similar UK-based multicentre trial that may set standards for VA ECMO use in this country [17]. Alternatively, NHS England's Commissioning through Evaluation (CtE) programme may enable a limited number of patients to access this treatment while clinical and patient experience data are collected within a formal evaluation programme.

There is currently no formalised training in cardio-respiratory mechanical support in the UK. Although cardiac surgeons are familiar with the general principles of cardiopulmonary bypass and various cannulation techniques, delivery of VA ECMO in non-specialist centres will remain an infrequent and unfamiliar activity, compromising the chances of success. It is essential that the skill mix necessary for a successful VA ECMO service is developed through formal fellowship schemes for surgeons and specialist physicians with individualised educational objectives for each group.

VA ECMO provision is often an out-of-hours service which impacts on the routine programmed activities of the involved clinicians. It is a challenging area of practice due to the often-critical state of patients. Traveling to other hospitals and transporting the VA ECMO-supported patient to the specialist centre requires advanced organisational skills and physical effort. Although the main driver for most clinicians in this area of practice is the ability and privilege to provide a high-end subspecialist service to the most critically ill, individuals will still need to be incentivised, not just financially, but also through other

provisions in the work environment. This, among others, will allow for the continued provision and wider adoption of a therapy that despite funding constraints and scientific criticisms, appears to be one of the most promising areas of modern cardiovascular medicine.

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Chapter 8

Heart Failure Surgery:
High-Risk Conventional Cardiac Surgery in Patients with Poor Left Ventricular Function

Marc R Moon & Rita L Gardner

"Dignus vindice nodus"

Introduction

As the cardiac surgery and cardiology communities develop less-invasive techniques to treat a growing number of index surgical cases, the patients who present for open surgical intervention are becoming increasingly complex. Comorbidities are more prevalent including patients with severely diminished, often end-stage left ventricular (LV) function. Advanced mechanical circulatory support backup has also elevated the high-risk threshold for open surgical intervention. The current report will address what defines high-risk, what is the impact of poor LV function on low cardiac output syndrome (LCOS) and mortality, preoperative assessment of functional status and frailty, and strategies for preoperative optimization and perioperative support to minimize complications in patients with poor LV function undergoing conventional cardiac surgery.

What defines high-risk and what impact does it have on outcomes?

At Washington University in Saint Louis, we consider a predicted mortality of greater than 5% to 8%, as estimated using the Society of Thoracic Surgeons (STS) risk-score algorithm, to be "high-risk". Such patients are worthy of consultation with a heart team or a senior surgical colleague as appropriate. In a recent internal review of our surgical series dating back to 1986 (unpublished), we noted that among patients undergoing reoperative cardiac surgery, less than one-half underwent a procedure that could be codified using the STS algorithm because of the complexity of these often-combined procedures. Clearly, diminished ejection fraction (EF) increases surgical risk of LCOS, operative mortality, and other postoperative complications, but other factors are important as well. The definition of high-risk includes a combination of both objective and subjective criteria, including the patient's ability to pass the surgical "eyeball test". An interesting study from Litton and Delaney in 2013 surveyed surgeons in Australia and New Zealand and found that low EF, increased EuroSCORE, and prior cardiac surgery were the leading factors considered to impact risk following coronary bypass grafting [1]. The percentage of surgeons who identified specific preoperative factors to be a predictor of increased risk for coronary bypass grafting is as follows:

- Low Ejection Fraction 77%
- Increased EuroSCORE 67%
- Previous Cardiac Surgery 50%
- Significant left main 40%
- Anticipated prolonged bypass 30%
- Elevated Creatinine 30%
- Unstable angina 27%
- Elevated Troponin 20%
- Elevated Brain Natriuretic Peptide 7%

The University of Toronto group reviewed 4,558 patients undergoing coronary artery bypass grafting (CABG) and found that 9% developed LCOS [2]. The operative mortality rate was nearly 20-fold higher in patients with LCOS versus those without LCOS (17% versus 0.9%, $p<0.001$). The most important risk factors for LCOS included low EF with an odds

ratio (OR) of 5.7, redo operation with an OR of 4.4, and emergent or urgent operation with an OR of 3.7. Other less important risk factors included female gender, diabetes mellitus, age over 70 years, left main or 3-vessel disease, and recent myocardial infarction, all with an OR less than 2.5. Stepwise logistic regression analysis identified EF grade, redo status, and emergent versus elective timing as independent risk factors with the greatest impact. Comparing patients with poor EF (less than or equal to 20%) to those with normal EF (greater than 60%), the incidence of LCOS was 27% versus 6% and mortality was 11% versus 1% ($p < 0.001$ for both). Comparing reoperative to primary CABG, the incidence of LCOS was 25% versus 8% and mortality was 8% versus 2% ($p < 0.001$ for both). Comparing emergent or urgent status to elective status, the incidence of LCOS was 27% versus 6% and mortality was 7% versus 2% ($p < 0.001$ for both). Other studies have corroborated these findings [[3,4].

In 2009, Shahian and coauthors reported the STS Database series of 774,881 patients undergoing isolated CABG [3]. For each 10% decline in EF, there was a 19% rise in operative mortality. They reported a lesser effect of EF on mortality with isolated valve procedures, in which case a 10% fall in EF lead to a 9% increase in mortality. With combined procedures, the impact of a fall in EF was amplified as the complexity of the procedure rose. A 10% fall in EF led to a 9% increased mortality for combined CABG with mitral valve (MV) repair, 10% increased mortality for CABG with AVR, and 23% increased mortality for CABG with MV replacement. Ahmed and colleagues from Australia reported the impact of low EF on long-term survival [4]. In this series of 2,054 CABG patients, operative mortality in the low EF group (less than 30%) was 5.6% compared to 1.3% in the high EF group (greater than 60%) with an OR of 5.11 and diminished 1-year survival (88% versus 98%, OR 2.28). In addition, the impact of low EF on long-term survival increased over time. Clearly, patients with impaired EF would benefit from optimization of preoperative cardiac function prior to undergoing high-risk cardiac surgery, not only to improve early morbidity and mortality but also late outcomes.

Preoperative optimization of congestive heart failure in patients with diminished LV function.

Complex patients should be appropriately risk-stratified for the specific unit considering performing the high-risk procedure. EuroSCORE or STS risk scores should be calculated when possible, and the surgeon should perform their own evaluation prior to determining how to proceed. It is essential for each unit to determine what type of patient is too high-risk. Each center must determine how high-risk is too high-risk. Surgeons must understand their own limitations, such that they only take on cases for which the risk remains similar to that in higher-volume, potentially more experienced units. The surgeon needs to consider not only his or her own experience with a certain surgical technique, but the experience of the entire preoperative, intraoperative, and postoperative teams that will be critical to ensure the most satisfactory outcome.

Initially, one must assess modifiable parameters of end-organ dysfunction. For example, obtain a complete blood count and correct anemia if present. An elevated EuroSCORE combined with a low hemoglobin can triple operative risk. Also, compare the current creatinine to the lowest creatinine level in the last 12 months. If the current creatinine level suggests new renal dysfunction or strain, either judicious hydration or preoperative inotropic support may improve perioperative outcomes. Liver function tests can also identify malnutrition (diminished albumin) which may portend a suboptimal outcome.

Preoperative interventions may benefit patients who are either identified to be at high surgical risk or are acutely decompensated. Is there time for outpatient therapy in a patient who is decompensated and has not been on maximal medical therapy? If so, consider sending the patient home for 3 to 6 weeks on angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and β-blocker therapy to improve diastolic and potentially systolic biventricular function preoperatively. If the patient is acutely decompensated but cannot be discharged for outpatient therapy, consider a right-heart catheterization with placement of a pulmonary artery catheter to guide goal-directed therapy with fluid balance optimization and consideration of inotropes or counterpulsation therapy for afterload reduction.

Prophylactic intraaortic balloon pump (IABP) for high-risk surgery.

Christenson and others examined the impact of prophylactic IABP in high-risk cardiac surgery patients with impaired LV function [5-10]. In 2011, Theologou and coinvestigators summarized five randomized controlled trials which included 255 high-risk patients randomized to IABP versus no IABP before CABG [6]. All patients had EF less than 30% to 40%, prior CABG, and angina with tight left main disease. Contraindications to prophylactic IABP therapy included moderate to severe aortic insufficiency and peripheral vascular disease. Meta-analysis revealed that prophylactic IABP decreased mortality by 82% in this high-risk population ($p< 0.001$). Similarly, the incidence of LCOS fell by 86% ($p<0.001$). In a more recent meta-analysis in 2016 which included both randomized and non-randomized studies, Wang and coauthors reported a similar benefit for prophylactic IABP use [10]. In 17 studies totaling 2,539 patients, prophylactic IABP use in high-risk patients decreased short-term mortality by 74%, LCOS by 84%, and postoperative myocardial infarction by 64%. In addition, the incidence of acute kidney injury fell by 46% overall and by 72% compared to those who underwent unplanned IABP after CABG. The need for renal replacement therapy also fell by 82% with a prophylactic IABP ($p<0.03$). Dunning and associates from Blackpool developed a scoring system to predict IABP needs during high-risk cardiac surgery with 96.5% specificity [11].

The Blackpool algorithm is as follows:

- One intravenous inotrope 2
- Two or more inotropes 9
- Left main > 50% 2
- Previous cardiac surgery 3
- Catheterization during current admission 3
- Ejection Fraction 30% to 50% 3
- Ejection Fraction < 30% 8
- Cardiogenic shock 5
- Emergency priority 6
- Salvage priority 9

With a Blackpool score greater than 10, 50% of patients will require an IABP during surgery. This scoring system can identify a group of patients who should be considered for prophylactic IABP support as long as there is no contraindication.

Potential mechanisms through which prophylactic IABP use improves outcomes following CABG include: 1) decreased myocardial oxygen consumption, 2) diminished LV afterload, 3) diminished wall tension, 4) diminished systemic vasoconstriction, 5) increased cardiac output, and 6) increased myocardial perfusion and graft flow during diastole in the early postoperative period. With preoperative IABP support, Christenson and coinvestigators found that cardiac index (CI), always measured with the IABP on standby, increased by 78% before surgery (Table 1) [7]. Following CABG, CI remained elevated following weaning from cardiopulmonary bypass, and the elevation persisted after IABP removal (IABPs were removed at 24 hours). In the non-IABP group, CI did not increase substantially after CABG and remained significantly lower than the prophylactic IABP group up to 96 hours postoperatively ($p<0.0008$). Thus, prophylactic IABP increased CI more than 2-fold higher postoperatively compared to the non-IABP control group. Increased duration of prophylactic IABP preoperatively did not increase benefit to cardiac function. Patients receiving a prophylactic IABP for one to two hours preoperatively experienced the same augmentation in CI as those receiving a prophylactic IABP for 24 hours preoperatively. The impact of prophylactic IABP is immediate and long-lasting. Prophylactic IABP patients were also compared to patients who needed an IABP placed during surgery. While all prophylactic IABPs were removed at 24 hours, those that were placed for LCOS remained an average of 4 ± 2 days [5].

Prophylactic IABP was also found to have an important impact on graft flow after CABG [8]. Maximum graft flow increased by 40% and the pulsatility index rose by 50%. The Brussels group reported an aggressive approach to using prophylactic IABP in patients with diminished EF undergoing off-pump CABG and noted a 67% decline in mortality and improved completeness of revascularization [9]. Talley and associates performed a cost analysis after MI that supports the practice of prophylactic IABP as cost effective [12]. In a randomized controlled trial, 102 patients after myocardial infarction underwent IABP versus no IABP. The median costs were similar at $17,903 for IABP versus $17,913 for no IABP ($p=0.45$).

Table 1: Impact of prophylactic intraaortic balloon pump (IABP) on cardiac index compared to control (all measurements made with IABP on standby).

Cardiac Index ($L/min/m^2$)	No IABP	Prophylactic IABP	p value
Before IABP	1.86 ± 0.16	1.52 ± 0.22	< 0.0001
Before CPB		2.69 ± 0.66	
After CPB	1.99 ± 0.54	3.20 ± 0.70	< 0.0001
24h postoperatively	2.80 ± 0.64	3.36 ± 0.58	= 0.002
96h postoperatively	2.82 ± 0.92	3.23 ± 0.73	= 0.05

Data from Christenson JT, Simonet F, Badel P, et al. Optimal timing of preoperative intraaortic balloon pump support in high-risk coronary patients. Ann Thorac Surg1999; 68:934-9 [7]. CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump.

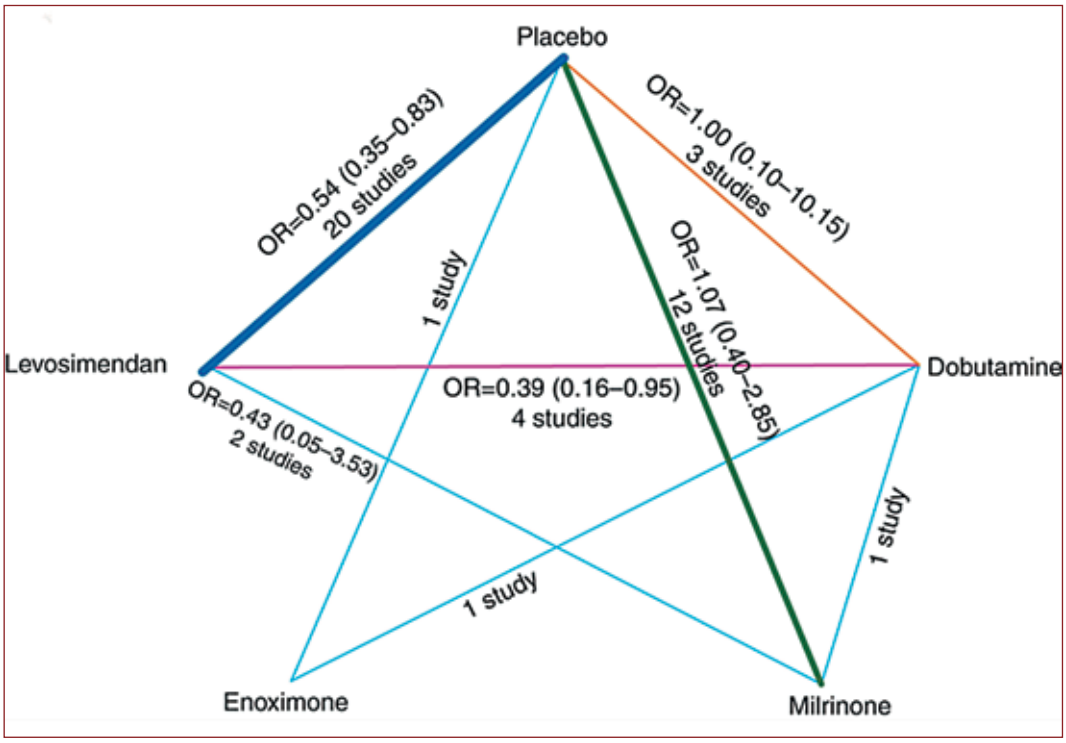

Figure 1: Bayesian-network meta-analysis suggesting improved outcomes with prophylactic levosimendan compared to other intravenous inotropic agents. Reproduced from Greco T, Calabrò MG, Covello RD, et al. A Bayesian network meta-analysis on the effect of inodilatory agents on mortality. Br J Anaesth 2015; 114:746-56 by permission of Oxford University Press [15].

Prophylactic intravenous inotropes for high-risk surgery

Patients can present for complex cardiac surgery in a decompensated state. They may have been unaware of underlying cardiac disease with a progression of symptoms that was insidious until their initial presentation in florid congestive heart failure. This is most often the worst time to operate on a high-risk patient. If time permits, a four to six-week period of maximal medical therapy as an outpatient may substantially improve functional status facilitating surgical intervention. If the anatomic situation does not allow outpatient therapy or the patient remains in failure despite satisfactory medical management, then preoperative inotropic therapy can be beneficial. Intravenous inotropes can also be of benefit in high-risk patients as prophylaxis against postoperative cardiogenic shock. Levosimendan, a potent inodilator, has received a good deal of attention recently as a potential prophylactic agent in high-risk patients.

Levosimendan is a Ca2+-sensitizer with both inotropic and vasodilatory effects. In 2012, a multicenter, randomized controlled trial included 252 patients undergoing CABG with LV EF less than 25% [13]. Patients were randomized to levosimendan or placebo for 24 hours preoperatively. Drug therapy was discontinued for hypotension, supraventricular or ventricular tachycardia, mental status changes, or the need for intubation, all know

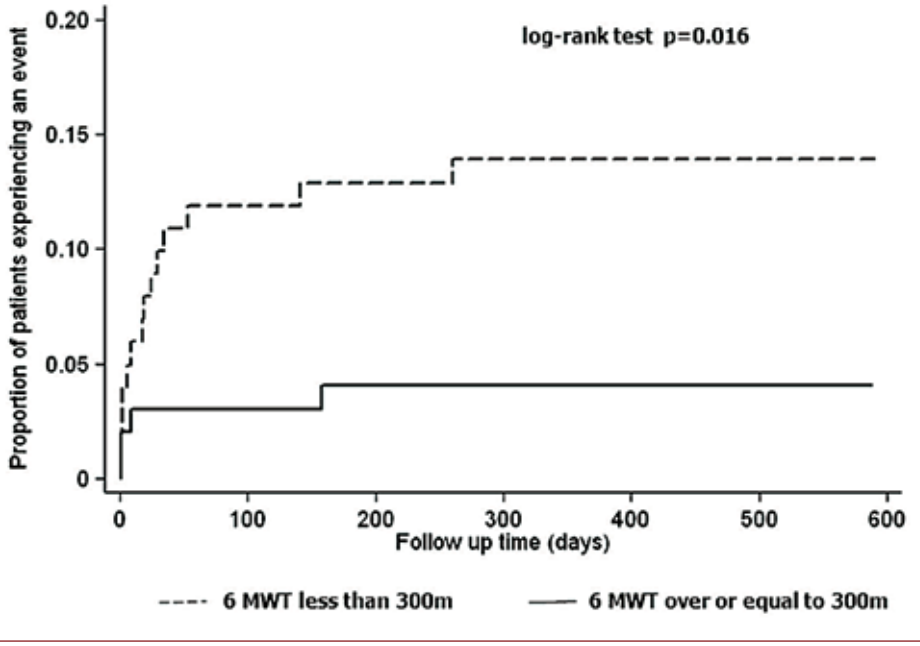

Figure 2: Impact of frailty on event-free survival after aortic valve replacement as assessed with a six-minute walk test. Reproduced from Heart [de Arenaza DP, Pepper J, Lees B, et al. 96;113-7, 2010] with permission from BMJ Publishing Group Ltd [17].

potential side effects of levosimendan therapy. Levosimendan routinely increased CI by 50% and decreased pulmonary artery pressure by 33%. The levosimendan group also experienced diminished mortality (4% versus 13%), LCOS (7% vs. 21%), renal failure (6% versus 14%), and prolonged ventilation (6% versus 17%). A recent multicenter, randomized controlled trial reported in the New England Journal of Medicine identified a lesser impact with prophylactic levosimendan, but the study group had better underlying LV function than previous reports (EF < 35% rather than EF < 25%) [14]. Mehta and coinvestigators randomized 882 patients to levosimendan versus placebo. There was no difference in 30-day survival but LCOS syndrome was less common in the levosimendan group (18% versus 26%, p = 0.007), and there was a tendency toward improved 90-day mortality (4.7% levosimendan versus 7.1% placebo, p = 0.12). Dobutamine (β1 agonist) and Milrinone (PDE-3 inhibitor) can also be used to optimize LV function preoperatively although an intriguing Bayesian-network meta-analysis of 46 trials encompassing 2,647 patients identified levosimendan as the ideal agent in this setting (Figure 1) [15].

Frailty in high-risk patients

Frailty also needs to be considered when evaluating patients for high-risk cardiac surgery. Patients who pass the "eyeball test" tend to do better than those who overtly appear frail. A cause and effect relationship exists, however, between comorbidities and frailty and the combination becomes multiplicative to ultimately yield disability [16]. Frailty has been defined as three of five of the following: 1) unintentional weight loss (10 pounds in one year), 2) self-reported exhaustion, 3) poor grip strength, 4) slow walking speed, and 5) diminished

physical activity. The Royal Brompton in London reported the impact of a six-minute walk test in predicting outcomes [17]. There was a 3-fold improvement in event-free survival up to two years postoperatively in patients who could walk 300 meters (Figure 2 previous page). The difference was even more profound in high-risk patients (EuroSCORE > 6), in which case frail patients had a 5-fold higher incidence of death, myocardial infarction, or stroke (Figure 3).

High-risk patients who are being considered for aortic valve replacement can undergo balloon aortic valvuloplasty (BAV) as a "bridge to decision" if they are anatomically suitable candidates. Initial BAV can help determine reversibility of symptoms, reversibility of frailty, and hemodynamic improvement. In addition, successful BAV can differentiate the relative contribution of aortic stenosis to the patient's frailty from coexisting lung disease, hepatorenal disease, and underlying irreversible myocardial dysfunction, in which case functional improvement will be limited. If the patient's rehabilitation potential is in question, heart failure therapy can be initiated, BAV performed, and the patient reevaluated in four to eight weeks. A month or two is generally adequate to identify a potential benefit of aortic valve replacement. Patients can be reevaluated for improvement in symptoms and functional capacity after BAV, and if symptoms are mostly due to other causes, the patient will experience limited improvement in functional capacity. In the era of transcatheter valve interventions, it is essential to differentiate patients who may benefit with intervention from patients in whom an intervention will likely be futile.

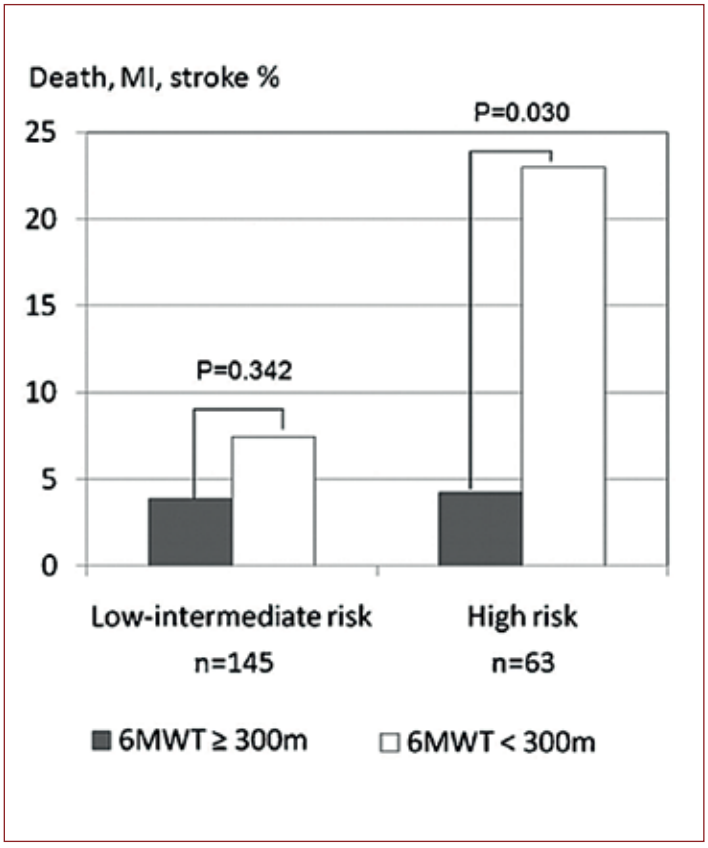

Figure 3: Impact of six-minute walk test to assess frailty in patients with low to moderate risk (EuroSCORE ≤ 6) compared to high risk (EuroSCORE > 6). Reproduced from Heart [de Arenaza DP, Pepper J, Lees B, et al. 96;113-7, 2010] with permission from BMJ Publishing Group Ltd [17].

What if the ventricle still doesn't work?

Despite all efforts to optimize ventricular function in the preoperative period, postoperative cardiogenic shock can still manifest, typically characterized by sustained hypotension (systolic blood pressure less than 90 mmHg), depressed CI (less than 2.2 L/min/m2), elevated wedge pressure, and ultimately end organ malperfusion. Initial management strategies include pharmacologic resuscitation and identification of potential reversible causes of failure to wean (diminished graft flow, air embolism, etc.). For patients in need of advanced therapies, the anticipated level and duration of support must be considered in addition to univentricular versus biventricular support and whether pulmonary support (extracorporeal membrane oxygenation) will be needed. Extreme-risk patients may best be served in a unit that can provide high level mechanical circulatory support or that has a collaborative relationship with such a unit and can ensure safe transport if needed.

In summary, as the patient population undergoing cardiac surgery becomes increasingly complex, surgeons are going to be expected to perform more high-risk operations than in previous years. Understanding the options to maximize function and provide support in the postoperative period, as well as knowing when to defer to a less-invasive therapeutic modality or tertiary unit that can provide mechanical circulatory support options is paramount.

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Chapter 9

Heart Failure Surgery: Surgical Technique and Management of Temporary Mechanical Circulatory Support for Acute and Post-Cardiotomy Cardiogenic Shock

Neil Howell

"Omnes movere lapidem"

Introduction

The use of temporary mechanical circulatory support (MCS) is not new and occurred early in the development of the specialty [1]. Mechanical circulatory support is used as a "bridge" to a number of endpoints which are:

- Bridge to decision (BTD),
- Bridge to recovery (BTR),
- Bridge to candidacy (BTC),
- Bridge to transplant (BTT),

MCS strategies may either be temporary/short-term or durable/long-term. Temporary short-term strategies suit those patients in acute cardiogenic shock/respiratory failure as BTD, BTR or BTT. This is generally for those patients who are in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) classes 1 and 2, in comparison to durable MCS which in the UK is reserved for patients as BTC or BTT in INTERMACS 2-4 [2].

Extra-corporeal membrane oxygenation (ECMO)

The terminology around describing temporary MCS remains confusing. The term extracorporeal membrane oxygenation (ECMO) in the UK refers to any circuit with an oxygenator. In Europe, veno-arterial ECMO (VA-ECMO) is termed Extra Corporeal Life Support (ECLS) to differentiate it from veno-venous ECMO (VV-ECMO).

The principles for establishing a patient on VA-ECMO are the same as for a standard cardiopulmonary bypass circuit. Blood is siphoned from the venous system, passes through an oxygenator, and is returned to the arterial side of the circulation. There are however subtle differences between ECMO and bypass. VA-ECMO circuits are closed circuits using partial bypass without a reservoir and the flow is always determined by venous drainage. In general, VA-ECMO should be considered a short-term salvage procedure only. Both morbidity and mortality increase in a linear fashion with time and consideration should be made to convert VA-ECMO to a ventricular assist-based support without the requirement for an oxygenator as soon as possible [3]. VA-ECMO may be placed peripherally (pVA-ECMO) or centrally (cVA-ECMO). When placed peripherally, it can be done by either a percutaneous or an open approach [4].

Peripheral ECMO

The femoral approach is the most common (Figure 1). It is familiar to surgeons, cardiologists, and anesthetists alike. If placed percutaneously, doing so under image guidance with a single stab technique will reduce bleeding complications that are often encountered in a patient who has required multiple punctures. Performing the procedure in an imaging suite, either a catheter suite or hybrid theatre allows confirmation that lines are correctly positioned [5]. In critically sick patients on extremely high doses of vasoactive drugs and those receiving cardiopulmonary resuscitation (CPR), placement of peripheral arterial cannulae may be challenging. Experience or circumstances may necessitate an open approach. The main complications of femoral ECMO are bleeding and leg ischemia [3]. To reduce bleeding, we routinely mobilise as little as possible of the vessel. Two separate purse strings are placed with a 5-0 polypropylene suture 2-3 cm apart in the femoral artery and then guide wires passed, the first distally in an antegrade and the second proximally in a retrograde fashion. These are then tunneled through the skin away from the incision

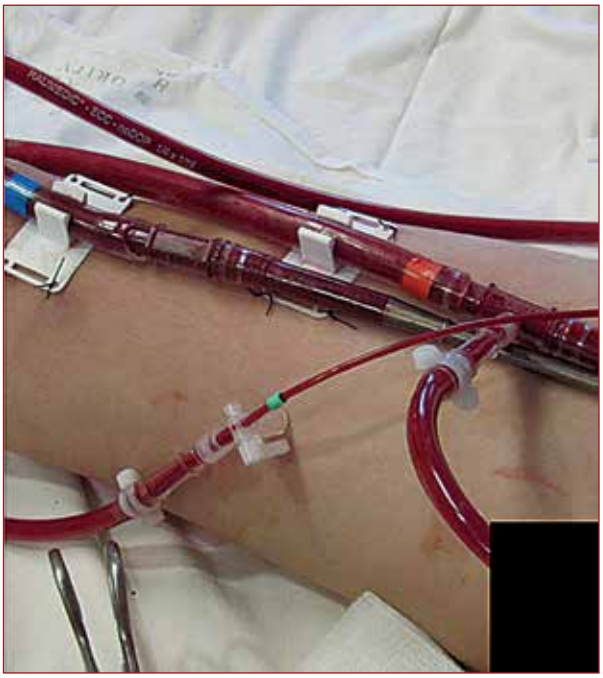

Figure 1: Standard peripheral ECMO with femoral venous drainage to femoral arterial return and distal perfusion

and the soft tissue tracts dilated to allow smooth passage of a small distal perfusion cannula, typically 8Fr and a larger main arterial return cannula depending upon the patient's BSA and estimated flow (usually between 17 and 21Fr). A long femoral venous cannula is used for drainage. We prefer one with multiple fenestrations to facilitate optimal drainage which is positioned under TOE guidance. At the beginning of the procedure an ACT should be performed with an ACT of >200 seconds being adequate to commence VA-ECMO. Many critically ill patients require little or no heparin to cover the procedure. If the ACT is normal or if the long femoral venous cannula is placed and left without flow for any period, 5000iu heparin will usually adequately cover the procedure (taking into account the addition of heparin to the ECMO circuit prime). Once adequate flow has been achieved, we would recommend correcting any clotting abnormality before there is significant bleeding.

Leg ischemia should always remain a concern and its diagnosis requires constant vigilance. It may occur at any time with a patient on femoral ECMO and its consequences are extremely serious. Significant ischemia requiring amputation is invariably lethal. It is essential that perfusion beyond the arterial return is adequate. The set up described above uses an antegrade distal perfusion cannula, however, there are several other solutions described in the literature including placing a graft on the femoral artery, retrograde arterial perfusion via the tibialis posterior or dorsalis pedis artery and newly developed cannulae with bidirectional flow [6]. If there is any concern over the placement of the distal perfusion line then invasive angiography or CT should be taken to confirm position.

Vigilance should be maintained with regular clinical observation and duplex examination of flow. Near Infra-Red Spectroscopy (NIRS) can be used to monitor adequacy of calf perfusion [7]. Distal perfusion cannulae are of small diameter and prone to thrombose especially when ECMO flows are lowered during weaning, prophylactic low dose Heparin can be infused down this line. If adequate distal perfusion cannot be obtained the arterial return should be removed and moved to a different site. The artery should then be fully mobilised and carefully repaired to prevent late ischemic complications. Other arterial return sites include the axillary artery and in the paediatric population the carotid artery is used. These should be approached in a standard fashion and the principles detailed above adhered to.

Once full flow has been achieved it is important to assess the response of the left ventricle (LV). The LV will continue to receive blood through both the pulmonary system and collaterals. Peripheral VA-ECMO will generate high aortic pressure and if LV function is very poor, the LV may be unable to open the aortic valve. This will lead to stasis in the LV with resultant pulmonary oedema and possible ventricular thrombosis. Numerous methods have been described to vent the LV [8].

In some circumstances, appropriate blood pressure and inotropic management may allow native LV ejection. This approach is often inadequate and the next step to consider is placement of an intra-aortic balloon pump (IABP) [9]. This is sometimes adequate but it is important to confirm on TOE that the counter-pulsation is indeed allowing the LV to vent. This requires confirmation that the aortic valve is opening and the LV non-distended.

If the LV function is very poor, a more invasive approach is invariably required. The Abiomed Impella 5.0 (Abiomed, MA, USA) can be placed under fluoroscopic control across the aortic valve and into the ventricular cavity [10]. With pVA-ECMO-Impella, the ECMO flow can be weaned to 2-3 l depending on patient size. The Impella can be simultaneously increased to provide >3 l flow. If PVR is low and RV function adequate then the Impella will maintain this flow and help predict a successful bridge to left ventricular assist device (LVAD) implantation.

The other option is to perform a small left thoracotomy over the ventricular apex and insert a drainage cannula into the left ventricle. If it is planned to bridge the patient to a long term LVAD then it is important that this is done under TOE guidance to confirm the position of the true ventricular apex. Both these approaches have the advantage of facilitating weaning of right sided support. If the LV has been vented surgically then a gate clamp can be placed on the venous drainage cannula and a 2nd flow probe placed on one of the drainage cannulae. The venous drainage can then be gradually occluded, the function of the right ventricle assessed and the venous drainage cannula potentially removed thereby converting the pVA-ECMO circuit into a short term LVAD. The oxygenator can then be removed from the circuit.

In patients with inadequate pulmonary function due to the combination of pulmonary oedema and acute lung injury, deoxygenated blood can be ejected by either native contraction of the ventricle or the Impella into the ascending aorta and it is therefore imperative that adequate oxygenation is confirmed via a right upper limb arterial line. Inadequate oxygenation of ventricular blood can lead to myocardial or cerebral hypoxia [11]. Treatment may include adjustment of the ventilator or a complete change of the circuit to either central aortic return, veno-arterial-veno (VAV) ECMO with an additional arterially pressured return to the venous system, or direct venting of the LV [12].

Central ECMO

This may be more appropriate if a median sternotomy has already been performed, or if there is concern over peripheral access and distal ischemia. Cannulae should be tunneled under the costal margin first. Teflon pledgetted purse-strings sutures should be placed in the right atrium and ascending aorta. The aortic return should be kept low to avoid stasis and thrombosis at the level of the aortic valve. If a long term LVAD is being contemplated then it may be appropriate to return to the aorta in this position just on the right of the aorta. If the destination is heart transplantation, it is prudent to keep the return within the proximal ascending aorta that will be removed at the time of recipient cardiectomy. Once

full cVA-ECMO has been commenced, it is vital that these cannulation sites are completely haemostatic. These sites will not otherwise stop bleeding and a return to theatre will be inevitable. If left ventricular function is very poor then direct venting of the LV cavity as described earlier is prudent. In some circumstances, e.g. post-cardiotomy syndrome or following heart transplantation with biventricular impairment, then a simple vent placed through the right superior pulmonary vein may be sufficient. If only a short period of right ventricular support is anticipated then central aortic return and LV drainage can be combined with peripheral venous drainage to facilitate weaning of right side support and conversion to a short term LVAD.

Ventricular Assist

This term is given to any circuit that drains primarily the atrium or ventricle and returns to the respective great artery and can include an oxygenator to provide additional support. Although this may be associated with serious complications, especially bleeding, it can provide stable support for patients for many months. It can be configured as a right-sided VAD (RVAD), a left-sided VAD (LVAD) or in parallel to provide biventricular support (BiVAD)

There are many commercially available products with the Centrimag system (Thoratec, CA, USA) being one of the most popular. It includes a magnetically levitating centrifugal pump head with specific drainage and arterial return cannula [14]. The pump head and cannulae are inexpensive but they require investment in a controller unit. The pump head is guaranteed for 30 days of continuous use after which the manufacturer suggests it should be changed.

Patients being considered for temporary MCS are critically unwell and induction of anaesthesia may be poorly tolerated. They are often auto-anticoagulated due to liver insufficiency. Loss of sympathetic tone after anaesthesia may precipitate a downward spiral of hypotension that may respond poorly to further inotropic stimulation. Following surgery, the main complication faced by these patients is bleeding and hypotension due to profound vasodilatation. If a patient is very unstable, pVA-ECMO may be a more appropriate salvage measure.

The most common configuration of a temporary VAD is a BiVAD. This is configured with drainage of either the right atrium (RA) or right ventricle (RV) to pulmonary artery (PA) return. Right ventricular drainage has a theoretical benefit but drainage of the RA is usually adequate. Left-sided support is provided via left ventricular drainage to ascending aortic return. Left atrial drainage offers no advantages and risks left ventricular thrombosis. Moderate or greater aortic insufficiency and atrial or ventricular septal defects need addressing using CPB to prevent recirculation and shunts respectively [15]. Otherwise implantation without CPB appears to offer advantages with a reduction in significant bleeding and vasoplegia. This approach should not be undertaken lightly. A cell saver and packed red cells should be available in theatre and a primed bypass machine offers a bail out option. Cerebral monitoring with NIRS confirms adequate brain perfusion during periods of permissive hypotension. If the procedure is poorly tolerated, cVA-ECMO can be used as an intermediate step and the oxygenator removed as soon as lung function allows.

Firstly, the BiVAD sash should be brought to the table, clamped with multiple heavy line clamps, divided, and secured. After sternotomy, the focus should be on ensuring the chest wall is as dry as possible. Throughout the procedure the surgeon should be mindful of the high rate of re-exploration for bleeding necessary with such procedures [16]. Both pleural

cavities should be opened and effusions drained. The left pleura should then be widely opened to facilitate later LV apical access. The pericardium is then opened with an inverted T down to the apex of the left ventricle. All four cannulae should then be tunneled below the costal margin in line with their site of cannulation (Figure 2). Exteriorisation of the LV cannula can be difficult and it should exit away from the other three cannulae directly below the LV apex. Unfortunately, the ideal lie of the LV drainage cannula may risk injury to the superior epigastric artery whose course should be mentally visualised to avoid this complication. Haemostasis of the cannula tracts should be obtained before cannulating the heart. Once this has been completed satisfactorily, the procedure should be covered by 5000iu heparin.

The ascending aortic return should be established first. Our preference is to use two 2-0 polypropylene purse-string sutures incorporating a 10mm Dacron graft. The return cannula is then pushed through the graft and then the aorta cannulated in a standard fashion. The purse-strings are then snugged down and the cannula secured with multiple heavy ties around the snuggers and graft.

Access to the left ventricular apex can be difficult and the manoeuvres to achieve this poorly tolerated. The patient should be placed in a steep reverse Trendelenburg position and the operating table rotated to the surgeon as far as safely possible. It may be necessary to open the retractor widely. A stitch placed deeply in the posterior pericardium may help access but impedes TOE imaging of the ventricle. Our preference is to slowly manoeuvre the heart into position with large wet swabs. It is often surprising how these steps can bring even the most impaired ventricles into the surgical field. Once a satisfactory position is obtained, surgery should be paused and cardiovascular stability confirmed with anaesthesia. NIRS monitoring will help confirm cerebral perfusion. If satisfactory the planned site of LV drainage should then be confirmed on TOE. The site of cannulation is important if the patient may require later conversion to a long-term VAD. The Centrimag cannula has a sewing ring to help secure it to the ventricle. This ring should

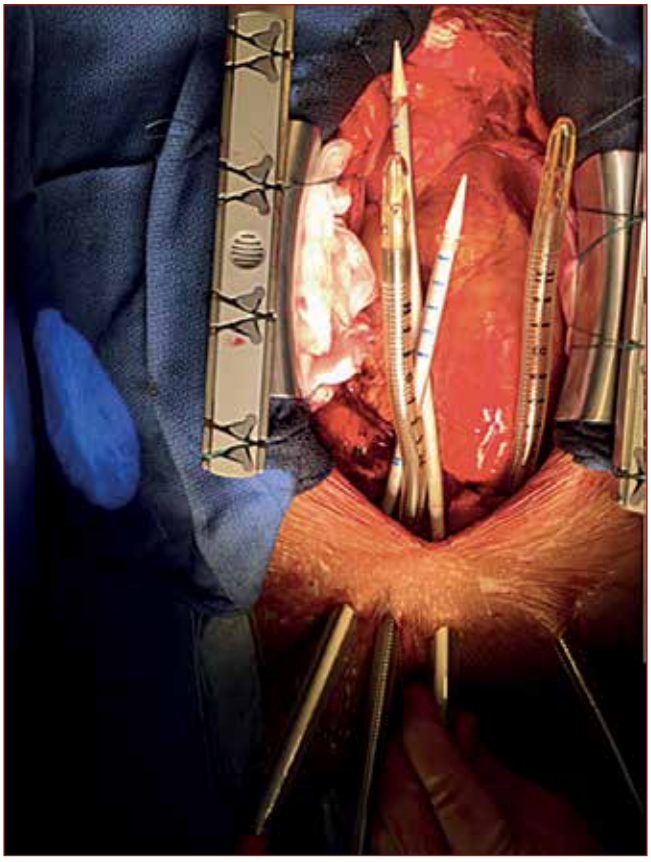

Figure 2: Configuration of BiVAD pipes prior to cannulation. The pulmonary artery, right atrial drainage and aortic return cannula are seen together. The LV drainage cannula is tunneled separately in a direct line with the LV apex.

be sewn onto the ventricle with multiple Teflon-pledgetted sutures. Great care should be taken; the ventricle will be tense, tissue quality is often poor and especially so in the setting of an acute infarction, and major haemorrhage at this point is problematic. Once the sewing ring is secured, it is often advisable to obtain a biopsy to aid with the diagnosis of the cause of heart failure. The ventricle is incised with a No. 11 blade, bleeding controlled with digital pressure and the cannula inserted and then clamped. The position of the cannula should be confirmed on TOE. It is important that the ventricular wall does not occlude the side holes of the cannula. Once the position is confirmed the cannula can then be secured with multiple heavy silk ties. Cannula migration is always a risk and this step should be carried out with due diligence. The LVAD circuit can then be connected and the VAD started. If RV function is poor, LVAD flows at this stage should be kept low.

Figure 3: Standard BiVAD setup using Centrimag pump heads

Attention can then be turned to the RVAD cannula. The pulmonary artery is cannulated and the cannula secured in an identical way to the aortic cannula. In the dilated and very poor right ventricle, the RV apex should be cannulated in a manner identical to that of the LV. In most circumstances, however, cannulation of the right atrium is satisfactory with the cannula bent to approximately 100° so when inserted it points directly at the tricuspid valve. This can be secured with two Teflon-pledgetted purse-strings, which are snugged down and secured with heavy silk ties. These cannulae can then be connected to the RVAD.

Flows on the RV and LV can then be simultaneously brought up to provide full flow. If the blood pressure remains inadequate without significant vasopressor support, the flow can be increased to greater levels to mimic the normal physiological response. Theoretically, LVAD flows should be higher than RVAD flows due to physiological shunting through the heart but in practice the flows should simply be adjusted to provide a central ventricular septal position. Changes in flow may take time to manifest and so should be done slowly and carefully.

Once full flow has been established, all cannulation sites should be examined carefully for bleeding. The right atrium can be problematic and may only be evident when the RA is full. It is sometimes worth dropping RVAD flows and ensuring the atrial cannulation site is haemostatic when filled in this manner. Full correction of any clotting abnormality is recommended. In some patients, typically those with acute hepatic insufficiency prior to surgery, packing the chest and planning for delayed closure 24hrs later may be a useful technique.

Short term MCS for post cardiotomy syndrome

Post-cardiotomy syndrome refractory to inotropic support has a universally high mortality rate and temporary MCS with VA-ECMO has been the treatment of choice but controversy remains due to the associated cost. The cost is driven by resource utilisation and displacement of other activity rather than the cost of ECMO per se. In appropriate patients, the use of MCS as a temporising bridge-to-recovery or bridge-to-decision strategy would seem reasonable. Such circuits can be configured easily by any department without specialist equipment. Central ECMO with either RA or femoral drainage to ascending aortic return with a pulmonary vein vent offers safe biventricular support.

Management and weaning of MCS

Detailed management of patients supported with temporary MCS is beyond the scope of this chapter. In general, full flow should be calculated as per standard cardiopulmonary bypass protocols. If the patient still needs significant doses of vasoactive agents to achieve MAP ≥ 60mmHg then flows can be increased further. High dose infusions of beta agonists are unnecessary and there is an assumption that weaning such drugs off will aid bridging the myocardium to recovery.

The length of time required on temporary MCS to bridge patients to recovery is variable and is clearly dependent on aetiology. In patients with post-cardiotomy syndrome, improvements in ventricular function may be seen on TOE within 48-72hrs. These improvements may be inadequate to allow removal of support but they suggest a more optimistic trend. If no such improvement is seen at this stage, it may be reasonable to consider options other than bridging to recovery.

Once ventricular function is seen to improve and weaning is possible, inotropic support should be recommenced, flows reduced and the haemodynamic response should be observed. If these appear favourable then further imaging of the ventricles with TOE is a reasonable next step and, if this remains satisfactory, then removal of the circuit may be considered which should be performed in the operating theatre. A clear plan should be formulated to deal with circulatory failure following MCS removal. All patients should have a pulmonary artery catheter in situ and prophylactic inotropic and vasoconstrictor support. An IABP may useful in more borderline cases. If there is concern, then the patient can be systemically heparinised and the circuit temporarily clamped.

Conclusions

The results of temporary MCS have improved considerably over the last decade although the incidence of lethal complications remains high. Such therapies are temporising measures and, in many patients, myocardial function will not improve sufficiently to allow simple

explantation and some form of heart replacement therapy will be required. Improving outcomes with durable LVADs now mean that a broader range of patients can be treated, for whom heart transplantation may not be possible in a more acute situation. Mechanical circulatory support with VA ECMO should be reserved for very short-term support only and the risk of complications should not be under-estimated. Success for both patients and cardiac surgical units depends on minimising complications and therefore the associated resource requirements.

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Chapter 10

Aortic Surgery:

Subspecialisation in Aortic Surgery: The Acute Type A Dissection On Call Rota

In favour: *Giovanni Mariscalco, Marcin Wozniak, Gavin Murphy*

Against: *Jonathan Unsworth-White*

Editorial: *A Plan for the UK - Aung Y Oo*

"Ducunt volentem fata, nolentem trahunt"

In favour: Subspecialisation in Aortic Surgery: The Acute Type A Dissection On Call Rota

"Faber est quisque fortunae suae"

Background

The prevalence and incidence of thoracic aorta disease (TAD) is steadily increasing [1-3]. In the UK over the last decades, hospital admissions for thoracic aortic dissection have increased from 7.2 to 8.8 per 100000 inhabitants [2]. Despite refinements in surgical techniques and perioperative care, mortality and morbidity of acute type A aortic dissection (ATAAD) remains high, with a wide variation across centres [4-9]. In the UK, the overall in-hospital mortality of ATAAD undergoing surgical repair is almost 20% [4,10], while specialized centres across the world have documented lower mortality rates, ranging from 2% to 10% [5,7,8]. In the face of this disparity, recent studies have shown that dedicated specialised aortic centres may improve postoperative ATAAD outcomes [4,6,8-11]. This volume-outcome relationship is irrefutable and supports the need to centralise ATAAD surgery [4,6,8-11]. A recent comprehensive study analysing national data from England has demonstrated unwarranted variation in the quality of ATAAD patient care [4], and the most effective referral model/organization of services for the management of TAD has not been identified [12].

Benefits of a dissection rota

Amongst strategies to ameliorate the quality of care for patients with ATAAD, aortic dissection teams have been proven to play a critical role [5,13-16]. A recent study from Andersen and colleagues [5] documented that ATAAD repair performed by high-volume aortic surgeons has results approximating those of elective surgery. Over a 10-year period, they analysed 128 ATAAD consecutive patients, comparing surgical outcomes before and after the introduction of a dissection-rota. Patients operated on by dedicated aortic surgeons had significantly lower hospital mortality compared with those who did not (2.8% vs 33.9%, $P<0.0001$) [5]. Despite this evidence, a recent national English survey revealed that only 31% of cardiac surgical units have a dedicated on-call rota for ATAAD condition (Figure 1).

Systematic review of literature and UK experience

In order to evaluate the clinical benefits of acute type A dissection on-call rotas, we conducted a systematic review of existing studies that have explored this issue. The review adhered to MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17,18]. Briefly, literature searches were systematically performed with electronic databases (PubMed/MEDLINE, EMBASE, and the Cochrane Library) without date or language restriction from inception to the end of October 2017. Key words and MeSH terms pertinent to the exposure of interest were used in relevant combinations, including "aorta, thoracic", "aortic dissection", "adult", "cardiac surgery", "surgeon volume, "mortality", and "patient outcome". References of all eligible studies and review articles were also screened to identify relevant resources that were not previously identified. All adult major thoracic aortic procedures were considered.

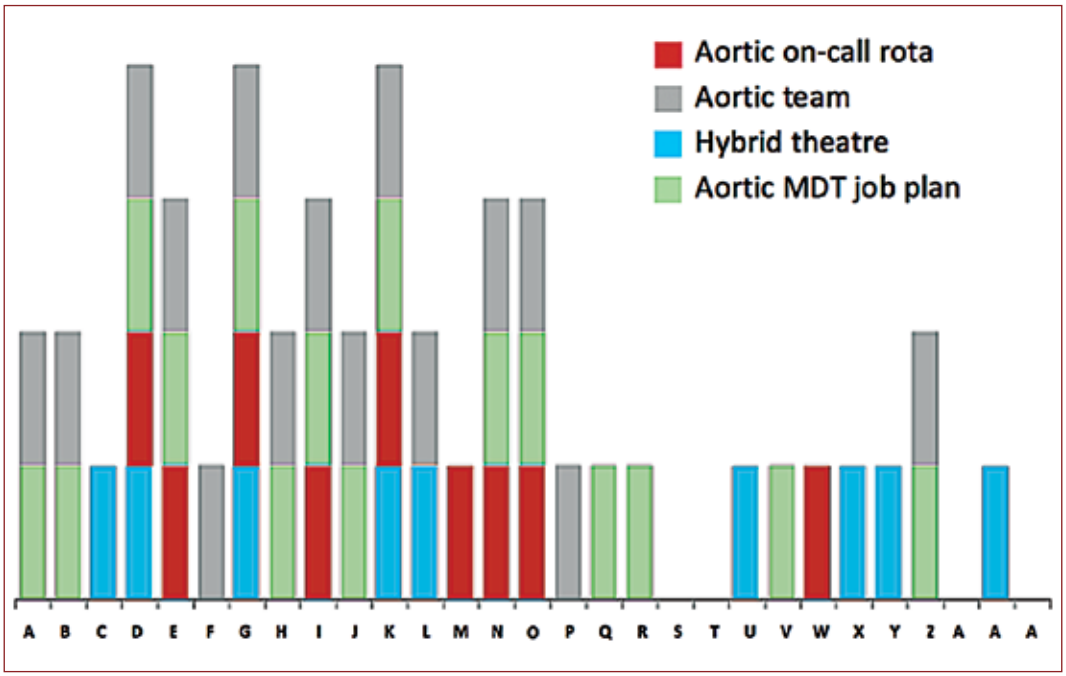

Figure 1: Results of the national survey assessing current service organization for thoracic aortic disease in cardiac surgery centers across England. Surgeons were queried on the presence of a dedicated aortic team, a specific on-call rota for thoracic aortic disease, a hybrid theatre, and an aortic multidisciplinary team (MDT) recognized in the consultant job plan. Adapted from Bottle et al. [4]

The primary outcome of interest was all-cause mortality in hospital or within 30 days from the index surgical procedure. Secondary outcomes included re-exploration for bleeding, stroke, renal failure requiring dialysis, length of stay in the hospital, and late mortality. Year of publication, study design, country, sample size, recruitment period, number of patients in each group, measured outcomes, and baseline patient demographics were extracted. Study quality was assessed using the Newcastle-Ottawa Scale [19]. Treatment effect on operative outcomes was reported as odds ratio (OR) with a 95% confidence interval (CI). Individual ORs (OR <1: centers with dissection rota better) and variance were computed by using number of events and sample size and pooled by using the Mantel–Haenszel method and random-effects model [20]. I2 statistic was used to estimate the percentage of total variation across studies attributed to heterogeneity rather than chance. Suggested thresholds for heterogeneity were used, with I2 values of 25% to 49%, 50% to 74%, and ≥75%, indicative of low, moderate, and high heterogeneity [21]. Publication bias was evaluated using visual inspection of funnel plot asymmetry and by Egger's test [39]. $P<0.05$ was used as the level of significance and 95% CIs were reported where appropriate. Statistical analysis was conducted using meta package for R (version 4.3-2; R Foundation for Statistical Computing, Vienna, Austria) [23,24].

Of the 8,564 records identified, 5 eligible observational cohort studies were identified and included in the systematic review, comprising a total of 813 patients (Table 1, page 158) [5,13-16]. The identified studies were published between 2014 and 2017. No publication

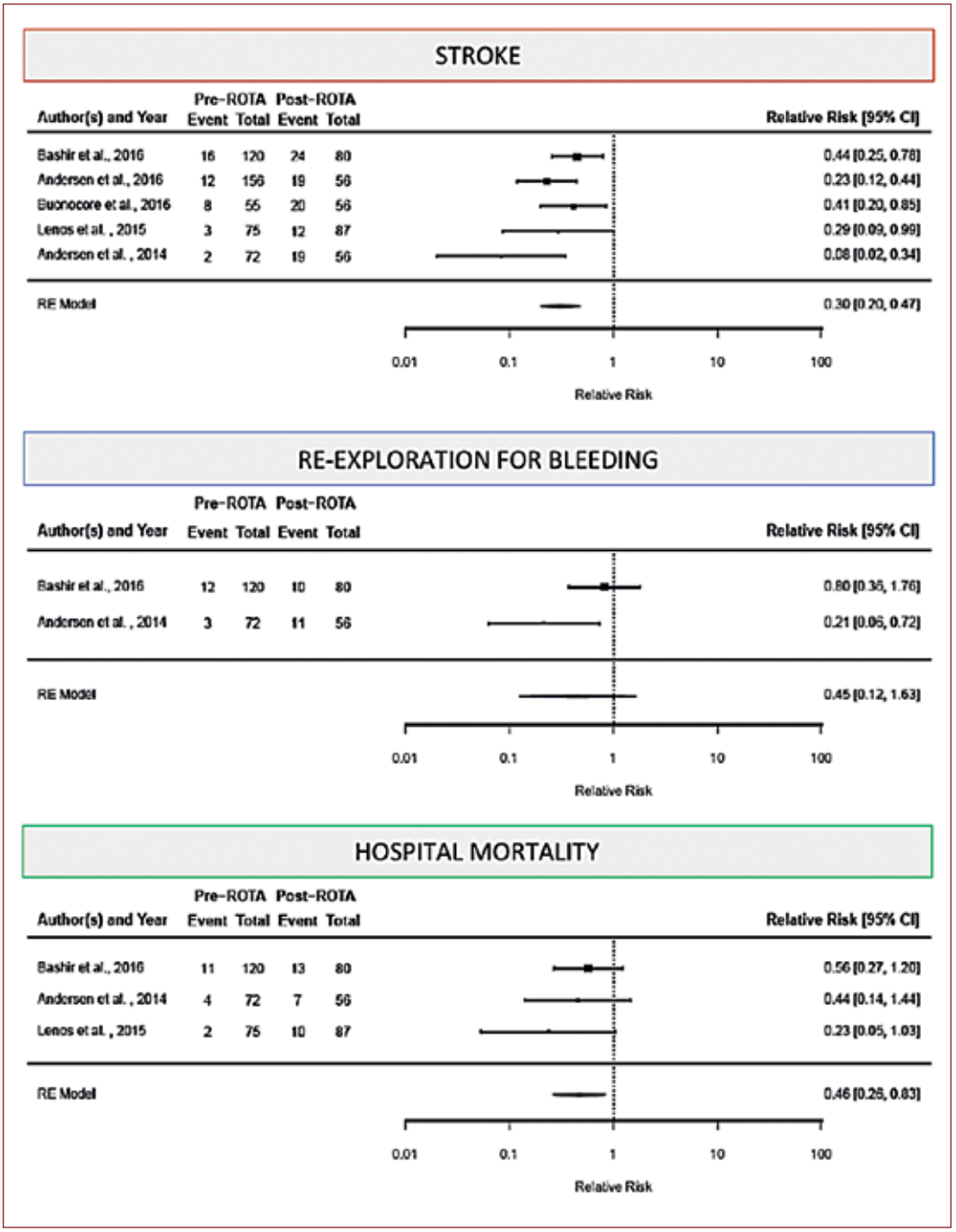

Figure 2: Forest plot with unadjusted risk estimates for in-hospital/30-day mortality (upper panel), re-exploration for bleeding (central panel), stroke (lower panel) in patients undergoing repair for acute type A aortic dissection. RR indicates relative risk; CI, confidence interval.

bias was found for the primary outcome (p=0.11). Centers that introduced the on-call dissection rota reported a significant reduction in mortality (RR [Relative Risk], 0.30; 95% CI [Confidence Interval], 0.20–0.47; I2=29.6%), and stroke occurrence (RR, 0.46; 95% CI, 0.26–0.83; I2=0%), but no reduction in re-exploration for bleeding (RR, 0.45; 95% CI, 0.12–1.63; I2=58.8%) (Figure 2). Two studies analysed the survival benefits of the dissection rota in the late postoperative period [5,14]. Andersen and colleagues [5] demonstrated improved 5-year survival rates for patients operated on by dedicated aortic surgeons compared to those who did not (85% vs 55%, P = 0.0017). Only one study originated from the UK [14]. From October 1998 to November 2015, 200 patients undergoing surgical repair for ATAAD were operated on at Liverpool Heart & Chest Hospital, of which 80 individuals were identified from the pre-dissection rota era and 120 from the post-dissection ones. Comparative analyses revealed that patients treated in the post-dissection rota had lower in-hospital mortality and acute renal failure rates (13.3% vs 30%, P=0.004 and 14.2% vs 26.3%, P=0.033, respectively). A significant improvement in 5-year survival was also noted (p=0.004).

Conclusions

A dedicated on-call rota for patients affected by ATAAD plays a central role in improving outcomes in this patient population [5,13,14]. Dedicated aortic surgeons with consistent numbers of ATADD operations are one of the main factors for reducing postoperative mortality and morbidity [5,9-11]. In the UK, data from the NICOR (National Institute for Cardiovascular Outcomes Research) database have clearly demonstrated that ATAAD patients operated on by lower-volume surgeons experience significant higher mortality and morbidity [4,9]. A threshold of 4 annual ATAAD operations seems to be the minimum requirement for better outcomes [9]. Despite this evidence in the UK, the on-call dissection rota is not adopted as a standard of care for ATAAD pathology. Certainly, other parameters are of utmost importance in the ATAAD care such as the implementation of the ATAAD pathways, the presence of a multidisciplinary standardized care for ATAAD, and the regionalization of (high-volume) aortic centres [4,10-12,25-28]. Harris and colleagues [25] with the standardization of ATAAD protocols in community hospitals, interhospital coordination and transport to regional aortic centres demonstrated a significant time reduction from the initial diagnosis to the surgical operation (113 min vs 51 min, p=0.006). This is especially important considering the high mortality that in untreated ATAAD patients is estimated at more than 1% per hour after symptom onset. Similar data has also been published by other groups [26,27]. Finally, the availability of new technologies as well as the hybrid theatres allowing the treatment of more complex aortic pathologies and related complications is another complimentary element of the on-call dissection rota for improving surgical results in patients affected by ATAAD [29].

In summary, an on-call rota of specialist aortic surgeons should be established as the standard of care in the treatment of acute Type A aortic dissection.

Table 1: Characteristics of the studies included in the systematic review.

Study (Author, year)	Design	Country	Sample size	Study period		Demo-graphics		Hospital mortality (%)		Newcastle-Ottawa scale *		
					Age (yrs)	Female (%)	BMI (kg/m^2)	Pre-rota	Post-rota	Selection	Compara-bility	Outcome
Andersen et al. 2016	Retrospective case controlled, Monocenter	USA	212	1999-2015	-	-	-	33.9%	7.7%a	**	**	*
Bashir et al. 2016	Retrospective case controlled, Monocenter	UK	200	1998-2015	-	33.5%	-	24%	16%b	**	**	**
Buonocore et al. 2016	Retrospective cohort study, Monocenter	Italy	200	2007-2014	63.6 ± 11.6	35.1%	27.3 ± 3.7	34.5%	14.3%b	**	**	*
Lenos et al. 2015	Retrospective cohort study, Monocenter	Germany	162	2002-2013	63 ± 14	32.3%	-	13.8%	4%a	**	*	*
Andersen et al. 2014	Retrospective case controlled, Monocenter	USA	128	1999-2011	-	43%	-	18.2%	2.8%	**	**	**

Abbreviations: BMI, body mass index.
aP <0.0001, and bP< 0.05.

For the NOS, a study can be awarded a maximum of 4 points for the Selection category, 2 points for the comparability category and 3 points for the Outcome/Exposure categories. Therefore, the maximum points a study can obtain is 9 which indicates a high-quality study (please see

http://www.obri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December 31, 2017).

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Against: Subspecialisation in Aortic Surgery: The Acute Type A Dissection On Call Rota

"Ex vitio alterius, sapiens emendat suum"

Introduction

When your car breaks down on the motorway you breathe a sigh of relief when the mechanic lifts the bonnet and uses their wealth of knowledge to diagnose the problem and begin to put it right. "It's your lucky day," they might say, "I'm a carburetor specialist and that's precisely what's wrong with your car. I have a new one with me so I'll get on and fit it for you straight away". You might, though, be forgiven for uttering one or too expletives if they were to say instead "well, as a specialist in carburetors, I can confidently state that yours is fine but I can see that the problem lies instead with the exhaust manifold. Sorry, but that is not my area of expertise. I will need to have you and your car transferred 100 miles to an exhaust specialist". If the required specialist was only just around the corner, however, you might not mind so much.

OK, so we are not talking cars here but aortas. We are debating whether patients presenting with, say, an aortic dissection, would be better served if they were to be transferred to a "specialist aortic unit".

What is driving this discussion? Is it a reflection of the perceived "poor results" of dissection surgery in the UK [1]? Is there a justifiable argument that a replacement of the ascending aorta without an arch procedure for selected individuals (possibly outside of the comfort zone for non-aortic surgeons) is not in the best interests of those patients? Is it driven by non-aortic surgeons who just want a quiet life on call?! It certainly seems to reflect the relentless move towards knowing more and more about less and less, from the day we leave medical school.

That movement has been evident amongst our general surgical colleagues for many years. "General surgeons" were once just that - generalists who operated from head to foot, utilizing their skills in a dazzling variety of ways, usually to the good of their patients. However, in our own working lifetimes, we have seen how this concept of "jack of all trades, master of none" has become increasingly frowned upon, and with good reason too. The relationship between volume and outcome was quite clear in esophageal surgery. There seemed to be a step in improved operative mortality amongst surgeons performing more than 12 oesophago-gastrectomies per year [2]. Now, even thoracic surgeons are no longer performing this operation which, until recently, was a "fair game" topic in our part three exams. Instead, we have upper GI, lower GI, hepatobiliary and vascular, all specializing in their zone of the abdomen, with separate on call rotas to match, and patients moving between units to find the nearest on call team to meet their needs when required.

I am not saying this is a bad thing - I am merely debating whether such a move is applicable to the thoracic aorta. Are we not already specialized enough as "cardiac" surgeons? There is data to suggest we are not. Volume vs. outcome data does indeed support the notion

that better outcomes, and more extensive procedures, are more likely in higher volume units [1,3]. I contend, however, that, even allowing for this, there may yet be a case against restricting emergency aortic surgery to just a few "aortic mega units". An over rigorous application of such a concept might have unintended unfavourable consequences.

When I began my own consultant career as a cardiothoracic surgeon in Plymouth, I performed two cardiac and one thoracic lists per week. When colleagues were away I might spend all week in theatre. There was no shortage of work to do and I felt competent in my work. I had a lot to learn, but with that amount of operative experience, and especially with the support of my more senior colleagues, I learnt quickly. However, I was not sorry to step away from thoracic surgery ten years later. Thoracic work was drying up with the appointment of another cardiothoracic surgeon and I was feeling that I wanted to re-focus on cardiac surgery. Job planning was changing too. There was simply no way to fit three lists per week plus a lung cancer MDT etc into a 12PA (planned activity) contract. Since then I have developed my mitral and aortic practice, whilst continuing with plenty of coronary work. I do not now feel that I should step away from my mitral and coronary work to focus entirely on the aorta.

When I start my on-call shift, I wonder whether my night will be disturbed by an aortic dissection, a post infarction ventricular septal rupture, penetrating trauma, or a blown mitral valve. There really aren't many other things that are going to keep a cardiac surgeon out of bed. The last three on this short list are either vanishingly rare or can be supported overnight to the following day or two. Aortic dissections, though, need emergency treatment.

If I, as an "aortic surgeon", take on the dissections for my non-aortic specialist colleagues, just what exactly will they be doing on call? Am I going to be on a 1 in 2 rota with my aortic colleague? Perhaps I should participate in a supra-regional rota with my aortic colleagues in the next nearest unit, Bristol, which is more than 100 miles away? Whilst I may then be on a 1 in 4 rota instead, my on calls will be very busy, comparatively speaking, and, more worryingly for our patients, some of them will be traveling well over 100 miles, past their own local unit, to reach me for their emergency operation. It is true that many patients with dissections wait several hours between diagnosis and surgery, rarely out of choice, patient's or surgeon's. However, we are also aware of patients who have succumbed in the interval, either in the ambulance on transfer, or in the cardiac unit waiting for theatre teams to arrive. Time matters [4]. There must surely be a risk that any gains made in transferring patients across country to an on call aortic surgeon might be at least partially, if not wholly, offset by the delays incurred. This also raises the speculation that some of our variance in mortality from, say, American centres of excellence, might be explained by selection bias [5]. Whilst I don't doubt their surgical expertise, their transfer distances are much greater and their exclusion of the sickest dissection patients ("Patients are generally considered unsuitable for transfer if undergoing active CPR or in refractory shock with impending arrest at the outside facility") makes perfect sense. These same patients probably have no hope of surviving the larger transfer distances in America yet might gain a chance of surgery in the UK provided the "local" UK surgeon is prepared to take them on, and is truly close at hand. Such patients have the most to gain and not much to lose by undergoing emergency aortic replacement. In other words, the variance in outcomes from aortic dissection surgery are only partly explained by the experience of the operating surgeon. Ischaemic gut, significant neurological injury or myocardial ischaemia will kill any patient irrespective of the brilliance of their operation. Simply using one's "experience" to select

the most favourable subjects will certainly improve that surgeon's figures but will not serve the population's best interests.

So, yes, if or when I have my own type A dissection, I would personally really like an aortic surgeon to perform my operation. However, that will be futile if I die on my way to reach them. Transfers between units might well be feasible and expeditious in some parts of the country but they won't be expeditious in our more rural areas. Air transport might sound great in theory, but in practice it won't always be available when required. In such circumstances, the regional or supra-regional aortic rota will be a real disadvantage as the local non-aortic surgeon, now tasked with performing the lifesaving surgery, will be even less experienced than he or she would otherwise have been.

When it comes to dissection surgery, I don't believe that one size fits all. Surgeons appointed to our more isolated units need, in my opinion, to be prepared to step up to the mark and maintain their competencies in a broader range of emergency procedures than their colleagues in more densely populated parts of the UK where sub-specialisation is already occurring. To give our rural patients the best possible chances, aortic surgeons in such groups need to work collaboratively with their non-aortic colleagues to provide as much support as busy lives and commitments elsewhere allow. Most dissection patients are very well served by replacement of their ascending aorta with or without replacement of their root at the same time. A much smaller cohort of younger patients with extensive disease or connective tissue abnormalities probably do indeed do best under the care of an aortic specialist who might extend the operation to include surgery to the arch and proximal descending aorta. If surgeons in our bigger cities want to arrange themselves into ever more restrictive practices, developing innovative techniques and training our future colleagues in a fellowship, then this is to be applauded. Such centres will rightfully become referral hubs for thoracoabdominal operations and PEARS (Personalised External Aortic Root Support) procedures [6]. My strong contention, however, is that referral to such centres of every emergency dissection, root replacement and arch procedure in the country is not only unnecessary but probably dangerous for those patients coming from the further corners of our country.

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Editorial: Subspecialisation in Aortic Surgery: The Acute Type A Dissection On Call Rota – A Plan for the UK?

"Quot homines, tot sententiae"

Introduction

Acute Aortic Dissection was first described following the death of King George II in 1760 [1]. However, it was not until 7 July 1954, that the first successful surgery was performed to treat this lethal condition in Houston, Texas by DeBakey and colleagues [1]. Subsequently, DeBakey described classifications of acute aortic dissection based on the anatomical involvement of aorta [2] which was superseded by the commonly used, simplified Stanford classification [3]. It classified acute aortic dissection affecting the ascending aorta as Stanford Type A and that affecting the aorta distal to the left subclavian artery as Stanford Type B. The incidence of this life-threatening condition is 3-6 per 100,000 population in the UK and Iceland (4,5). If untreated, patients with Acute Type A Dissection (ATAD) face a devastating natural history with mortality of one percent per hour during the first 48 hours. Therefore, timely diagnosis and referral to a local cardiothoracic centre for emergency life-saving surgery is of paramount importance in effective management of this group of patients. Traditionally, once the patient is referred to a local cardiothoracic unit, the patient is then assessed and operated on by the on-call cardiothoracic or cardiac surgeon as an emergency. Postoperatively, patients are reviewed in the cardiac surgical out-patient clinic for a period of follow up and discharged to the care of a local cardiologist or general practitioner.

The Need for Change

Despite advancing knowledge of pathology and surgical technology, the mortality following surgery for ATAD remains high internationally. The UK Society for Cardiothoracic Surgery (SCTS) Blue Book (2004-2008) reported a surgical 30-day mortality of 22.8% [6], the Society of Thoracic Surgeons (STS) reported 21.6% mortality [7] and the International Registry of Acute Aortic Dissections (IRAD) reported 25.1% mortality [8]. The UK Cardiothoracic Trainees Research Collaborative studied the timing of surgery for ATAD across UK cardiothoracic units and found that there was a median time delay of 14.8 hours between and diagnosis and operation.

Moreover, it is well recognized that ATAD is a life-long disease with a natural history leading to subsequent complications in adjacent aortic segments and if not diagnosed and treated in a timely fashion leads to poor outcomes. As the disease process is recognised, it is accepted that the best way to manage these patients is by life-long surveillance in a multi-disciplinary team-based service, where all available treatment options can be considered and tailored for individual patients at various stages of disease progression. This has led to the concept of developing specialist thoracic aortic services supported by interdependent specialities and services, providing a comprehensive service to patients with aortic

pathology including emergency management of ATAD. In an attempt to improve outcomes in ATAD, the Liverpool Thoracic Aortic Aneurysm Service introduced an aortic emergency on call rota in 2007, where only cardiac surgeons with a specialist interest in aortic surgery perform emergency surgery for this group of patients. There was a significant reduction in mortality from 28.3% to 11.7% within a short duration. The introduction of this rota not only improved early outcomes but also improved 5-year survival [9]. It was followed by a further introduction of two dissection rotas streamlining services between 3 hospitals each in North West London and South London. The improvement in outcomes was reproducible. The introduction of these dissection rotas and the associated improvement in surgical outcomes for ATAD, has highlighted the weakness of the traditional system of surgical management where the on call cardiac or cardiothoracic surgeon (who may not have a routine aortic surgery practice or experience) normally performs surgery on this group of patients with highly complex aortic pathology in an emergency setting. It was apparent in an audit performed prior to the introduction of the dissection rota in Liverpool that some surgeons performed less than 1 operation per year for ATAD. The influence of surgeon and institutional volume on outcomes of surgery for ATAD was established, where surgeons with an average annual volume of <1 procedure had a mean operative mortality of 27.5%, compared with 17% for those with an average annual volume of 5 or more. Institutions with an annual volume of 3 or less had a mortality of 27.4% compared to 16.4% for those with an annual volume of 13 or more in the US [7].

Moreover, as the specialty has evolved into an era of subspecialisation in various areas, many cardiac/cardiothoracic surgeons do not perform a significant number of elective aortic surgical procedures. In a UK study, there was a lack of strong evidence relating surgeon caseload to outcomes in surgery of the ascending aorta and arch [10]. However, Andersen et al from Duke University Medical Centre demonstrated a significant improvement in outcome of management of ATAD by implementation of a high volume multidisciplinary thoracic aortic surgery programme in North Carolina [11]. Recent publication of surgeon volume-outcome relationships in the management of ATAD in the UK between April 2007 and March 2013 has revealed unpalatable truths [12]:

- the mean annual volume of procedures surgeons ranged from 1 to 6.6 with an overall in-hospital mortality rate of 18.3%.
- surgeons with a risk-adjusted mean annual volume < 4, had significantly higher in-hospital mortality rates in comparison to surgeons with a mean annual volume ≥ 4 (19.3% vs 12.6%; p = 0.015).

With this knowledge at hand, is it still acceptable to continue with the present model of care for ATAD patients in UK?

It is inarguable that to achieve a high probability of good outcome in this complex pathology, a surgeon must be well equipped with knowledge of all the possible options of cannulation to institute cardiopulmonary bypass with true lumen flow, knowledge of perioperative assessment, recognition, monitoring and treatment of end organ malperfusion, knowledge of various techniques of cerebral and spinal protection, surgical skills in aortic root and arch replacement including the hybrid Frozen Elephant Trunk technique, as well as perioperative and postoperative management. Such knowledge and skills can only be acquired and maintained by a focussed subspecialty aortic practice either individually or within a team. In 2017, treatment of ATAD cannot just focus on purely saving life by replacement of the ascending aorta while leaving a dissected aortic arch and root sinuses for future complex surgical treatment especially in young patients. The

primary treatment should also be designed to influence the natural history of the down-stream aorta with reduced life-long disease burden. Patients should be referred for genetic counselling and genetic testing to identify family members at risk as well as to guide the subsequent decisions in the management of residual dissected aorta.

While the medical community continues to debate and investigate the reasons why we cannot significantly reduce the mortality of ATAD, patients and family have united internationally to raise awareness with International Aortic Dissection Awareness day on 19th September in many cities all round the world. This international movement has been gaining momentum to improve knowledge and awareness of the general public through educational events and social media, and it has also been well supported by international experts in aortic surgery. It is clear that the need to change is now driven by both clinicians and the public alike.

Proposed Plan of Change for the UK

Now that we have seen the reason for change, the plan for change is tabled for further discussion. A drastic change is required to achieve a significant impact in an acceptable time frame. A one-size-fits-all approach may not be suitable for every individual cardiothoracic unit as smaller units with less manpower will find it difficult to run three (Cardiac, Aortic and Thoracic) emergency rotas. However, it is the duty and responsibility of all individual units to commit to improve their outcomes in ATAD by the implementation of change in their service delivery model. It has already been proven that a simple reorganisation of service delivery in each unit or each group of units is all that is required to improve outcomes in ATAD.

This reorganisation needs to be moved forward in a bottom up manner through the local and regional clinical networks of care for cardiovascular diseases. The involvement of medical and administrative leads in STPs (Sustainable and Transformation Partnerships) is important and should be adopted as one of the KPIs (Key Performance Indicators) for each network of care. This will lead to a formation of a local or regional taskforce committee where all stakeholders and interdependent specialties can discuss a plan to implement change by reorganisation of services to save lives.

There should be a local solution for this national plan as the geographical location of cardiothoracic units in each region is somewhat unique and requires careful consideration of the logistical issues the emergency services will face. However, this issue must not be the obstacle in the way of change as the reorganisation of major trauma care and primary percutaneous coronary intervention services were implemented in a not too dissimilar fashion. Therefore, individual unit's clinical representatives with a corresponding administrative lead in each NHS region must meet to explore local plans for improvement of outcomes in ATAD. Once it is implemented, the additional benefits from reorganisation will be numerous in the way of clinical audit, collaborative research, training and effective support of patients and family.

We must listen to our patients and families. We must open our eyes to the evidence. We must prepare to change. We must take charge of the process of reorganisation in developing Acute Type A Dissection On Call Rotas to improve outcomes of this patient group.

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Section 2

Thoracic Surgery

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Chapter 11

Improving Perioperative Outcomes - Prehabilitation

Tim JP Batchelor

"Lege totum si vis scrire totum"

Introduction

Surgery for lung cancer involves the removal of functional lung tissue. It is also associated with significant homeostatic disturbance and a surgical stress response characterised by catabolism and increased oxygen demand [1, 2]. The extent of lung resection is an important factor in determining the risk of postoperative morbidity and mortality and central to all guidelines on determining fitness for surgery. The importance of the stress response to surgery, however, is less appreciated. It is proportionate to the magnitude of surgery, and a greater stress response is associated with an increased risk of developing postoperative complications [1].

Patients who experience postoperative complications have a longer hospital stay. Their long-term survival is also reduced, and this effect is more pronounced for more serious complications [3]. Quality of life appears to be affected by the length of hospital stay rather than the complication itself [4].

Poorer pre-operative exercise capacity is associated with worse long- and short-term clinical outcomes including postoperative complications, length of stay and survival following curative lung cancer surgery [5–8].

Only 16.8% of patients with a diagnosis of lung cancer undergo surgical resection in the UK [9]. Many patients present late with advanced disease and are therefore not eligible for surgical intervention. However, only 55% of patients with early stage disease (I-II) undergo surgery. In this group, the reasons for denying surgery are likely to be multifactorial and may include lack of fitness, poor performance status, poor lung function, other comorbidities, and inequity in access to thoracic surgical services.

Addressing the fitness of patients with lung cancer at the time of diagnosis may have two potential benefits. Firstly, those patients previously deemed fit for surgery may have improved outcomes both in hospital and in the long term. Secondly, those patients with early stage disease but initially deemed unfit for surgery may be able to have a number of preoperative interventions to improve their fitness, enabling them to proceed with a lung resection.

Historically, there have been limited efforts to improve patients' fitness for surgery. Measures to improve outcomes initially focused on improvement of surgical and anaesthetic techniques (led by surgeons and anaesthetists respectively). More recently, enhanced recovery after surgery (ERAS) pathways have addressed the patient pathway from admission through to discharge – multiple small improvements and efficiencies along the entire pathway, adopted in an evidence-based manner by a multi-disciplinary team, appear to accelerate recovery and reduce the length of hospital stay (the so-called "aggregation of marginal gains"). There is now a growing realisation that identifying modifiable risk factors such as smoking, poor nutrition and poor exercise capacity at the earliest possible stage, and certainly well before hospital admission, may not only improve outcomes but also increase the pool of patients eligible for radical cancer treatment.

The role of ERAS pathways in surgery have sometimes been compared to the preparation required for running a marathon [10]. The stress response of surgery is not dissimilar to the effects of running a marathon on the human body. In the same way that an athlete would not fast in preparation for a race, a patient should not starve from the day before their surgery. Similarly, no sane person would contemplate running a marathon without training to improve cardiac and respiratory fitness as well as muscle conditioning. The corollary in surgery is prehabilitation.

Definition and elements of prehabilitation

Preoperative physical conditioning, or prehabilitation, is the process of enhancing the functional and physiological capacity of an individual to enable them to withstand a stressful event, and may aid recovery after surgery [11].

There are four main components to prehabilitation:

- Patient education,
- Nutritional assessment and optimization,
- Smoking cessation,
- Pulmonary rehabilitation.

In colorectal surgery, prehabilitation is more effective than postoperative rehabilitation in returning a patient to baseline function [12]. Patients with poor physical capacity have the most to gain.

Prehabilitation is a proactive approach to care that enables patients to become active participants. Patients are engaged to take control of their health at a difficult time. In non-thoracic specialities, exercise in preparation for surgery is associated with a lower postoperative complication rate and earlier restoration of functional status [12, 13]. Most interventions in ERAS pathways attempt to reduce the stress response on the body. Prehabilitation would appear to work in the same way, although the exact mechanisms by which physical conditioning affects the stress response are not well established.

Patient education

Preoperative counselling is not only a vital component of prehabilitation but of ERAS pathways generally. Education helps to manage patient expectations regarding surgical and anaesthetic procedures, and also with regards to length of hospital stay. If a patient is told they should be fit for discharge on the fourth postoperative day, this will help motivate them towards this goal. Similarly, positive counselling about fitness for surgery, smoking cessation and nutrition may improve outcomes.

Patient education is a means to diminish fear, fatigue and pain. It may also enhance recovery and promote early discharge [14]. Oral education, leaflets, and multimedia information containing explanations of the procedure and cognitive interventions may improve pain control, nausea and anxiety after surgery and general anaesthesia [15, 16]. Patient empowerment through diary keeping also appears to improve post-operative pain control [17]. Similar results have been demonstrated in patients provided with pre-operative video information prior to lung resection [18].

In summary, although high quality evidence is lacking, most studies show that counselling provides beneficial effects with no evidence of harm. In particular, pain control appears better following lung resection.

Smoking cessation

Smoking is associated with a high risk of postoperative complications. 70% of patients with lung cancer will have COPD [19]. The GOLD guidelines on managing COPD are remarkably similar to the elements of prehabilitation [20]:

- Smoking cessation is vital.
- Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.
- Nutritional supplementation for malnourished patients is recommended.

Smoking cessation is one of the most cost-effective ways of managing COPD [21]. The pulmonary effects of smoking can be improved within four weeks of stopping [22]. An early study indicated that current smokers are twice as likely to experience postoperative pulmonary complications after lung resection surgery than non-smokers or those who had not smoked for more than 4 weeks [23]. Paradoxically, the same study appeared to show that patients who had stopped smoking within 4 weeks of surgery (recent quitters) had an increased incidence of pulmonary complications than current smokers. The recommendation was that preoperative smoking abstinence of at least 4 weeks is necessary prior to admission for lung resection. Some physicians interpreted this advice in a different way –patients were advised to carry on smoking rather than risk an increased incidence of pulmonary complications. This approach has been criticised for sending out the wrong healthcare message at a teachable moment in the patient journey. Thankfully, further studies could not corroborate this paradoxical effect [24, 25]. They confirmed that smoking increased the risks of hospital death and pulmonary complications after lung cancer resection, but these risks were mitigated slowly by preoperative cessation.

More recent experience from Salamanca in Spain has shown no influence of recent smoking cessation on postoperative pulmonary outcomes [26]. Their overall incidence was an extremely low 3.7% and 4.5% in recent quitters and current smokers respectively. The other studies mentioned previously demonstrate an incidence of around 20% (and half that in non-smokers) indicating that the preoperative preparation of the patient and the postoperative regime in Salamanca is extremely effective in managing perioperative lung health.

Continued smoking at the time of lung cancer surgery is associated with poor post-operative quality of life and fatigue [27]. It also appears to reduce long-term survival [28].

In summary, smoking is associated with an increased risk of postoperative morbidity (especially pulmonary complications) and mortality. While no optimal interval for smoking cessation can be identified, patients should be counselled to stop smoking irrespective of surgical timing and ideally should stop at least four weeks before surgery.

Nutrition

Nutritional components of ERAS include avoiding of fasting on the day of surgery, carbohydrate loading 2 hours prior to induction, and early recommencement of oral diet as well as oral nutrition supplements (ONS) [29,30]. Preoperative malnutrition and low body mass index (BMI) are potentially modifiable risk factors that can be addressed to protect against adverse outcomes after major surgery.

In recent thoracic surgical studies, including large national database studies from France and the USA, malnutrition and/or weight loss were identified as important risk factors for complications after surgery [31, 32]. A BMI of less than 18.5 was associated with an increased risk of mortality (OR 1.89-2.96) and an increased risk of pulmonary complications.

It is not clear whether modifying or optimising perioperative nutritional state results in a reduction in complications. In rehabilitation programmes for chronic obstructive

pulmonary disease (COPD), ONS are recommended and improve patients' quality of life and muscle function [33]. In addition, malnutrition and a loss of muscle mass are frequent in cancer patients and can have a negative effect on clinical outcome. In abdominal surgery, the routine use of pre- and/or postoperative ONS may reduce postoperative weight loss, improve nutritional status and muscle strength and reduce complication rates [34–37]. Evidence in thoracic surgery is currently lacking.

Immune-enhancing nutrition (IEN) has shown some promise over standard ONS. Although a recent meta-analysis in abdominal surgery did not show any benefit of preoperative immune-enhancing nutrition over standard ONS, postoperative IEN may improve outcomes, particularly in patients with pre-existing malnutrition [37, 38]. Whether these findings are applicable in lung resection patients is not clear. There has only been one small study. Patients were randomised to receive preoperative IEN or normal diet. Immune-enhancing nutrition was not compared to standard ONS. There were benefits in terms of a reduced complication rate, but this was mainly due to a difference in air leak [39].

Nutritional screening should be performed routinely on all patients undergoing thoracic surgery. Screening tools include the Nutritional Risk Score (NRS), the Malnutrition Universal Screening Tool (MUST) and the Subjective Global Assessment (SGA) tool [30, 40]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend delaying surgery to allow for preoperative enteral nutrition in patients with at least one of the following criteria:

- weight loss >10–15 % within 6 months
- BMI < 18.5 kg/m2
- serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction) [40].

As the guidelines suggest that only 7 to 14 days of ONS is required before surgery in patients, delays in cancer treatment should not be significant and may result in improved outcomes.

Pulmonary rehabilitation

Physical inactivity is common in patients with lung cancer. Only a third meet current recommended activity levels. Indeed, activity levels in lung cancer patients appear to be lower than healthy age-matched controls. One explanation is that these patients tend to come from a demographic that have led sedentary lifestyles for a large proportion of their lives. At the same time, fatigue and weight loss as a result of the disease itself can come to bear.

Poorer pre-operative exercise capacity is associated with worse long- and short-term clinical outcomes including postoperative complications and length of stay [6, 8]. There is now evidence that it impacts on long-term survival following curative lung cancer surgery [5, 7, 41]. The obvious question, therefore, is whether health outcomes can be improved by intervening to improve physical fitness.

Several recent systematic reviews, a meta-analysis and a Cochrane review have concluded that prehabilitation is beneficial [42–45]. There was much heterogeneity between studies. Consequently, the exact duration, intensity, structure, and patient selection required to achieve maximum efficacy has yet to be defined. Preoperative interventions are usually delivered in the outpatient setting or in a training facility. Prescribed exercises included

aerobic training (lower and/or upper limbs) with the addition of strength training in some studies. Respiratory exercises were also included in the majority of studies.

Fitness, as measured by peak oxygen consumption (VO_2max), improves significantly in patients with potentially operable lung cancer subjected to pulmonary rehabilitation programmes before surgery [46–48]. In one study, medically inoperable patients became operable over a 4-week period (VO_2max improved from 12.9 to 19.2 ml/kg/min) [47]. In another study, those patients randomised to preoperative high intensity training before lobectomy experienced levels of postoperative fitness comparable to baseline while those in the control arm were significantly impaired [48].

Arguably, it is improvements in postoperative outcomes that are more important than improvements in physiological measures. Hospital length of stay (LOS) and morbidity were reduced in comparison with standard care in a recent meta-analysis and in a current Cochrane review [[42, 45]. There was also a significant reduction in postoperative pulmonary complications. The effect on pulmonary complications seems to be most important in patients with poor preoperative lung function.

VO_2 max and long-term survival

Peak oxygen consumption is not only a preoperative measure used to determine fitness for surgery. It is also a strong independent predictor of long-term survival in lung cancer patients [7]. In one observational study in patients with early lung cancer undergoing lobectomy or segmentectomy, a VO_2 max of greater than 60% of predicted was associated with a near doubling of the 5-year survival probability compared to a VO_2 max of less than 60% [5].

Other measures derived from cardiopulmonary exercise testing may discriminate further. The ventilatory efficiency slope (VE/VCO_2) shows promise. In one study, a value of greater than 35 was associated with a one-year survival probability of only 40% compared to 80% if the VE/VCO_2 was below 35 [41].

Summary

Prehabilitation is an umbrella term for a number of low-tech preoperative interventions. It aims to improve fitness for surgery while engaging the patient in their care. There are two target populations of patient. Firstly, those patients already fit for surgery should experience better postoperative outcomes. The mechanisms remain unclear but it is likely that a reduced surgical stress response is important. Secondly, those patients initially deemed unfit for surgery may become fit enough for treatment. Consequently, surgical resection rates may improve. Prehabilitation may also improve compliance with other lung cancer treatments (such as chemotherapy and radiotherapy). Intriguingly, it may also improve long-term cancer survival.

Much work still needs to be done to truly define the role of prehabilitation interventions within an ERAS pathway. The components are yet to be fully defined. In particular, preoperative exercise programmes have yet to be standardised in this patient population. The effects of prehabilitation on both short- and long-term outcomes following lung cancer surgery merit further study in high quality randomised trials.

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Chapter 12

Innovation in an Era of Surgeon Specific Outcomes

Robert J Cerfolio

"Nondum omnium dierum sol occidit"

Introduction

Innovation is defined as the action of bringing new ideas or products to an established market or process. Importantly, we believe it is to make the process more efficient, better, or profitable. Innovation today in medicine is drastically different than it was just 50 years ago mainly because of regulations, the intent of which is to protect patients but, in reality, most commonly add to costs and slow down the pathway to implement positive innovation. We believe the single most important change is to eliminate much of the administrative and legal red tape that provides little to no value.

Perspective

In 1953, Michael E. DeBakey thought that a nylon artificial arterial graft would be a suitable material to help shunt or direct blood from one diseased or blocked artery to another. Because of limited regulations then, as opposed to now, he went to a nearby department store and was told they had run out of nylon so he purchased Dacron instead. The next morning, he sewed a few pieces of the Dacron together on his mother's sewing machine and later that day sewed it into a patient. His process of innovation took two days to go from idea to patient implantation - today it would have taken over ten years most likely. This is the major disadvantage of today's regulation but there are advantages as well. If the store had what DeBakey really wanted, nylon instead of Dacron, the patient's results would have been worse since the former tends to be less durable.

There are pluses and minuses to our current system. The pluses are that patient safety is paramount but new disruptive ideas that have the chance to save millions of patients' lives take years to come to the bedside and meanwhile thousands of patients die or have morbidity. In the business world, innovators quickly die or become millionaires, in medicine innovators often have to partner with industry and wait years for their ideas to become reality. And then there is usually little capital left for the initial generator of the idea, and this further disincentivises innovation in medicine.

In 2003, we had an idea. We theorised that if we could close the ribs and avoid trapping, crushing or injuring the intercostal nerve, we could reduce the pain of thoracotomy

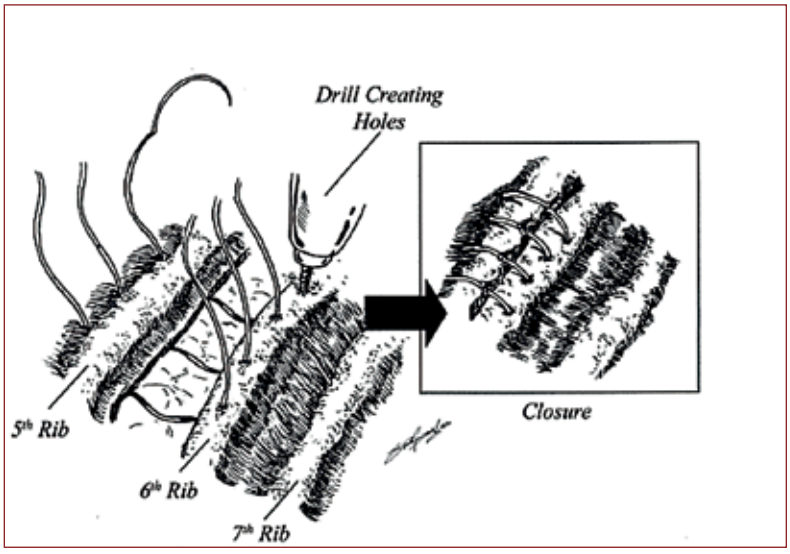


Figure 1: This shows how the sutures were placed in the group of patients who received intracostal sutures.

(Figure 1). Although others may have thought of this type of idea before, we were unaware of these few case reports. We went ahead and performed three prospective randomized trials. In the first trial titled, Intracostal sutures decrease the pain of thoracotomy [1] we showed improvement in pain score at 2 weeks, 1 month, 2 months, and 3 months after thoracotomy. This idea of drilling holes in the inferior rib and preventing sutures from compressing the intercostal nerve as the thoracotomy was closed was shown to decrease pain.

In the second paper from 2005 titled, Intercostal muscle flap reduces the pain of thoracotomy: a prospective randomized trial [2] , we showed that patients who underwent thoracotomy with intercostal muscle harvested from the lower rib had less pain as shown in figure 2. The concept of this study was that if we could avoid crushing the inferior intercostal nerve with the chest retractor, we could reduce pain. We found that pain was less at 1, 2, 3, 4, 8, and 12 weeks postoperatively and patients were less likely to be using narcotics compared to patients who had a standard posterolateral thoracotomy.

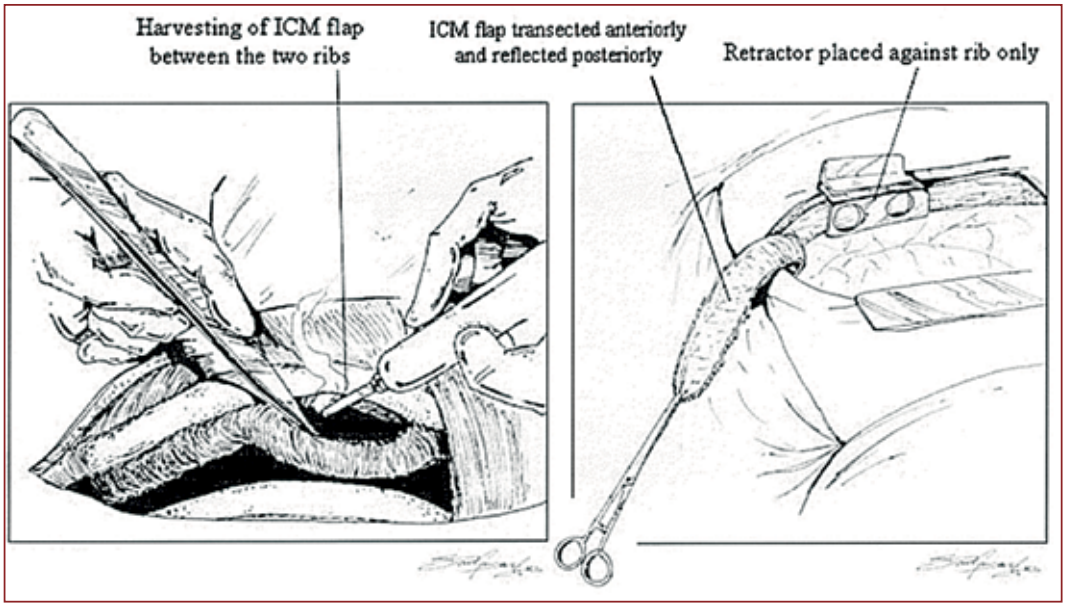


Figure 2: Intercostal muscle(ICM) flap

In 2008, we conducted out third study on the same idea, A non-divided intercostal muscle flap further reduces pain of thoracotomy: a prospective randomized trial (3) . In this study, we showed that patients with an intact intercostal muscle flap (it was not cut distally as shown in figure 3) had less pain compared to patients who had their intercostal muscle divided distally at weeks 3, 4, 8, and 12 postoperatively with a faster return to baseline activity and less need for analgesics.

These three studies above were all based on the spirit of innovation, on a single idea that decreasing injury to the intercostal nerve in any way would decrease the pain of thoracotomy. Yet, these "new techniques" did not risk patients' outcomes and were a mere modification of existing methods. New disruptive technology, like robotic surgery which adds a necessary learning curve during which patients may be injured is a different type of clinical research. Today, how do we add these techniques to our practice which have the chance to improve patients' outcomes but on the way may injure other patients?

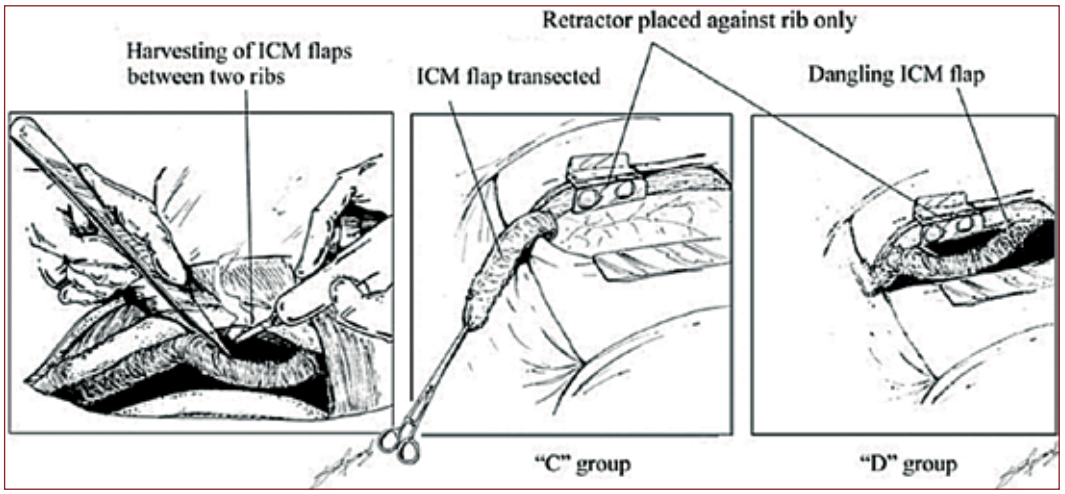


Figure 3: Drawings show the technique of creating an intracostal muscle (ICM) flap. The middle panel shows the group with the intercostal muscle flap cut ("C group"), and the right panel shows the ICM dangling ("D group").

Moreover, how do we ethically do this? And how do we do it in an era when we have to report every minor morbidity we incur, consent every patient with our experience or lack of experience? The answer is in four ways: Definitions / Metrics / Experienced Teams / Standardized training through medical societies.

First, we need definitions and nomenclatures. We cannot teach or credential that which we cannot define. The second is the selection of the appropriate metrics. We cannot measure or objectify quality or competency until we define each metric we use that serves as a surrogate of it. We must ensure that these are the best metrics of true quality and not imposters as many use today. Third, not everyone can or should try to innovate, only those with the appropriate team, volume, experience and support. Fourth, once we have shown safety in small isolated series we must roll out standardized pathways to establish competency via surgical societies that run courses or training pathways.

We should have one goal: safe and responsible surgeons or healthcare providers who provide high quality outcomes to their patients and know when to apply the technology and when to convert to more standard techniques. The pathway is different for fellows and residents than it is for those already in practice but the endpoint is the same.

Definitions and Nomenclature

In 2017, we reported a nomenclature [4] that defines exactly what is a thoracic robotic operation, how they can be done and what makes it completely portal versus robotic-assisted. There terms are needed to ensure we a comparing the same operation across the world. It is described later in greater detail in Chapter 14.

Training

The optimal way to train residents is in a standardized fashion with measured benchmarks and metrics of competency. When new technology is added such as robotics, we believe it is up to the surgical societies to define the optimal pathway for credentialing. They are the only true stakeholder in this process that does not have a financial bias unlike the

hospital, the payers, the surgeon or industry. The process must include appropriate patient selection and avoid bias. In 2013, The American Association of Thoracic Surgeon (AATS) approach us via the Graham Foundation. We outlined a specific pathway for credentialing for residents and fellows. First, you need to identify surgical champions who believe in the new technology or procedure, who honestly think it helps patients and improves their outcomes and have found a way to set up a program at their own institutions. This is critical because we cannot train surgeons over a weekend course for many of these skills. They have to go back home and have their skills further refined with local mentors repeatedly in the operating room. So, we identified a few of these champions in training programs. We required that they had performed at least 20 robotic pulmonary operations with acceptable outcomes and operative times. We then set up an application process where fellows applied but we chose the institution not the fellows. This is because we needed the fellows to be able to go back home when the course ended and do more operations under supervision. Some outstanding programs did not get their fellows accepted in the first year or two or even now in our fourth year because they lacked a champion doing high quality robotic surgery at their training program / hospital and we did not think we could train them in a two-day course three times a year. You have to have qualified mentors in your home institution.

Once a training program and their fellow was accepted we then required the fellow and his mentor (the attending at their home hospital) to travel to training centers where myself for year 1 and 2 and now two other faculty members for years 3 and 4 trained them. We used metrics to report everything from their number of camera clutches to their ability to perform certain parts of the operation. The training was standardized in a granular manner. The course was a two-day course, one day of didactics and one day of cadaveric training. Importantly we train teams not surgeons. So, we trained the residents, the attending and if their bedside physician assistant was available, we wanted to train him or her as well. Teams win the day, not individuals. Once the course ended we tracked the number of cases the fellows performed and what parts of the operation they did as well as the patient's outcome.

The above framework is one example of a way to add technology and make sure patient outcomes are good in an era where outcomes are so carefully monitored. This AATS Graham Robotic Fellowship Training Program has now grown from 10 to 20 to 30 and now to 34 fellows and many programs in the United States. We are now in the process of adding international programs.

Training Those Out of Training

The next question is how you do this with practicing surgeons who are not in an academic setting and in private practice but fully trained and quality independent surgeons. This is a more difficult task but a similar technique can be used via training courses. Once completed, very specific metrics can be measured to ensure that surgeons are performing these techniques with safe and good outcomes at home. The ability to honestly and publicly measure and report these outcomes remains an elusive goal in the United States and in other countries but is critical as described below.

Once a pathway has been set as to how to train all surgeons, we must then find a way to measure the value of the operation using this new technology. We have written a lot about value recently [5] and it depends on whose vantage point we take: the patient, the hospital, or the surgeon. If we only consider the patient's point of view, you cannot go wrong.

Value = quality / cost

Thus, we must find a way to measure quality over time and not just in the standard myopic currently used 30 and 90-day metrics. With the addition of technology there is always - ALWAYS - cost and time and these must be measured if we are to show improved patient value. At New York University Langone Health, via our Operating Room (OR) Efficiency Team, we measure the following metrics.

Metrics

Many teams measure operating room utilization which is an example of exactly the wrong metric to measure when drilled down to one surgeon. The amount generated per operating room minute is a better quality but that measures speed and/or efficiency, not quality.

Few metrics actually measure quality surgery. We can measure speed and / or other metrics per OR minute such as: charges, collections, profit margin, etc. Perhaps the most egalitarian metric for surgeons from one department to be compared to surgeons in another is the federal allotted Relative Value Unit or RVU used in the United States. Although we have argued that the RVU system has many inherent injustices and inaccuracies, it is the most commonly used financial metric adopted by most hospital systems in the United State and therefore familiar to most surgeons. It eliminates the bias of the payer mix. The RVU per operating room minute affords the comparison across different operations and across surgical departments. This is the defined by the equation:

RVU per operation / Operative time in minutes

However, this only measures operative speed and again is not a good reflection of quality or value. If the surgeon is very fast but every patient bleeds and has to go back to the operating room this is not value. Speed without high quality is of no value. When we add new technology like robotics, speed falls at first and capital cost rises. So, we need to add a quality qualifier. Therefore, we have developed the metric of surgical quality index. The surgery quality index score can be measured in many ways. It can be the addition of a few simple metrics or it can be a composite of a more complex set of outcomes such as some of the ones we choose to use for pulmonary lobectomy in our thoracic division:

1) Time to see patients once they call the office.
2) Protocol adherence to preoperative clinic tests such as staging tests for patients with lung cancer.
3) Intra-op metrics such as obtaining an R0 resection.
4) The removal of at least 5 level N2 and 2 level N1 lymph nodes for lung cancer resections.
5) A total lymph node count of least 17 lymph nodes for right-sided operations and 13 for left.
6) Actual blood loss.
7) Surgeon behavior scores from team members in the operating room based on quarterly surveys.
8) Surgeon behavior scores from team members on the floor based on quarterly surveys.
9) Patient length of stay.
10) Patient pain scores at 1, 2 and 3 weeks post-operatively.
11) Patient 30-day readmission rate.
12) Patient quality of life scores at 1, 2 and 3 weeks.
13) Most importantly, the stage specific 5-year survival rate at 1, 2, 3, 4 and 5 years.

Table 1: The recorded sequential steps of each lobectomy (in order of conduct) and allotted time to be completed

Step no.	Description	RUL	RML	RLL	LUL	LLL	Time (min)
1	Mark out ports on skin	Same	Same	Same	Same	Same	2
2	Place ports	Same	Same	Same	Same	Same	9
3	Inspect pleura	Same	Same	Same	Same	Same	1
4	Resect inferior pulmonary ligament	Same	Same	Same	Same	Same	2
5	Remove LNs 9, 8, 7	Same	Same	Same	Same	Same	7
6	Identify RUL and RLL bronchus posteriorly	Same	Skip this step	Same	Remove 10L LN off PA	Same	5
7	Divide fissure between RUL and RLL	Same	Between RUL and RML	Same	Divide fissure between LUL / LLL	Divide fissure between LUL / LLL	10
8	Remove LNs 2R and 4R	Same	Same	Same	#5, #6	#5, #6	7
9	Retract the lung with robotic arm 3	Same	Same	Same	Same	Same	1
10	Remove 10R LN under azygous vein	Same	Same	Same	11L off PA and LMSB	11L off PA and LMSB	1
11	Identify and dissect PA arterial branches	Same	Same	Same	Same	Same	10
12	Identify and dissect PV	Same	Same	Same	Same	Same	5
13	Encircle PV	Same	Same	Same	Same	Same	2
14	Encircle PA	Same	Same	Same	Same	Same	2
15	Guide stapler under PA branches	Same	Same	Same	Same	Same	1
16	Guide stapler under pulmonary vein	Same	Same	Same	Same	Same	1
17	Encircle bronchus, guide stapler	Same	Same	Same	Same	Same	1
18	Divide remaining fissure	Same	Same	Same	Same	Same	10
19	Bag specimen	Same	Same	Same	Same	Same	3

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, lymph node; PA, pulmonary artery; LMSB, left main stem bronchus; PV, pulmonary vein

Table 2: Teaching outcomes for lobectomy training

Steps performed	Brief description of steps % perform by resident	Patient 0-100 % perform by resident	Patient 101-200 % perform by resident	Patient 201-300 % perform by resident	Patient 301-400 % perform by resident	Patient 401-520 % perform by resident
Dates		2/2010-3/2011	3/2011-4/2012	4/2012-9/2013	9/2013-10/2014	10/2014-12/2015
Steps 1-5	Ports, ligament, inferior N2 LNs	NR/50%	20%/70%	60%/70%	70%/90%	80%/90%
Steps 6-7	Post bronchus and fissure	NR/NR	0%/20%	0%/10%	30%/50%	20%/60%
Step 8	Superior N2 LN	30%/50%	60%/75%	80%/100%	100%/100%	90%/100%
Step 9	Retract lung	NR/NR	NR/NR	0%/15%	30%/40%	0%/20%
Steps 10-12	N1 LN, dissect out PA	0%/10%	0%/60%	20%/50%	50%/60%	40%/70%
Steps 13-14	Encircle PV and/or PA	0%/0%	10%/30%	30%/70%	30%/70%	40%/80%
Steps 15-16	Staple PA and/or PV	NR/NR	NR/NR	0%/0%	10%/30%	20%/60%
Step 17	Bronchus	NR/NR	40%/50%	30%/70%	70%/80%	80%/95%
Step 18	Remaining fissure	NR/NR	NR/NR	0%/0%	30%/70%	50%/70%
Step 19	Bagging	15%/40%	30%/50%	70%/90%	90%/100%	90%/100%

LN, Lymph node; NR, not recorded; PA, pulmonary artery; PV, pulmonary vein

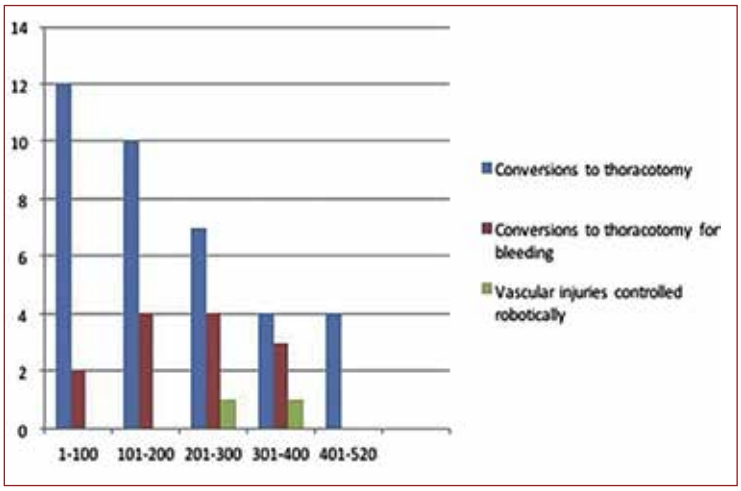


Figure 4: Total robotic lobectomies performed with incidence of all conversions and those from bleeding from major vascular injuries (N=520)

Table 3: Patients Outcomes from Robotic Lobectomy

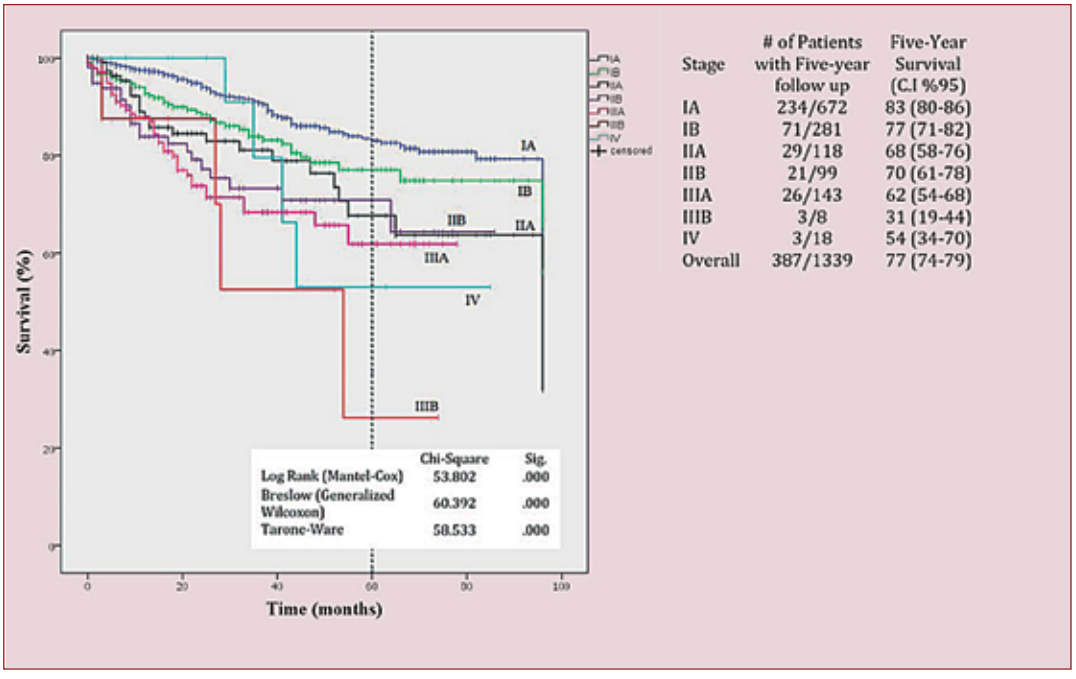
Metrics	Patient 0-100	Patient 101-200	Patient 201-300	Patient 301-400	Patient 401-520
Median operative time (skin-to-skin), min	195	160	144	123	126
Median blood loss (range), mL	35 (15-100)	39 (10-3000)	37 (10-650)	43 (10-400)	47 (10-750)
Median No. of LNs removed (range)	21 (12-25)	21 (12-31)	23 (13-43)	24 (10-34)	24 (10-66)
Median No. of N2 LN stations resected	5	5	5	5	5
Median No. of N1 LN stations resected	3	3	3	3	3
Conversion to thoracotomy	12%	10%	7%	4%	3.3%
Major vascular injury	2%	4%	4%	3%	0%
Transfusion in OR	0	0	1%	0	0
Median length of stay (range), d	3 (1-42)	3 (2-12)	3 (1-21)	3 (1-11)	3 (2-11)
Morbidity of any type	50%	45%	12%	14%	4.2%
Major morbidity	16%	16%	5%	6%	2.5%
30-d mortality	0	0	1%	0	0
90-d mortality	0	0	2%	0	0.83%

These are not just intra-operative quality indices but ones that also should be measured when new technology is added. This is the only way to assess true value. The quality index is added to the ratio of RVU/OR minute and this finally gets to the desired goal of quantified value. When measured together we have coined the term, the *Surgeon's Efficiency and Quality Index* or the SEQI:

"Surgeon's Efficiency Quality Index" SEQI = (RVU per operation / Operative time in minutes) x Quality index score

This allows for the efficiency of an operation to be assessed as well as its quality and this finally gets to our desired goal of value comparisons. As the surgeon learns robotics or any new technology these must be compared to the old numbers if the same patients could be treated in this way.

Once we can finally measure quality the next question is can we maintain it while we are teaching our fellows and residents? In 2016, we published a paper titled 'Robotic lobectomy can be taught while maintaining quality patient outcomes' [6]. In that study, we reported how we divided robotic surgery into 19 steps and allowed residents and fellows to participate in each step under time constraints (Table 1). We finished the steps if they could not do so in the allotted time and then allowed them to start the next one. This allowed them to do parts of all 19 steps of the operation. As shown in Table 2, the percentage of successful steps completed over the allotted time per resident increased as experience increased.



Stage	# of Patients with Five-year follow up	Five-Year Survival (C.I %95)
IA	234/672	83 (80-86)
IB	71/281	77 (71-82)
IIA	29/118	68 (58-76)
IIB	21/99	70 (61-78)
IIIA	26/143	62 (54-68)
IIIB	3/8	31 (19-44)
IV	3/18	54 (34-70)
Overall	387/1339	77 (74-79)

Figure 4: Stage-specific survival for non–small cell lung cancer after robotic lobectomy. CI, Confidence interval.

Most importantly, as we allowed the residents and fellows to perform even more of the operation our quality improved as shown in Figure 4 and Table 3 – the incidence of conversion to thoracotomy and major vascular injuries both decreased. Now, as of November 2017, we have performed over 1720 robotic operations and over 1000 robotic pulmonary resections with only one 90-day mortality. We can perform a robotic lobectomy in about 1.5 hours skin-to-skin, with a median blood loss of 20 cc, with only 1 patient who needed a blood transfusion and with only one 30 and 90-day mortality.

Yet the most important quality metric for a cancer operation is the stage-specific survival. In October of 2017, we reported one of the highest survivals for stage for non-small cell lung cancer as shown in Figure 4.

Summary

New technology can and must be safely implemented into our practices or we are not progressing and getting better. When a surgeon says, "we do it the same way every day" then he or she is not evolving nor is their patient getting better care over time. Standardization of course has advantages and having a process that we implement day after day to prevent errors of omission is good and a part of 'lean'. However, the optimal ratio of standardisation and innovation, or of improvisation and scripted, is the paradox that we all as innovators strive to maximise to increase value. As we evolve and innovate, however, we must maintain great patient outcomes.

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Chapter 13

Oncological Outcomes after Video-Assisted Thoracoscopic Surgery Resections

Robin Wotton, Michael Shackcloth

"Medicus curat, natura sanat"

Introduction

The procedure of video assisted thoracoscopic surgery (VATS) lobectomy was first described in the early 1990's [1–4]. The technique offered thoracic surgeons an alternative approach to traditional thoracotomy. Although the initial worldwide uptake of this new approach was slow, more recently the adoption of minimally invasive pulmonary resection has rapidly gathered pace. The definition of VATS lobectomy was published in 2007, highlighting the need for true anatomical dissection and division of broncho-vascular structures [5]. A standardised VATS operation includes an anatomical division of lobar structures, hilar lymph node dissection or sampling using one, two or three ports, and no retractor use or rib spreading. These principles can be implemented using either a posterior or anterior approach to the hilar structures and hence the names derived for the two techniques, anterior and posterior VATS lobectomy. With the standardisation of VATS lobectomy, uptake of this technique by institutions around the world has increased exponentially. Large case series from single institutions have been published [6,7], whilst rates of VATS lobectomy within single units are reported as high as 70-80 % of cases performed [8, 9].

Comparative evidence of the benefits of VATS lobectomy over thoracotomy has also been steadily increasing. Reported benefits include shorter length of stay [5-7, 10], reduced post-operative pain [11, 12], improved pulmonary function [13, 14] and improved delivery of adjuvant chemotherapy [15, 16]. Cost effectiveness of thoracoscopic lobectomy over traditional thoracotomy has also been shown [17, 18]. More recently, several studies including large single institution studies, multi-institutional registries and meta-analyses have demonstrated the operative safety of VATS lobectomy in addition to those advantages already described [19-22]. This culminated in the publication of a consensus statement from world experts in VATS lobectomy establishing a standardised practice [23].

Despite the mounting evidence from both the UK and US, take up of the procedure remains modest with only 43% (2013-14 UK data) [24] and 44% (2010 USA data) [25] of lobectomies being performed minimally invasively. So why has adoption of VATS lobectomy been so slow? Several reasons have been proposed, including the belief that bleeding cannot be controlled thoracoscopically, difficulty in training of pre-VATS era surgeons and the steep learning curve making the transition from open to thoracoscopic procedure unachievable. However, one of the major criticisms of performing VATS lobectomy is the perceived inferior oncological efficacy of VATS for early stage non-small cell lung cancer (NSCLC). Uptake of VATS lobectomy appears to be still hampered by the view that lymph node dissection is inadequate, thus providing an inferior oncologic operation to that performed by thoracotomy.

Lymph node evaluation

Concerns that an adequate lymph node assessment cannot be achieved by a minimally invasive approach have hindered uptake of VATS lobectomy across the world. It is believed that the number of lymph node stations and number of lymph nodes dissected or sampled during VATS is lower than at thoracotomy and this may adversely affect survival. This is despite comparable, and even superior short and mid-term survival rates of VATS over open lobectomy [6, 26].

So, does a VATS technique impact on lymph node analysis when compared to an open procedure? Several studies, including retrospective and propensity-matched studies, have shown that a smaller number of lymph nodes are removed when comparing VATS

lobectomy to open lobectomy [22, 27-29]. The reduction in number was statistically significant in two studies [27, 29], whilst the other two reported a non-significant trend of fewer lymph nodes in the VATS group [22, 28]. This evidence is however not supported by data from the Danish Lung Cancer Registry which showed that the number of lymph node stations sampled was not statistically different whether the patient underwent lobectomy via VATS or thoracotomy [30].

The detection of lymph node metastases during evaluation of surgical specimens provides important information regarding prognosis and influences the post-operative requirement for adjuvant therapy. This in turn influences survival. Detection of unsuspected lymph node metastases in clinical stage I NSCLC depends on an adequate lymph node dissection or station sampling. Opponents of VATS resections present the argument that using a minimally invasive technique does not allow as thorough a lymph node station dissection as at thoracotomy. This is however unjustified as thoracoscopic radical mediastinal lymph node dissection has been shown to be technically feasible and safe [31, 32].

Nodal upstaging

Opponents to minimally invasive lobectomy argue that VATS conveys an inferior lymph node assessment and hence results in fewer patients being upstaged after pathological analysis of the resected specimens. This viewpoint is supported in the literature despite the evidence demonstrating the efficacy of lymph node dissection during VATS as compared with open lobectomy. Data from The Society for Thoracic Surgeons (STS) database showed that nodal upstaging was significantly lower after lobectomy by VATS than after thoracotomy [33]. The same conclusion was reached by researchers in Denmark, who also found a significantly lower rate of nodal upstaging after VATS for clinical stage I NSCLC [30].

In clinical practice, what does this mean? On one hand, the identification of occult lymph node metastases in patients with early stage NSCLC permits the use of adjuvant oncological therapies and hence hopefully improves survival. Is it, in fact, that the lower rates of nodal upstaging associated with VATS resections are simply a result of selection bias? In expert hands, VATS resections are pushing the boundaries with an ever-expanding list of indications. However, for patients with small peripheral tumours, the default operation will be VATS. In addition, surgeons at the beginning of their minimally invasive experience will select these perceived easier smaller tumours to resect by VATS. Hence, there is an inherent selection bias as patients with larger more central tumours are more likely to undergo a thoracotomy; and this type of tumour is more likely to have developed micrometastases detected on histological examination. This hypothesis could explain why rates of nodal upstaging are higher after open lobectomy.

Outcomes after VATS lobectomy

Survival data for patients with clinical stage I NSCLC has been drawn from a variety of sources including case series, prospective multi-institutional feasibility studies and national registries. There are multiple studies from both Western countries and Asia showing that survival for patients undergoing lobectomy by VATS is comparable to, and in some instances superior to, that by thoracotomy [6, 26, 34-42]. The data is summarised in Table 1 overleaf.

For example, 5-year survival for patients with stage I NSCLC undergoing VATS lobectomy is reportedly as high as 86% in Western populations [6, 26, 34, 35]. Comparatively impressive results from Asia have also been reported, with 5-year survivals in the VATS and open groups being up to 96% and 97%, respectively [36-42].

Table 1: Reported 5-year survival after VATS or open lobectomy for stage I NSCLC

Reference	VATS	Open	p-value
McKenna [6]	80%	NR	-
Walker [26]	77.9%	NR	-
Flores [34]	79%	75%	p = 0.08
Marty-Ané [35]	86.3%	NR	-
Sugi [36]	90%	85%	0.74
Hanna [37]	66.4%	73.1%	0.2
Koizumi [38]	83.9%	60%	0.53
Shigemura [39]	96.7%	97.2%	NS
Shiraishi [40]	89.1%	77.7%	0.14
Sawada [41]	94.9%	81.5%	0.002*
Sakuraba [42]	82%	72%	0.93

*NR – not recorded, NS – no statistical significance, *denotes statistical significance (p <0.05)*

Comparing survival of VATS versus open lobectomy, a meta-analysis concluded that minimally invasive operations conveyed a significant 5-year survival benefit [19]. The same study compared rates of locoregional recurrence (no significant statistical difference) but found a significant difference in rates of systemic recurrence favouring VATS lobectomy over open surgery.

The apparent parity or even superiority of VATS, as compared with open lobectomy for early stage I NSCLC comes despite differences in the number of lymph nodes/stations sampled or dissected. Despite smaller numbers of VATS patients being upstaged, survival appears not to be compromised. The reasons behind this apparent mismatch remain unclear, with some postulating a reduction in surgical stress and immunological suppression accounting for the advantages of a minimally invasive lobectomy [43].

Segmentectomy versus Lobectomy

The primary treatment for early stage NSCLC has been resection by lobectomy for eligible surgical candidates. Not all patients however have sufficient fitness to withstand a lobectomy. In patients with significant co-morbidities or poor pulmonary function, sub-lobar resections maybe appropriate. Non-anatomical wedge resections offer the highest risk surgical patients an operative strategy at the expense of a suboptimal oncological operation. Hence the evolution of anatomical segmentectomies, which minimise functional parenchymal loss, whilst adhering to oncological principles. VATS segmentectomy thus potentially offers a valid oncological option to those high-risk patients unsuitable for lobectomy. The published data remains controversial, in part due to the heterogeneity of published studies, variable patient selection criteria, size of lesions and presentation of combined results for anatomical and non-anatomical sub-lobar resections.

Although the number of patients reported in the literature is low, a sub-group analysis of segmentectomy versus lobectomy, within a meta-analysis of sub-lobar resection compared

to lobectomy, found similar survival outcomes [44]. The authors acknowledged that patients in the analysis generally had early-stage NSCLC and often ground glass opacities, identified by the introduction of a screening program. In addition, the level of evidence was low, with only one randomised control trial, whilst the rest of the studies were level C evidence. A second meta-analysis of observational studies concluded for stage I NSCLC and tumours <2cm in size, survival after segmentectomy was equivalent to lobectomy. However, in stage 1 NSCLC and larger (2-3cm) tumours, lobectomy conveyed a survival advantage [45]. This advantage should be interpreted with caution due to several limitations with the data, possible bias in the primary studies, heterogeneity between studies and the inherent limitations of a meta-analysis of observational studies.

The literature is sparse when comparing minimally invasive to open segmentectomy. In one recently published intention-to-treat paper comparing VATS to open segmentectomy, 5-year survival for stage I NSCLC was reported as 100% and 61.3%, respectively [46].

The exact role of segmentectomy in the treatment of early stage I NSCLC remains to be fully elucidated. Two prospective studies of segmentectomy versus lobectomy for ≤2cm NSCLC are currently underway (CALGB 140503 and JCOG0802/WJTOG4607L) and should clarify this issue.

Conclusion

The evolution of VATS lobectomy since the first description in the 1990s has been one of the greatest recent advances in thoracic surgery. It is has now become a widely available technique, although worldwide uptake has lagged. Expertise has focused around dedicated centres in Europe, North America, and Australasia. In the last 20 years, VATS lobectomy has developed from concept through to standard of care, some advocating it as the standard of care [47].

Minimally invasive surgical resections have been shown to be safe and have peri-operative advantages over traditional open procedures. These include reduced short-term post-operative pain, shorter duration of chest tube drainage, shorter hospital stays, and fewer post-operative complications. Coupled with potential parenchyma-sparing techniques, VATS resections preserve pulmonary function and expedite a return to full activity for patients with early stage NSCLC. Thoracoscopic lobectomy additionally conveys a similar survival advantage to open lobectomy as the same oncological principles of complete hilar dissection and individual vessel ligation are followed. Performing VATS lobectomy does not convey additional cost and may in fact be cheaper than an open resection.

So why has the adoption of this technique not been more widely achieved? Barriers include a perceived oncological disadvantage, steep learning curve and concern over the ability to control haemorrhage if complications arise. Evidence to counter the barriers to adoption has steadily accumulated as expertise with minimally invasive surgical techniques has grown. Original publications described a multi-port minimally invasive lobectomy technique, but with time and development the number of ports has been reduced. It is now possible to perform a VATS lobectomy through three, two and even single port techniques. Further advances in technology have also led to the development of robotic lobectomy.

Although long term data is not yet available for these newer techniques, it won't be far away. There are arguments for a prospective randomised controlled trial comparing VATS and open lobectomy, which is currently lacking. However, as it becomes more widely adopted, proponents favouring thoracoscopic lobectomy may not have sufficient clinical

equipoise to randomise patients. Additionally, there are logistical difficulties in recruiting sufficient numbers of patients to show small differences in long-term outcomes. However, the need for high level evidence remains and thus these challenges need to be overcome.

For future thoracic surgeons, video-assisted thoracoscopic surgery is likely to be a core component of their practice. The challenge will be keeping up with the rapid development of minimally invasive techniques.

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Chapter 14

Can Robotic Surgery Improve Outcomes in Lung Cancer Surgery?

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"Damnant quod non intelligunt"

Introduction

Robotic surgery represents an advancement of minimally invasive surgery, improved optics, increased dexterity of the instruments, and better ergonomics. Can these subjective advantages to the surgeon translate into better outcomes for patients? Does the improved physician's experience offered with a seated surgeon at a robotic platform translate into better patient outcomes or larger financial windfall? Similar to video-assisted thoracoscopic surgery (VATS), robotic surgery offers the benefits of fewer overall complications, reduced pain, shorter length of stay, better postoperative pulmonary function, lower blood loss and a better 30-day mortality rate comparing to open thoracotomy [1-5] but at a higher initial cost. In this chapter, we review the surgical technique of robotic surgery and some of the most recent data on long-term outcomes compared to other surgical approaches.

Initial evaluation

In order to really compare outcomes in cancer patients, the patients themselves must be carefully staged in the same way. Most studies are flawed because patients are not staged in the same way. The evaluation of candidates for robotic lobectomy includes the standard preoperative work up for patients undergoing pulmonary resection. For patients with suspected or biopsy-proven lung cancer, a whole-body PET-computed tomography (PET-CT) scan is currently the standard of care, pulmonary function testing including measurement of diffusion capacity (DLCO) and spirometry is routine. Mediastinal staging can consist of either endobronchial ultrasound-guided fine-needle aspiration biopsy (EBUS-FNA) or mediastinoscopy, depending on expertise of the physician performing the procedure. Certain patients may warrant additional testing, including a stress test with a history of heart disease, brain MRI if concern exists about metastatic disease, or CT scan with intravenous contrast or MRI if concern exists for vascular or vertebral/nerve invasion, respectively. Investigators have shown that thoracoscopic lobectomy is safe in patients with a predicted postoperative forced expiratory volume in 1 second (FEV1) or a diffusion capacity of less than 40% of predicted [6]. We consider robotic lobectomy feasible in these patients as well.

One possible advantage of the robotic technique is that more patients can have a minimally invasive operation when a robotic platform is chosen. Obviously, many expert VATS surgeons would disagree with this statement but it is probably true across a large population of surgeons. At present, there are no absolute contraindications to robotic surgery. In the past, some have suggested that vascular invasion, locally invasive T4 lesions, Pancoast tumors, and massive tumours (>10 cm) are relative contraindications to a robotic approach to lobectomy but we have performed safe successful robotic operations in all of these situations now and in many patients. The need for reconstruction of the airway, chest wall invasion, presence of induction chemotherapy and/or radiation, prior thoracic surgery, and hilar nodal disease are not contraindications for robotic-assisted lobectomy in the hands of experienced surgeons.

Equipment

Since the robotic platform has evolved so quickly and continues to do so, to ensure we are fairly and correctly comparing outcomes we need to know what system each operation was performed on. The Da Vinci Surgical System is currently the only FDA-approved robotic system for lung surgery but other computer-assisted platforms are on the way.

The most current Xi technology offers the surgeon the ability to autonomously staple and use infrared technology in all patients. Da Vinci currently offers both the Xi and Si systems. The Xi system is newer and features an overhead beam that permits rotation of the instrument arms, allowing for greater flexibility in terms of direction of approach of the robot to the patient. Compared to the Si, the Xi also has thinner instrument arms, longer instruments themselves and the option to switch the camera to any arm/port. However, the older models such as the Si and S are also safe and effective for pulmonary resection. We performed over 600 robotic lobectomies using an Si robot with only one 30 and 90-day mortality. The surgeon sits at a console some distance from the patient who is positioned on an operating table near the robotic unit with its 4 robotic arms attached to trocars that are inserted into the patient.

The robotic arms incorporate remote center technology, in which a fixed point in space is defined, and the surgical arms move about that point to minimise stress on the thoracic wall during manipulations. The small proprietary Endowrist instruments attached to the arms are capable of a wide range of high-precision movements. These are controlled by the surgeon's hand movements, via 'master' instruments at the console. The 'master' instruments sense the surgeon's hand movements and translate them electronically into scaled-down micro-movements to manipulate the small surgical instruments. Hand tremor is filtered out by a 6-Hz motion filter. The surgeon observes the operating field through console binoculars. The image comes from a maneuverable high-definition stereoscopic camera (endoscope) attached to one of the robot arms. The console also has foot pedals that allow the surgeon to engage and disengage different instrument arms, reposition the console 'master' controls without the instruments themselves moving, and activate electric cautery. A second optional console allows tandem surgery and training.

Patient Positioning and Port Placement

The patient is positioned in the lateral decubitus position. Precise placement of the double lumen endotracheal tube and the ability to tolerate single lung ventilation should be established before draping the patient. Axillary rolls and arm boards are unnecessary (Figure 1) as we have previously shown [7].

The robotic ports are inserted over the ninth rib in the right chest and we have moved to the eighth rib for the left. Typical port placement is shown in Figure 2 for a right robotic

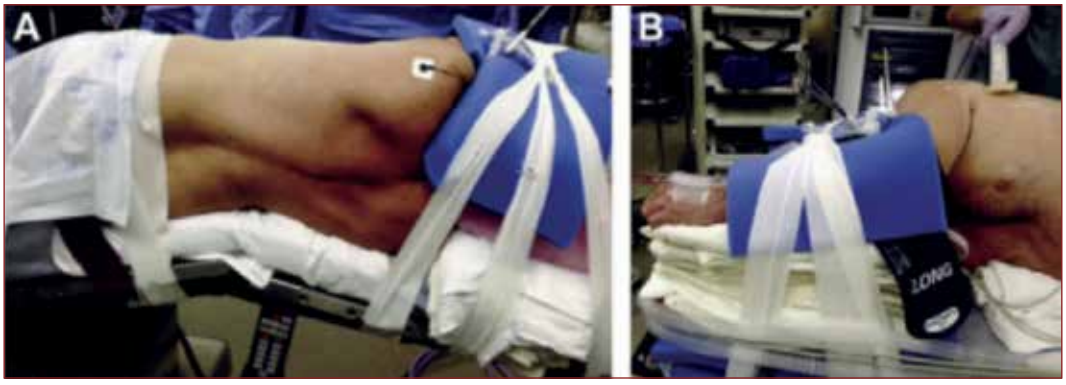

Figure 1: The patient is placed in a lateral decubitus position with only foam and tape, posterior view (A) and anterior view (B).

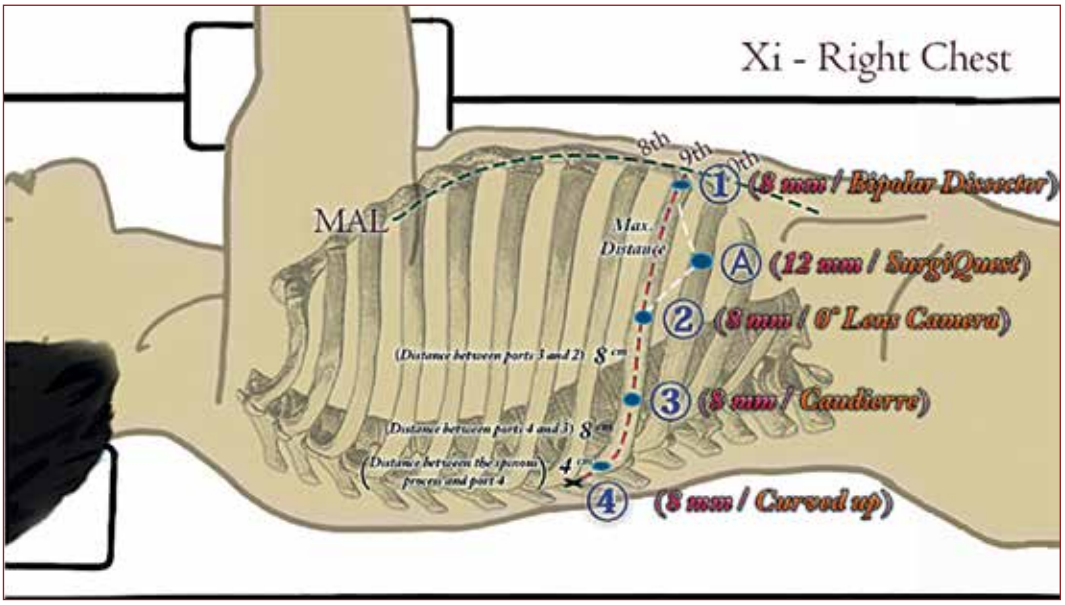

Figure 2: Portal robotic lobectomy using 4 arms (PRL-4) for right-sided pulmonary lobectomy using the da Vinci Xi robotic arms 1, 2, 3, 4 and access port (A).

lobectomy. The ports are marked as follows for the Xi robot: robotic arm 3 (8mm port) is located 1 to 2 cm lateral from the spinous process of the vertebral body, robotic arm 2 (8 mm) is 10 cm medial to robotic arm 3, the camera port (we prefer the 12-mm camera) is 9 cm medial to robotic arm 2, and robotic arm 1 (8 mm) is placed right above the diaphragm anteriorly.

The assistant port is triangulated behind the camera port and the most anterior robotic port, and as inferior as possible without disrupting the diaphragm. We use a zero-degree camera for this operation. Insufflation of the camera or assistant port with carbon dioxide is used to depress the diaphragm, decrease bleeding, and compress the lung.

Brief Description of Robotic Lobectomy (using the Si robot)

We prefer a posterior to anterior approach to most lobectomies. After using the port placement shown in Figure 3 and then insufflating CO_2 using the SurgiQuest system (Conmed Linvatec Corporation, Edison, NJ, USA) via a 7-mm port, the first task is to examine the pleura to confirm the absence of metastases. Next, for robotic lobectomy for non-small cell lung cancer, is removal of the N2 then N1 lymph nodes for staging which are sent for frozen section. The removal of some key N1 lymph nodes also aids in exposure of the hilum. If the patient cannot tolerate a lobectomy based on lung function, we do not send the N1 nodes but proceed directly with a segmentectomy only. If a tissue diagnosis is needed prior to lobectomy and the lesion is "wedgeable" then we perform this first, send it for frozen section and then remove the N2 and N1 nodes.

Brief Description of N2 Lymph Node Dissection

Right side: The inferior pulmonary ligament is divided and the lymph nodes at stations 8 and 9 are removed. Robotic arm 3 (this is the most posterior arm) is used to retract the lower lobe medially and anteriorly to remove lymph nodes from station 7, whereas it is

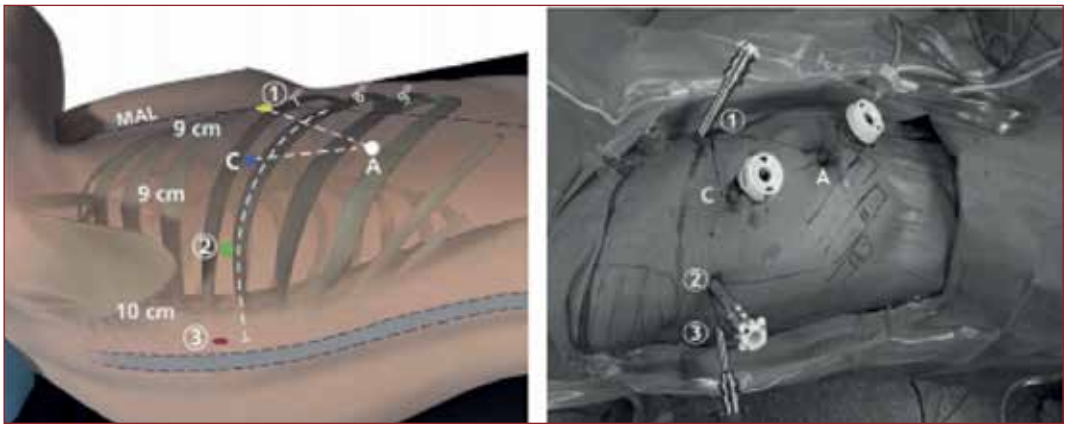

Figure 3: The figure shows a posterior approach with 4-port placement for right-sided pulmonary lobectomy using the da Vinci Si robotic arms 1, 2, 3, camera (C) and access port (A). MAL, mid axillary line.

used to retract the upper lobe inferiorly during dissection of stations 2R and 4R, clearing the space between the superior vena cava anteriorly, the esophagus posteriorly, and the azygos vein inferiorly.

Left side: The inferior pulmonary ligament is divided to facilitate the removal of lymph node station 9. The nodes in station 8 are then removed. Station 7 is accessed in the space between the inferior pulmonary vein and lower lobe bronchus, lateral to the esophagus. The lower lobe is retracted medially/anteriorly with robotic arm 3 during this process. Absence of the lower lobe facilitates dissection of level 7 from the left. Finally, robotic arm 3 is used to wrap around the left upper lobe and press it inferiorly to allow dissection of stations 5 and 6. Care should be taken whilst working in the aorto-pulmonary window to avoid injury to the left recurrent laryngeal nerve. Station 2L cannot typically be accessed during left sided mediastinal lymph node dissection owing to the presence of the aortic arch, but the 4L node is commonly removed.

Brief Descriptions of each Lobectomy

Right upper lobectomy

Recently we have championed a posterior approach to almost all right upper lobes and this has made the operation quicker and safer. All structures are taken from posteriorly and the lung is never flipped or turned. The order of ligation or removal is as follows:

1) Inferior pulmonary ligament and then the lymph nodes in stations 9, 8 and 7,
2) The station 11 lymph nodes between the RUL and bronchus intermedius are removed,
3) The posterior fissure in then stapled,
4) The small posterior-ascending right upper lobe pulmonary artery branch,
5) The right upper lobe bronchus,
6) The anterior apical pulmonary artery trunk,
7) The right upper lobe vein,
8) The anterior fissure.

Right middle lobectomy

1) Inferior pulmonary ligament and then the lymph nodes in stations 9, 8 and then 7.
2) Retraction of the right middle lobe laterally and posteriorly with the accessory robot arm helps to expose the anterior hilum.
3) The bifurcation between the right upper and middle lobar veins is developed.
4) The right middle lobe vein is encircled and divided.
5) The fissure between the right middle and lower lobes, if not complete, is divided from anterior to posterior. Care should be taken to avoid transecting segmental arteries to the right lower lobe.
6) The right middle lobe bronchus is then isolated.
7) Level 11 lymph nodes are dissected from around it. It is encircled and divided, taking care to avoid injury to the right middle lobar artery that is located directly behind it.
8) Dissection of the fissure should continue posteriorly until the branch to the superior segment to the RLL is identified, it is preserved.
9) Then the one or two right middle lobar segmental arteries are isolated and divided.
10) Stapling of middle lobar pulmonary arteries is facilitated by passing the stapler from posterior to anterior manner so the tip is not hitting other structures.
11) The fissure between right middle and upper lobes is then divided last.

Right lower lobectomy

1) The inferior pulmonary ligament should be divided to the level of the inferior pulmonary vein. The lymph nodes in stations 9, 8 and then 7 are removed.
2) The station 11 lymph nodes between the RUL and bronchus intermedius are removed.
3) The posterior fissure in then stapled between the RUL and RLL.
4) If the fissure is thick then dissection is started anteriorly near the RML vein.
5) The pulmonary artery is identified and a tunnel approach is used to stay on the pulmonary artery and then sequentially staple the fissure between the RML and the RLL and then finally RLL and the RUL.
6) The PA is identified specifically the superior segment artery.
7) The superior segmental artery and the right basilar pulmonary arterial branches are identified and taken together to allow the middle lobe bronchus to be easily seen. – they are not taken separately in general.
8) The inferior pulmonary vein is divided.
9) The surrounding lymph nodes, as usual, are dissected and the bronchus divided

Left upper lobectomy

Again, we favour a posterior approach. The order the structures are taken is:

1) The inferior pulmonary ligament and then the lymph nodes in the 9, 8 and 7 stations.
2) The 10 and 11 Lymph nodes are removed off the pulmonary artery posteriorly and the posterior segmental artery to the left upper lobe and the superior segmental artery to the left lower lobe are identified from the back.
3) This exposes the fissure and it is stapled.

4) Then the posterior segmental artery is taken.
5) Next the lingular artery is divided.
6) The left upper lobe vein is divided next by bringing the stapler from a posterior port.
7) The left upper lobe bronchus is taken next if the anterior apical trunk cannot be seen; if this step is not safe then cut the bronchus distally, then take the last PA branch and then staple the bronchus last.
8) The anterior apical pulmonary trunk is usually taken last.

Left lower lobectomy

1) The inferior pulmonary ligament and then the lymph nodes in stations 9, 8 and 7.
2) The 10 and 11 Lymph nodes are removed off the pulmonary artery posteriorly and the posterior segmental artery to the left upper lobe and the superior segmental artery to the left lower lobe are identified from the back.
3) This exposes the fissure and it is stapled.
4) If the fissure is thick then dissection is started anteriorly near the lingular vein.
5) The pulmonary artery is identified and a tunnel approach is used to stay on the pulmonary artery and then sequentially staple the fissure between the LUL and LLL.
6) The PA is identified specifically the superior segmental artery, there are often two on the left side and one is posterior and can be easily missed; they are usually taken separately unlike for a right lower lobectomy.
7) The inferior pulmonary vein is divided.
8) The surrounding lymph nodes on the bronchus are dissected and the bronchus divided.

Long-term results

What makes an operation valuable? If it is for cancer it is the 5-year stage-specific survival. That is the best judge of value for a cancer treatment. Recent literature has focused on short term metrics such as: operative time, estimated blood loss, number of total lymph nodes resected and number of N2 and N1 stations assessed, conversion rates to thoracotomy, transfusions rate, R0 resection rates and length of stay and readmission rates [5, 8-10]. We and others have also demonstrated an impressive 30-day mortality rate of 0.19%, 90-day mortality rate of 0.57%, and major morbidity rate of 9.6% in patients undergoing robotic lobectomy and segmentectomy as shown in Table 1 [11]. Kent and colleagues [5] suggested a lower mortality with robotic lobectomy in a national database study on over 33,000 patients but other data suggested no advantage to a robotic technique[12]. The data on lymph node resection is mixed and may be more operator dependent than operative platform or approach dependent [5]. In addition, there are many disadvantages of robotic surgery, some of which include the initial capital and operational cost as well as the training required [13]. There is also a learning curve when starting something new during which quality and operating efficiency can suffer.

Quality must be objective and assessed in monetary units, since quality is defined by the mathematical equation:

$$\text{Value} = \text{quality} / \text{cost}$$

Table 1: Results reported in series of robotic-assisted lobectomies

	N	Conversion Rate	Morbidity	Perioperative mortality	Median LOS (days)	Notes
Cerfolio et al, 2016	520	12% (first 100 cases)				
3.3% (last 120 cases)	50% (first 100 cases)					
4.2% (last 120 cases)	0.19% (30-d)					
0.57% (90-d)	3 d					
Yang et al	172	9%	26%	0%	4 d	Equivalent OS and DFS at 5 yrs. to VATS
Veronesi et al	54	13%	20%	0%	4.5 d	
Gharagozloo et al	100	-	21%	3%	4 d	
Echavarria et al	208	9.6%	40.4%	1.44% (in hospital)	5 d	
Louie et al	1220	Not reported	No difference from VATS	0.3 (in hospital), 0.6% (30-d)	4 d	8.44% nodal upstaging
Toker et al	102	4%	24%	2% (60-d)	5 d (mean)	104 min (mean operative time)
Adams et al	116	3.3%	No difference from VATS	0% (30-d)	4.7 (mean)	
Melfi et al	229	10.5% (first 69 cases), 5.6% (next 160 cases)	22% and 15%	1.4% and 0%	4.4 d and 3.8 d (mean)	

Abbreviations: DFS, disease-free survival; LOS, length of stay; OS, overall survival; QOL, quality of life; VATS, video-assisted thoracoscopic surgery. Data from Refs.

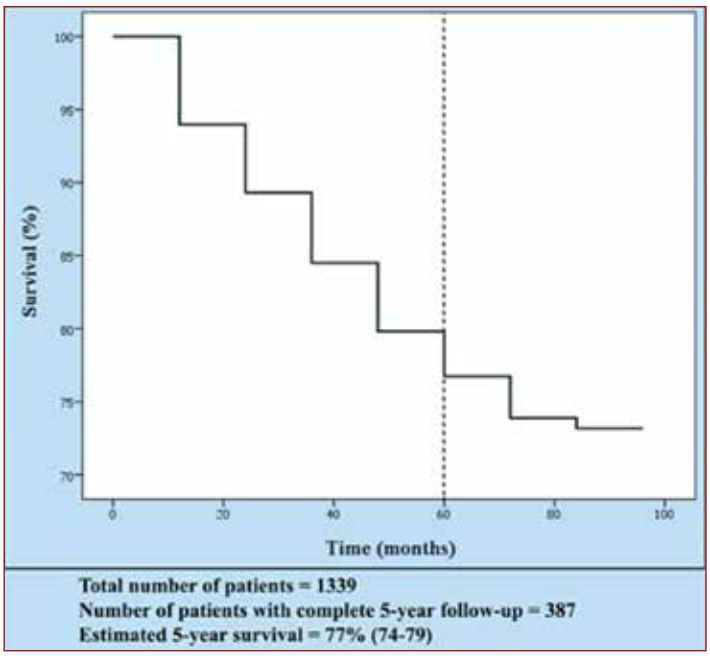

Figure 4: Overall Survival for NSCLC After Robotic Lobectomy

The quality of an operation has been viewed myopically via 30 and 90-day metrics by insurance companies and hospitals. The true value of an expensive purchase is its durability and how it measures over time, and how much money it might save over time – this should apply to an operation as well. There have been few reports that show perhaps the most important metric of quality for cancer surgery - long-term survival and recurrence rates. If something is going to cost more up front it needs to provide enhanced value over time. Therefore, a cost analysis is a complicated but necessary part of any study on quality. We must report the real metric of value. If it is a lobectomy for lung cancer, then it should be the stage-specific 5-year survival as shown in Figure 4.

This recently published report [14] shows this impressive stage specific survival of patients with completely resected NSCLC. This study is compared to several large series that reported stage-specific survival for VATS or thoracotomy [15-20] as shown in Table 2. As shown, the survival for patients who underwent robotic resection is favorable, but caution must be stressed. The trend toward a decreasing survival rate as patients are followed longer over time is seen in our series. When compared with the 2012 series by Park et al. [15] which was the first ever paper on long term survival for robotic lobectomy patients, only 12% of patients were alive at 5 years. This is commonly seen, and thus extreme caution must be warranted until further follow-up of these patients is obtained.

The improved survival rate for minimally invasive operations compared to those performed via thoracotomy may be secondary to reduction of an immunocompromised state. It has been theorised that a less invasive operation may produce fewer cytokines [21] which may lead to a lower systemic rate of solid organ metastases. A possible explanation of an increased survival rate of a robotic lobectomy is the improved staging of these patients because of the ease of lymph node dissection [22], which leads to greater upstaging [23]. A better N1 as well as N2 lymph node dissection may lead to better staging and a higher chance of adjuvant chemotherapy.

Table 2: Robotic Lobectomy Compared to Published VATS and Thoracotomy Five-Year Survival

Author/Year	Thomas 2002		Walker 2003	Yildizeli 2007	Flores 2009		Lee 2013		Park 2017	Cerfolio 2017
Type of operation	VATS	Thor	VATS	Thor	VATS	Thor	VATS	Thor	Robotic	Robotic
Total number of patients	110	405	158	218	398	343	208	208	325	1,339
Median F/U in months	N/A	N/A	38 (mean)	79	28	28	36	36	27	30
# pts alive at 5 years (%)	26 (24%)	108 (27%)	N/A	N/A	11 (3%)	30 (9%)	18 (9%)	92 (44%)	38 (12%)	387 (29%)
% overall survival reported	63%	63%	N/A	53%	79%	75%	75%	77%	80%	77%
Stage IA			Stage I	Stage I			Stage I	Stage I		
i. # pts	50	97	117 (48 IA, 70 IB)	69 (21 IA, 48 IB)	260	213	168 (120 IA, 48 IB)	146 (105 IA, 41 IB)	176	672
ii. # pts alive at 5 years (%)	11 (22%)	31 (32%)	N/A	N/A	N/A	N/A	16 (10%)	75 (51%)	27 (15%)	234 (35%)
iii. % survival reported	65%	80%	78%	57%	N/A	N/A	79%	84%	91%	83%
Stage IB										
i. # pts	60	308	N/A	N/A	69	62	N/A	N/A	72	281
ii. # pts alive 5 years (%)	15 (25%)	77 (25%)	N/A	N/A	N/A	N/A	N/A	N/A	6 (8%)	71 (25%)
iii. % survival reported	61%	58%	N/A	N/A	N/A	N/A	N/A	N/A	88%	77%

Stage IIA			Stage II	Stage II					Stage II	
i. # pts		N/A	N/A	33						
(8 IIA, 25 IIB)	86									
(6 IIA, 80 IIB)	19	17	N/A	N/A	56					
(41 IIA, 15 IIB)	118									
ii. # pts alive 5 years (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5 (9%)	29 (25%)
iii. % survival reported	N/A	N/A	51%	70%	N/A	N/A	N/A	N/A	49%	68%
Stage IIB										
i. # pts	N/A	N/A	N/A	N/A	12	15	N/A	N/A	N/A	99
ii. # pts alive 5 years (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	21 (21%)
iii. % survival reported	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	70%
Stage IIIA										
i. # pts	N/A	N/A	8	N/A	29	21	N/A	N/A	21	143
ii. # pts alive 5 years (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26 (18%)
iii. % survival reported	N/A	N/A	29%	N/A	N/A	N/A	N/A	N/A	N/A	62%

Robotic Segmentectomy

Another robotic procedure is robotic segmentectomy which has been considered a more demanding technical operation than lobectomy as it preserves more lung parenchyma. One investigator found longer operative times (219 mins vs 175 mins; $p<0.01$) for robotic segmentectomy compared with robotic lobectomy. We have reported on 100 consecutive robotic segmentectomies and shown excellent perioperative results (88 minutes median operative time, 7% conversion rate, 10% major postoperative complication rate, 0% 30-day and 90-day mortality rates) [24]. We have now completed over 200 robotic segmentectomy with no 30 or 90-day mortality. The indications for performing segmentectomy as opposed to lobectomy remain active areas of study and is out of the scope of this chapter.

Summary

Robotic lobectomy and segmentectomy have been demonstrated to be safe and feasible operations that can be done expeditiously and with low conversion rates. Perioperative morbidity and mortality are similar to VATS lobectomy/segmentectomy and improved compared with lung resection via thoracotomy. Long-term oncologic outcomes for robotic lobectomy seem to be similar at 3-5-year follow-up to those demonstrated after VATS and open lobectomy. Robotic procedures may even be better but more mature follow-up is needed. Improved optics, increased dexterity, and better ergonomics can yield subjective advantages to the surgeon but these advantages must be quantified and measured. The true value of any operation should be carefully defined and measured from the vantage point of the patient first, but also from the perspective of the surgeon, the resident, the fellow as well as the hospital and the payer.

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Chapter 15

Surgery for Stage IIIA Lung Cancer

Max Lacour, Isabelle Opitz

"Usus te plura docebit"

Introduction

Cancer is one of the leading causes of death worldwide with lung cancer being the cancer type with the highest mortality rate worldwide [1]. Currently, more than 75% of new lung cancer diagnoses are made in patients presenting with distant or regional metastatic disease [2]. At this stage, survival is very poor, with five-year survival rates of only 5%. In contrast, five-year survival could be increased up to 50% if patients were diagnosed at an earlier operable stage [3]. Therapy options for lung cancer include surgery, chemotherapy, and radiotherapy, or more recently, targeted drug therapy, depending on the molecular profile of the tumour. The establishment of a therapy plan for the treatment of lung cancer depends upon the histological classification (small cell vs. non-small cell carcinoma of the lung (NSCLC)) and tumour stage. The patient should be discussed in an interdisciplinary tumour meeting with the presence of experienced thoracic surgeons, oncologists, radio-oncologists and pathologists where a treatment plan can be developed taking into account the patient's performance status and co-morbidities.

Stage IIIA NSCLC includes a very heterogeneous group of patients depending on tumour localization and extension of disease. Tumour classification for NSCLC is based on the TNM staging system including the tumour characteristics (T), lymph node involvement (N), and presence or not of distant metastases (M). The TNM staging system has been updated recently, and the 8th edition was implemented by the Union for International Cancer Control as of January 1st 2017 [4]. Because of the heterogeneity of stage IIIA patients, therapy remains very controversial.

Stage IIIA is defined by loco-regional advanced tumour disease due to primary tumor extension or mediastinal lymph node involvement without evidence of distant metastasis. In the revised 8th edition of the TNM staging classification, Stage IIIA includes Stage T3 N1, T4 N0-1, and T1-2 N2. Stage IIIA patients with N2 disease are furthermore divided into 4 subgroups according to the Robinson classification [5].

For treatment allocation, correct and complete staging must be performed. According to international guidelines, the following staging procedures are recommended. Computed tomography (CT) remains the key tool for the staging of lung cancer. To evaluate the presence or not of lymph node involvement and distant metastases, positron-emission tomography combined with CT (PET-CT) is performed [6]. To exclude brain metastases, magnetic resonance imaging (MRI) should be performed. The National Comprehensive Cancer Network (NCCN) recommends MRI of the brain for all patients except Stage IA [7], whereas the American College of Chest Physicians (ACCP) limits it for patients in stage III/IV and symptomatic patients [8]. The ESMO Guidelines recommend performing brain MRI in patients considered for curative therapy [9]. Mediastinal staging of NSCLC patients is considered fundamental [9, 10]. If imaging studies (CT and/or PET-CT) suggest the presence of mediastinal or hilar lymph node involvement, further investigations including endosonography (endobronchial or oesophageal) with needle aspiration are recommended by international guidelines [9-11]. In recent studies, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) was superior to mediastinoscopy in terms of diagnostic sensitivity and due to being less invasive for mediastinal staging for cN1-3 non-small cell lung cancer [12]. As recommended by the ACCP and European Society of Thoracic Surgeons (ESTS), the initial mediastinal staging should be performed with needle-based techniques [13]. If the results after EBUS mediastinal staging are negative, further invasive staging including mediastinoscopy or thoracoscopy is recommended in patients with potentially resectable T2, T3, and T4 tumours, as well as for all patients with central tumours [12, 14].

Surgery remains the key component of the treatment of NSCLC, particularly in early stages, but also in advanced stages. In the following chapter, we will focus on the surgical aspects of the treatment of IIIA lung cancer in general and, in particular, the different subcategories.

General aspects

Surgical treatment of NSCLC consists of complete resection of the tumour in its anatomical unit including mediastinal lymph node dissection. At least six nodes, three from intrapulmonary (lobar, interlobar and segmental) and hilar N1 nodes, as well as at least three mediastinal N2 nodal stations (depending on the lobar location of the primary tumor) of which one should be subcarinal station 7, are recommended by international guidelines for accurate staging [4]. As recommended by ESTS, the aim of systematic lymph node dissection is to dissect and resect all mediastinal tissue containing lymph nodes within anatomical landmarks [15].

As reported by the International Association for the Study of Lung Cancer in 2005, the definition of complete surgical resection involves the following: clear resection margins proven microscopically, systematic nodal dissection or lobe-specific systematic nodal dissection, no extracapsular nodal extension and the highest mediastinal node removed must be negative [16]. Lobectomy with systematic mediastinal lymph node dissection is the gold standard treatment. Depending on tumour extension in advanced stages of NSCLC, parenchyma-sparing procedures such as bi-lobectomy, or sleeve techniques (Figure 1), must be discussed whenever possible and pneumonectomy only performed if needed and tolerated by the patient. However, it has been demonstrated that pneumonectomy can also be performed with low morbidity and mortality even after induction treatment if performed in high-volume centers [17]. Patients undergoing neo-adjuvant chemotherapy and/or radiotherapy followed by surgical resection present in general a higher risk of postoperative acute respiratory distress syndrome (ARDS) [18]. Nevertheless, it has been reported that morbidity or mortality are not increased with neo-adjuvant therapy prior to pneumonectomy [19]. Over the past decades, peri- and postoperative morbidity and

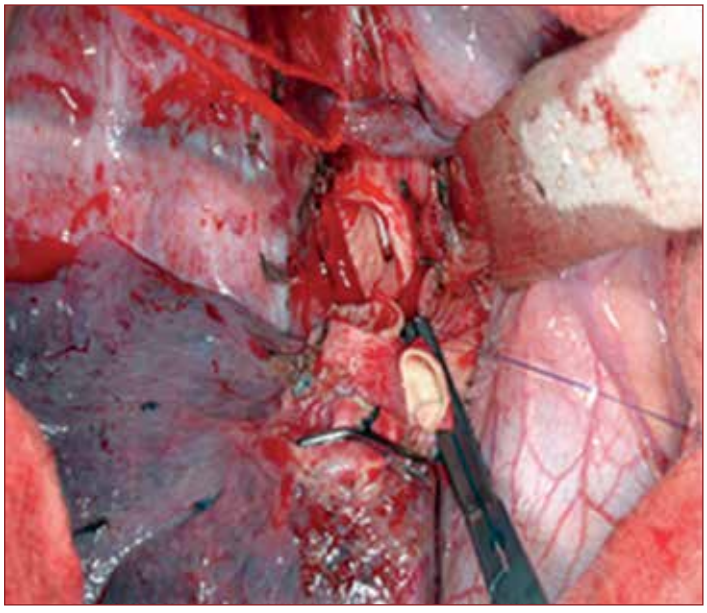

Figure 1: Combined arterial and bronchial sleeve-resection

mortality after extended resections have been significantly improved. However, the risks are still high and these operations should preferably only be performed in high volume and experienced centers.

The first detailed report on bronchial sleeve lobectomy was documented in 1956 by Sir Clement Price Thomas [20]. Bronchial sleeve resections are defined as surgical resection of a segment of a main bronchus, typically in conjunction with the involved lobar or segmental bronchus and associated lung tissue with subsequent construction of a bronchial anastomosis. This surgical technique allows preservation of lung tissue while achieving an oncological radical resection. Intraoperative management for bronchial sleeve resections follows the standards for anatomical lung resections. A right or left-sided double lumen tube is the procedure of choice to ensure correct airway management. Endobronchial jet-ventilation might be indicated for sleeve pneumonectomy or carinal resections. At our institute, we perform anterolateral thoracotomy for bronchial-sleeve resections. After preparation of the affected bronchus, dissection of the bronchus is performed with a knife to assure straight margins. Resection margins should be examined by frozen section to ensure complete tumour resection. If the margins are not tumour-free, more bronchus needs to be resected if feasible. End-to-end anastomosis is performed with a non-absorbable monofilament polypropylene suture. First, the posterior wall is anastomosed with a running suture then the anterior wall is anastomosed using interrupted sutures to ensure cartilage-to-cartilage approximation. After completion of the anastomosis, a water seal test is performed to ensure the anastomosis is air tight. To ensure uncomplicated healing of the bronchial anastomosis, preservation of sufficient blood supply is mandatory, which is obtained using a "no-touch" technique without direct manipulation of the bronchial ends during suturing. Furthermore, to avoid manipulation of the bronchial anastomosis, lymph node dissection should be performed prior to the anastomosis. To minimise complications of a bronchial anastomosis such as broncho-arterial fistula, coverage of the anastomosis can be performed. To separate the anastomosis from the pulmonary artery tissue, coverage with a pedicled anterior mediastinal fat pad or pericardial flap can be performed. It has

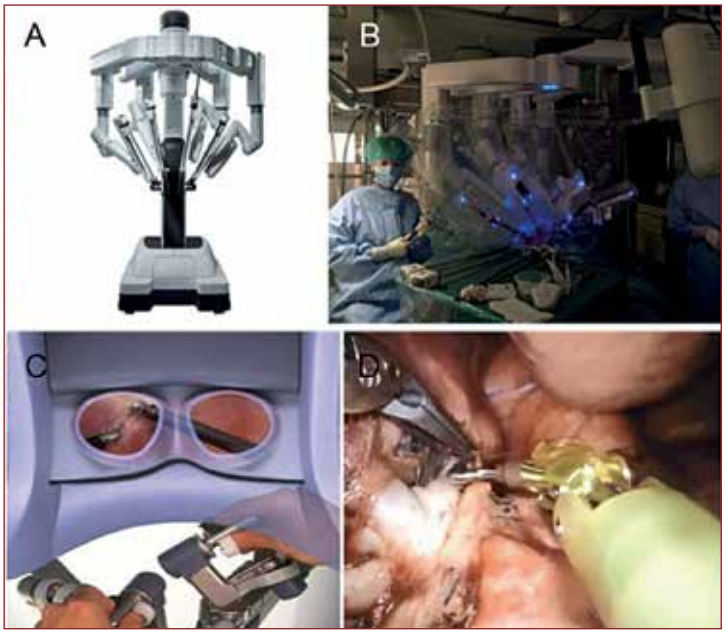

Figure 2: (A) Use of the Da Vinci® Surgical System at University Hospital Zürich, (B) Dissection of pulmonary artery with the Da Vinci® Surgical System.

been documented in retrospective series that sleeve resection without wrapping of the bronchial anastomosis with a tissue flap is safe, even in patients who have undergone neo-adjuvant chemo- or chemoradiotherapy [21].

Video-assisted thoracoscopic surgery (VATS) has been recognized as a modality for the treatment of early stages of lung cancer and is being increasingly applied to more advanced stages of disease [22]. The advantages to open surgery are obvious and well documented. Perioperative mortality with VATS is below 1% and patients can be discharged home after a few days. Oncological outcomes after VATS resections have been proven equivalent to open surgical resections [23]. Shao and colleagues demonstrated that VATS for stage IIIA lung cancer is safe and feasible and that minimally invasive techniques are being increasingly used for advanced stages and after induction treatment [24].

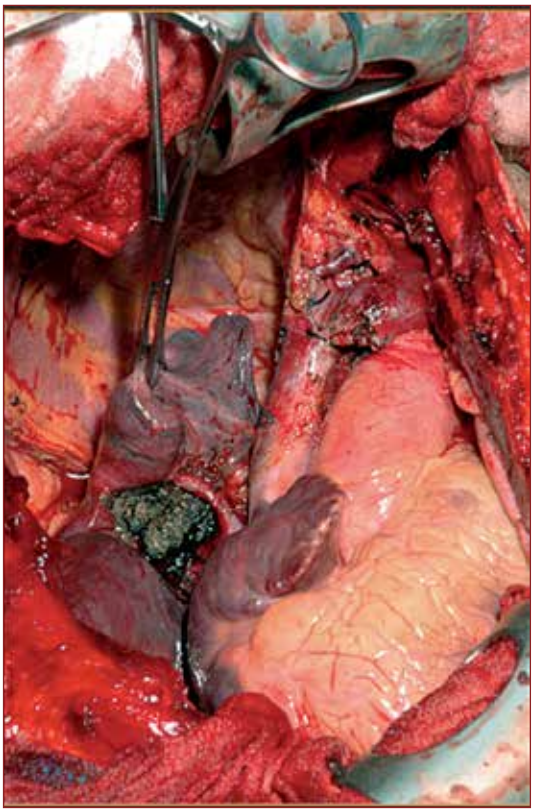

Figure 3: Right-sided hemi-clamshell incision

With the advent of the Da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) (Figure 2) and the establishment of robot-assisted surgical resections including mediastinal lymph node dissections, anatomical resections including lobectomies can be performed with unprecedented precision and efficiency [25]. Robotic lobectomy for lung cancer can be performed with low morbidity and mortality, but these data only exist for early stages of lung cancer up to now [26].

For locally advanced tumours, or neo-adjuvant treated tumours, open surgical approach via thoracotomy is often performed. At our institution, a muscle-sparing anterolateral thoracotomy is preferred over a posterolateral approach. Depending on tumour localization or extension, hemi-clamshell (Figure 3) or sternotomy must be performed in some cases to ensure good exposure and obtain complete tumour resection.

In the following chapter, we will focus on the surgical approach for lung resections in stage IIIA.

T3N1 Disease

Tumours greater than 5cm (and less then 7cm) associated with N1 lymph node involvement are considered stage IIIA according to the recent classification [4]. Tumours invading the chest wall, parietal pericardium, or associated with separate tumour node(s) in the same lobe are also classified in T3 stage. Treatment for T3N1 disease consists of surgical resection

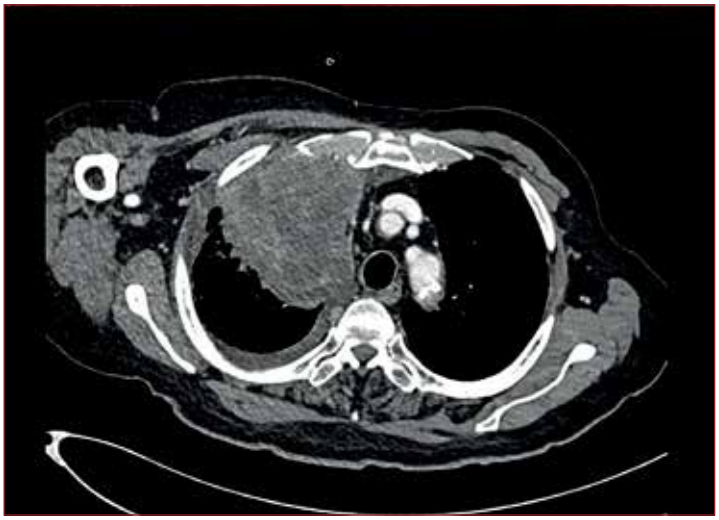

Figure 4: CT-scan with intravenous contrast showing late stage NSCLC with advanced chest wall infiltration.

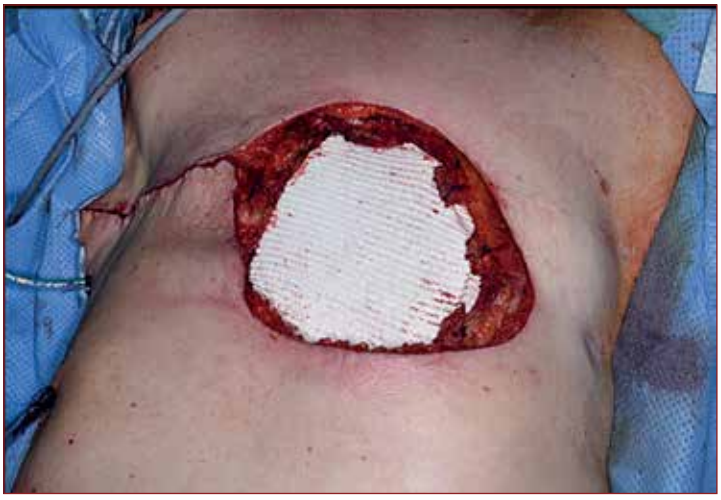

Figure 5: Chest wall reconstruction with polytetrafluoroethylene mesh (GORE-TEX®)

followed by adjuvant chemotherapy [9]. If a complete resection (R0 resection) is not achieved, adjuvant radiotherapy is indicated [9]. Due to tumour size in stage T3, lobectomy is usually performed. For central tumours, sleeve-lobectomy should always be first-line intervention whenever a complete resection can be obtained. Sleeve lobectomy does not compromise survival for stage T3 central tumours compared with pneumonectomy [27].

To ensure complete resection in T3 disease in case of chest wall infiltration, chest wall resection and reconstruction may be indicated. Chest wall involvement occurs in approximately 5% of all primary lung neoplasms (Figure 4) [28].

The first description of surgical management of chest wall invasion was reported in 1947 by Coleman [29]. The principle of chest wall reconstruction consists of maintaining anatomical structure and stability, protecting vital organs exposed after resection, and preserving the ventilatory mechanism. Polytetrafluoroethylene meshes (GORE-TEX®) are the most common materials used to reconstruct chest wall after extensive resection (Figure 5).

To ensure replacement of extended soft tissue defects, muscle flaps are commonly used in interdisciplinary team work with plastic surgery. Depending on the anatomical location

and extension of the defect, different muscle flaps can be considered. The most common muscle flaps in chest wall reconstruction are the pectoralis major, latissimus dorsi and rectus abdominis muscles. Amongst those, the latissimus dorsi muscle flap is the most frequently used for soft tissue coverage in thoracic surgery [30] and enables coverage of entire ipsilateral chest wall [31]. A latissimus dorsi flap can cover anterolateral as well as posterior tissue defects. Resection of a portion of the second or third rib is needed to pass the muscle flap into the intrathoracic space. The vascular supply for the latissimus dorsi is from the thoracodorsal branch of the subscapular artery. Due to collateral retrograde flow through the serratus branch, vascularisation of the latissimus dorsi is guaranteed even after previous trauma to the dominant pedicle, the thoracodorsal artery.

After extended chest wall resections, customized titanium implants can be used to reconstruct chest wall anatomy (Figure 6). Because they are flexible and pliable, titanium plates are used to reconstruct chest wall defects. Using titanium plates for chest wall reconstruction has been proven to guarantee chest wall stability while preserving physiological mobility allowing early postoperative mobilization and respiratory rehabilitation [32]. However, little data is available up to now for this technique of chest wall reconstruction.

As reported by Downey and colleagues, survival after chest wall resection depends on the completeness of resection and extent of nodal involvement and is not related to the depth of chest wall invasion [33]. Five-year survival for patients in stage T3N0 with R0 chest wall resection was reported as 49%, whereas for patients with T3N1 disease, 5-year survival was reduced to 27% [33].

T4N0-1 Disease

Tumours greater than 7cm and/or infiltrating the diaphragm, mediastinum, heart, trachea, aorta, or other structures are considered stage T4. As recommended by the ESMO guidelines, induction chemo-radiotherapy is indicated for superior sulcus tumours [9]. Surgery should be planned within 4 weeks after the end of induction therapy [9]. Resection can be performed technically and oncologically safely in specialised centres with acceptable morbidity and mortality [34-36].

Careful selection and planning, including multimodality treatment and cardiopulmonary bypass (CPB) if needed, are mandatory. With the establishment of CPB, resections of central tumors invading the aorta, heart, or great vessels can be performed. The first successful use of a heart-lung machine was reported by John H. Gibbon in 1953 [37]. The use of CPB during extended resections in advanced stages of lung cancer has become a major keystone.

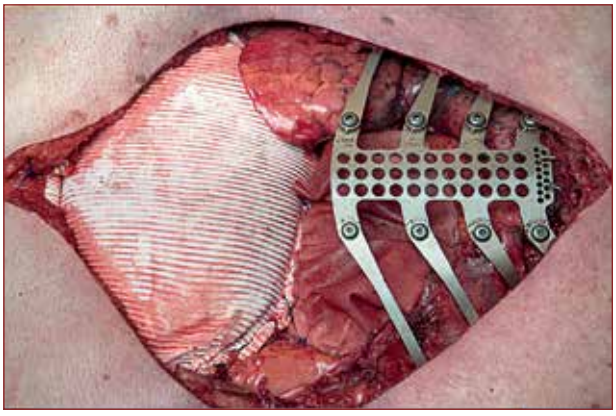

Figure 6: Chest wall resection with reconstruction with a customized titanium cage

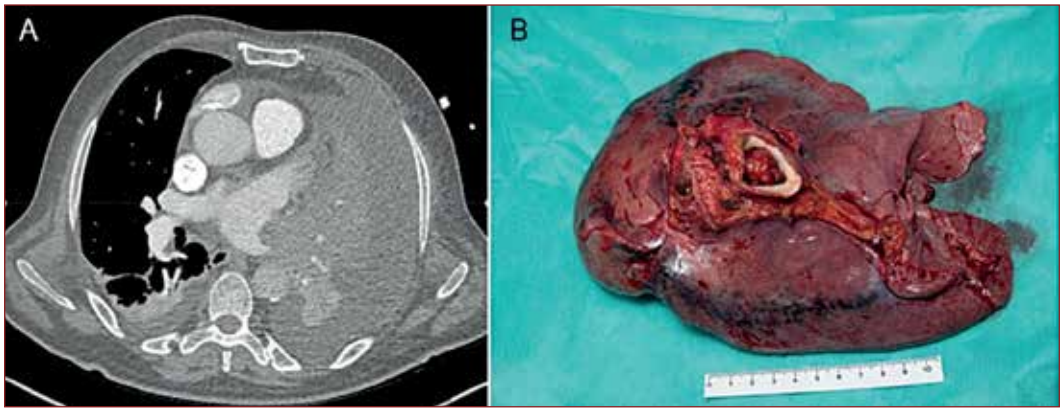

Figure 7: (A) CT-scan with iv contrast showing tumour infiltration of the left atrium with stage T4 non-small cell lung cancer, (B) Pneumonectomy specimen with left atrial resection and tumour embolus.

Anticipation of the necessity of CPB during extended resections has been reported to significantly improve postoperative mortality compared to unforeseen and emergency use of CPB [38].

Surgery for T4 stage disease is contraindicated in the presence of N2 lymph node involvement or if an incomplete resection cannot be avoided. Five-year survival rates can reach up to 48% for T4N0-1 patients [39]. Complete staging, including mediastinal lymph node involvement, is particularly important for careful patient selection, and cardiac and pulmonary assessment are vital in the planning of extended resections [9]. Induction therapy including neo-adjuvant chemotherapy and/or radiotherapy play a major role in T4 disease in order to downstage and obtain complete surgical resection [40]. Intraoperative dissection may be challenging because of tissue alteration after neo-adjuvant treatment.

In the case shown in the figure below (Figure 7), extended pneumonectomy with partial resection of the left atrium was performed under CPB to ensure complete tumour resection. Involvement of the left atrium might be due to direct tumour invasion or due to tumour embolus into the pulmonary veins. Extended resection can be performed in both cases but morbidity and mortality have been shown to be higher with embolic invasion [34].

For tumours invading the aorta, en bloc pulmonary and aortic resection can be considered if intrapleural or mediastinal metastases have been excluded [34]. Aortic resections can be performed under left heart bypass, a clamp-and-sew technique, or with passive shunts without bypass [35]. Ohta and colleagues reported a postoperative mortality of 12.5% and morbidity of 31% after thoracic aortic resections along with left sided pneumonectomy or lobectomy. The most frequent postoperative complication was bleeding [41]. After aortic resection, reconstruction is performed using a prosthetic graft. For minor and partial resections, direct closure can be considered. As described by Marulli and colleagues, preoperative aortic endografting can be performed to allow safe en bloc resection of tumors invading the aortic wall and thus avoid the need for extracorporeal circulatory support [42].

Aside from tumour invasion to the heart, complete tumour resection can also be performed with the presence of infiltration of the pulmonary artery or superior vena cava (SVC) (Figure 8). Direct tumour infiltration or metastatic lymph node involvement (N2 stage) can

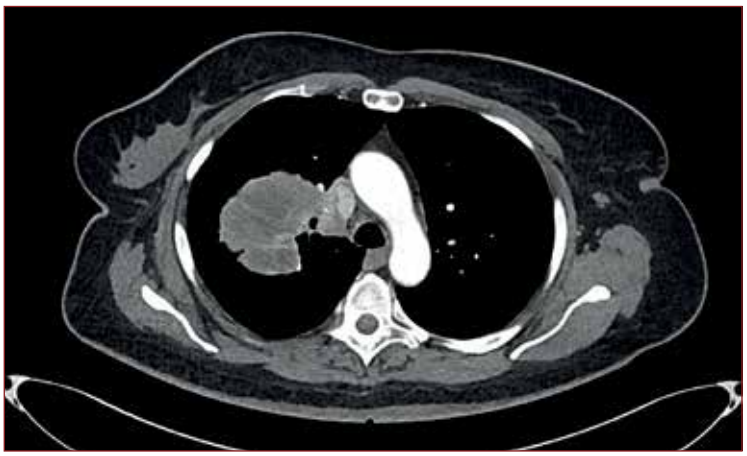

Figure 8: CT-scan showing partial SVC infiltration with the presence of a non-small cell lung cancer.

lead to tumour invasion of the SVC. Approximately 1% of thoracic resections require SVC resection and 5-year survival has been reported as 24-29% [43].

Surgical approaches for SVC resections include anterolateral thoracotomy in the 4th or 5th intercostal space, median sternotomy, or hemi-clamshell incision (Figure 3). Acute obstruction of the SVC due to intraoperative clamping may lead to potentially severe complications such as cerebral oedema, intracranial bleeding, and decrease of cardiac output [44]. The duration of SVC clamping should be kept as short as possible especially when the SVC was not completely occluded prior to surgery. Reconstruction should be performed in less than 60 minutes as it has been reported that a clamping time from 45-60 minutes is well tolerated with pharmacological support intraoperatively. Anticoagulation might be indicated during and immediately after the operation. Intravascular or extravascular shunts can be used to reduce the effect of SVC clamping, however thrombosis can occur and the devices can limit the exposure of the operating field and thus make reconstruction more challenging [45]. Partial resection of the SVC with tangential resection can be performed if less than 30% of the SVC circumference is involved. The defect can either be closed by a simple continuous suture or the use of specialized vascular staplers. Depending on tumour extension, resection of the SVC or combined SVC and innominate vein resection may be needed with reconstruction of the SVC. In general, patches of autologous or bovine pericardium are used [44]. Autologous vein such as the saphenous or femoral vein as well as prosthetic vascular grafts such as polytetrafluoroethylene (PTFE) can be used for SVC reconstruction. Five-year survival after total resection of the SVC is 24-29% [46].

Resection of lung tumours invading the spine (Figure 9) remains a challenging procedure with high morbidity and mortality. The treatment plan should always be discussed in a multidisciplinary forum with the presence of experienced spine surgeons. As recommended by the ESMO guidelines induction chemo-radiotherapy is indicated for resectable superior sulcus tumours [9].

Extended surgical resection for superior sulcus tumors have been reported to have favourable survival [47]. Selection criteria for vertebral resection involves exclusion of brachial plexus involvement above C7 and the anterior spinal artery should not be compromised. Furthermore, N2 disease needs to be excluded through preoperative mediastinal staging. To ensure that the intercostal artery supplying the anterior spinal artery is not involved by tumour infiltration, spinal cord arteriography may be needed preoperatively.

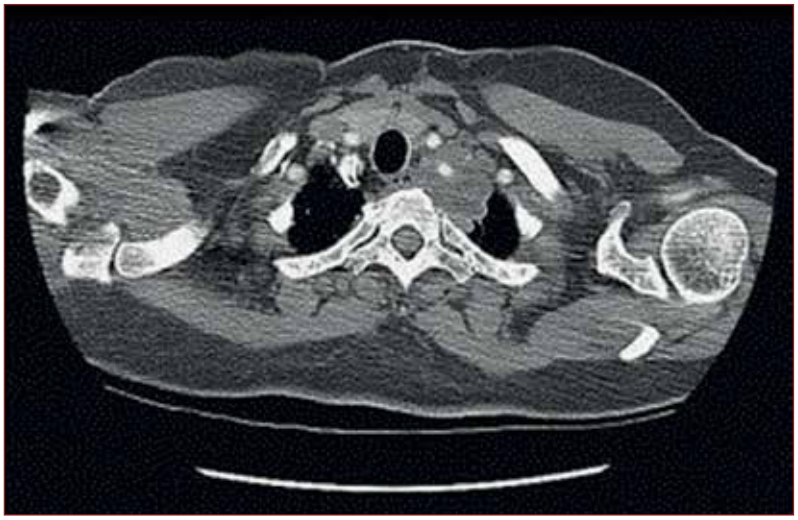

Figure 9: CT-scan showing vertebral T1 infiltration for non-small cell lung cancer

The classic posterior approach defined by Paulson and Shaw enables good exposure of the posterior chest wall but does not allow safe and direct visualisation of the more anterior anatomical structures, such as the subclavian vessels [48]. The incision begins as a posterolateral thoracotomy which extends around the tip of the scapula to the base of the neck. Division of latissimus dorsi, trapezius, serratus anterior, as well as the rhomboid muscles allows retraction of the scapula and enables good exposure to the posterior chest wall. Chest wall reconstruction is usually not necessary because the chest wall defect is covered by the scapula. Due to limited exposure of the more anterior anatomical landmarks such as the subclavian vessels, more anterior approaches have been described by Dartevelle and Grunewald [36]. The Dartevelle technique implements partial resection of clavicle, whereas the Grunewald approach saves clavicular resection. The Dartevelle approach enables good exposure of the subclavian vessels but also the brachial plexus [36]. However, this anterior approach does not allow lobectomy, and a thoracotomy is usually performed to accomplish anatomical lung resection. Surgical management of superior sulcus tumours can also be performed via a hemi-clamshell incision [36].

The most common postoperative complications after surgical management of superior sulcus tumours include cerebrospinal spinal fluid leakage, Horner's syndrome, chylothorax, and prolonged ventilator support due to extended chest wall resection and phrenic nerve involvement [36].

The mortality of surgical procedures for resection of superior sulcus tumours ranges between 0% and 6.9% [49]. The mortality is mainly related to respiratory complications, secondary to impaired chest wall mobility due to the extensive incisions affecting the chest wall musculature. Furthermore, reduction of performance status and toxicity of induction chemo-radiotherapy may increase postoperative morbidity. Five-year survival rates after vertebral resection for advanced lung cancer are reported as 15% [50].

IIIA-N2 Disease

Stage IIIA N2 disease is a particular subgroup of IIIA patients, which can be further subdivided into 4 subgroups (IIIA1-4) according to the Robinson classification [5]. Stage IIIA1 is defined by incidental lymph node involvement in the final pathological specimen after surgical resection. Stage IIIA2 is characterized by nodal lymph node involvement

recognized during surgical resection. For stages IIIA3-4 lymph node involvement was already diagnosed upon preoperative staging. Stage IIIA3 can be defined by preoperatively diagnosed lymph node involvement in single or multiple stations, which can be potentially resected. In stage IIIA4, multilevel and extended ("bulky") lymph node involvement with mediastinal lymph node involvement >2-3cm is described.

For stage IIIA1-3 surgical resection is recommended [9]. After surgical resection in stage IIIA1-2, adjuvant chemotherapy is recommended improving the 5-year survival up to 5% [9, 51]. For stage IIIA3 (unilevel) with potentially resectable N2 lymph node involvement, surgery should be in the context of multimodality treatment. Surgical resection followed by adjuvant chemotherapy, or neoadjuvant chemotherapy followed by surgical resection can be offered in this subgroup, but this should always be discussed in a multidisciplinary tumour conference [9]. For stage IIIA3 (multilevel) patients, treatment is still controversial. Currently, combined radio-chemotherapy is recommended but neo-adjuvant chemotherapy followed by surgical resection or radiotherapy can also be offered [9]. Patient performance status, pre-existing medical conditions and lung function will guide the treatment strategy.

Conclusion

Because of the heterogeneity of stage IIIA patients, therapy remains very controversial and the strategy should always be discussed individually in a multidisciplinary tumour conference. Surgery for advanced stages of lung cancer has made tremendous progress over the past decades by the use of new surgical techniques and the establishment of cardiopulmonary bypass during extended resections. Due to careful patient selection with improving imaging techniques for staging as well as increasing accuracy of non-invasive staging techniques, resection is performed in patient cohorts benefitting from surgical approaches at this advanced stage. Furthermore, by improvement of postoperative management in high volume centres, both morbidity and mortality after extended surgical resections can be significantly reduced.

For the future, surgery will remain an important modality for the treatment of advanced lung cancer. Despite recent developments in oncological therapy with the establishment of targeted drug therapy based on genetic mutations for lung cancer, we are facing an increased rate of drug resistance and many patients develop distant metastases. In the era of aggressive local treatment of 'oligometastatic' disease, the eradication by surgical resection of the primary tumour might be the best strategy for preventing further distant spread of disease.

Acknowledgement

We thank Dr. Spichiger for the support in the formatting and editing process of this chapter.

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Chapter 16

Surgery for T4 Lung Cancer

Federico Venuta, Erino A. Rendina, Marco Anile, Antonio D'Andrilli & Daniele Diso

"Saevis tranquillus on undis"

Introduction

According to the last version of the TNM Staging System [1], T4 lung cancer is defined as a tumour of any size invading the mediastinum, the heart, great vessels, trachea, carina, recurrent laryngeal nerve, vertebral bodies or oesophagus. Tumours with ipsilateral satellite nodules in another lobe are also included in this category. Thus, the T4 parameter includes a homogeneous group of tumours invading "vital" structures surrounding the heart, but from the surgical point of view it is extremely heterogeneous. To make this point, some variables are a clear sign of inoperability, such as invasion of the heart; others are more easily dealt with, such as invasion of the recurrent laryngeal nerve (RLN) or the presence of a satellite nodule; others are managed by technically demanding procedures, such as invasion of the great vessels, the carina, and the vertebral bodies.

Particular attention should be given to invasion of the superior vena cava (SVC), the trachea, carina, aorta, atria, pulmonary artery, and vertebral bodies. Pancoast tumours will not be discussed since they show other peculiarities and require different protocols for treatment.

Invasion of the superior vena cava: resection and reconstruction

The SVC might be invaded either by tumours of the right upper lobe or by mediastinal lymph nodes (stations R2 and R4) [2]. Most of these lesions are unresectable, particularly when mediastinal lymph nodes involve the vessel; when feasible, the resection often requires pneumonectomy, sleeve lobectomy or bronchial sleeve resection with reconstruction of the pulmonary artery. Invasion of the inferior vena cava (IVC) by lung cancer has been rarely reported and surgical treatment almost always requires the institution of cardiopulmonary bypass [3].

Options for SVC reconstruction include direct suture if a minimal portion of the vessel is involved, patch reconstruction (usually with a biological material), and prosthetic conduit reconstruction (either biological or synthetic materials). This technically demanding procedure requires different surgical strategies depending on whether the SVC is still patent. In fact, partial clamping of the vessel or clamping of an already fully obstructed SVC is usually well tolerated. On the other side, complete clamping of a patent SVC may cause marked hemodynamic change, particularly of the mean venous and arterial pressures, with consequent reduction of the brain arterial–venous pressure gradient; external shunts may be necessary [4]. In these cases, clamping time should be reduced as much as possible since complete closure of the SVC is usually tolerated up to 45–60 minutes with the appropriate pharmacological support such as steroids and vasoconstrictive agents. Sodium heparin is administered intravenously before clamping and is usually continued during the postoperative course because of the material used to reconstruct the vessel. Cardiopulmonary bypass (CPB) is rarely required but may be needed when the left atrium or the ascending aorta are invaded along with the SVC [5, 6].

The reconstruction strategy varies according to tumour location and extension. A relatively limited invasion of the vessel may require only tangential clamping with direct suturing. However, this technique is usually not reported as 'SVC reconstruction'. A relatively extended invasion without involvement of half of the circumference of the vessel requires patch reconstruction of the wall of the SVC. On the other hand, extended invasion of the vessel requires complete resection and replacement with a prosthetic conduit. If the confluence

of the innominate veins is involved, the revascularization is usually performed between one innominate vein only and the proximal SVC stump or right atrium; the other vein is left closed, leaving time during the postoperative course to develop adequate collateral circulation in the neck. If neck surgery or radiotherapy has been already performed, both innominate veins need to be revascularised [7].

Different materials can be used to reconstruct partial or complete SVC defects. They include both biological (autologous or heterologous) and synthetic options. The preferred synthetic graft is PTFE, usually reinforced with external rings. It has a relatively low infection risk, less platelet deposition and less thrombogenicity when compared with other synthetic materials, particularly Dacron; the risk of thrombosis is reported between 14% and 24% [8-11].

Biological materials have recently progressively gained acceptance; autologous pericardium has been extensively used either for patch or for limited conduit vascular reconstruction. However, this material cannot be used when a longer length of SVC needs to be replaced. Despite the high number of favorable characteristics like no cost, biocompatibility, adequate thickness and resistance, this material can be difficult to handle since it curls and shrinks. To minimize this problem fixation with glutaraldehyde has been described in order to increase stiffness [12].

Bovine and porcine pericardium are currently used as heterologous biologic materials [10, 11, 13-20]. Our group has proposed an original method of reconstruction using a biological conduit [21], trimming the pericardium on a syringe using a linear stapler allowing safe reconstruction and long-term patency [20, 22]. These materials have no size limits, show stiff edges which are easy to suture and have excellent biocompatibility. These characteristics, along with the results in terms of graft patency, have made these materials the preferred choice for SVC reconstruction.

Invasion of the tracheal carina

Carinal resection and reconstruction is required when lung cancer invades the take-off of a main bronchus or for primary tumours of the airway. In the past, this procedure was associated with significant operative mortality often exceeding any possibility of 5-year survival. However, recent advances in intraoperative management and surgical technique have resulted in a significant reduction of complications and mortality and consequent improvement of survival in a selected group of patients.

The most frequent presentation is related to tumours of the right upper lobe extending proximally towards the mediastinum. In these situations, SVC reconstruction is often required. Carinal pneumonectomy is usually performed on this side via a lateral thoracotomy with intraoperative ventilatory support of the contralateral lung. The use of jet ventilation has been reported. When only the proximal part of the main bronchus is involved and the airway distal to the right upper lobe is free of disease, the intermediate bronchus can be reimplanted either proximally or on the medial side of the contralateral left bronchus with a right upper lobe sleeve resection. When left side carinal pneumonectomy is required, median sternotomy with a transpericardial approach is recommended and CPB may be useful to improve exposure and intraoperative management. If only the carina is involved by a primary tumour (usually mucoepidermoid or adenoid cystic carcinoma), both main bronchi can be spared and reimplanted on the distal trachea shaping a neocarina. As with SVC reconstruction, carinal reconstruction is a technically demanding procedure and only recently have good results been achieved with standardisation of the surgical technique

at high volume centers [23]. Careful preoperative staging in patients with lung cancer is mandatory and N2 disease should be considered a contraindication to surgery. Careful selection of patients and meticulous surgical technique allow 5-year survival in N0 patients to reach 40%. Mortality in our experience was 3.3% in a series of 30 patients (unpublished data) whereas in recent published series mortality was 4 - 7.7% [23, 24].

Invasion of the thoracic aorta

Stage T4 lung cancer with invasion of the thoracic aorta in the absence of metastatic disease is a relatively rare presentation. Aortic wall invasion should be suspected when the tumour is in apposition to the aorta, when it is in contact with more than 25% of the aortic circumference or when the fat plane between the aorta and the tumour is lost. Since the surgical technique required for resection and reconstruction of this vessel in addition to lung resection is technically demanding and, as it usually requires the use of CPB with tube graft interposition, the series reported in the international literature are relatively few and the number of patients enrolled is small. A shunt between the ascending and descending thoracic aorta has also been employed to avoid the use of CPB [25]. Nevertheless, a relatively low mortality has been reported, although survival is often referred to in terms of months [26, 27]. Few reports have shown promising long-term results [28].

A new technique has recently been proposed to simplify the resection and improve outcomes. The first step requires placement of an endoluminal expandable covered prosthesis within the lumen of the vessel, protecting from inside the area infiltrated by the tumour. This allows safe resection of the aortic wall without bleeding or the need for CPB. The aortic wall can be reconstructed with prosthetic materials. In case of resection of the adventitia only, we have reinforced the area with a wrap of omentum transposed through the diaphragm [29, 30].

Invasion of the left atrium

Invasion of the take-off of the pulmonary veins and the atrial wall requires special considerations. Extending the resection to the atrial wall is more often associated with pneumonectomy and CPB may be required. Placement of a Satinsky clamp proximal to the tumour may sometimes be sufficient. The presence of an endoluminal thrombus mandates the use of transesophageal echo to monitor correct placement of the clamp [31]. Dissection of the interatrial groove may create room for central clamp placement, although this area is delicate both for clamping and suturing. In cases of extended infiltration of the atrium, CPB should be instituted and prosthetic reconstruction performed to allow adequate volume of the atrial chamber to be resected. Results are encouraging if R0 resection is achieved and the N2 nodes are not involved [32-34]. Cardiac arrhythmias are the most frequent complication. A 3-year survival of 39% has been reported [35].

Involvement of the pulmonary artery

Invasion of the proximal pulmonary artery is reported as T4 lung cancer. This situation is more frequent on the left side due to the anatomy. On this side, even the origin of the left pulmonary artery may be invaded by proximal tumours along with the left recurrent laryngeal nerve. Although distal reconstruction of the pulmonary artery has been extensively reported with good long-term results in terms of survival and patency, reconstruction of the take-off of the left PA is relatively rare and it is usually associated

with left pneumonectomy [36-38]. A large defect on the left side of the main pulmonary artery can be reconstructed with a patch of autologous pericardium or with other biologic or synthetic material during a run of cardiopulmonary bypass. The use of CPB is associated with an elevated risk during the postoperative course, but also because CPB is more often necessary after induction treatment. In rare cases, in order to avoid pneumonectomy, the involved pulmonary artery can be substituted with a conduit of prosthetic material or by the use of autologous left pulmonary vein resected en bloc with the left upper lobe [39].

Invasion of the vertebral bodies

Vertebral body invasion may be related to Pancoast and non-Pancoast non-small cell lung cancer (NSCLC). This presentation has shown poor prognosis for a long time and thus it was often felt to be unresectable. In 1989, for the first time, en bloc tangential resection of the vertebral bodies after preoperative radiation was reported with a promising 42% 5-year survival [40]. In 1999, Gandhi et al. from the MD Anderson Cancer Center in Houston reported 17 patients with superior sulcus tumors and vertebral body invasion undergoing complete resection [41]. They performed partial vertebrectomy in 7 patients, complete vertebrectomy in 7 and neural foramina or transverse process resection in 3. The 2-year survival in those receiving R0 resection was 80%. Grunenwald and colleagues in 2002 described en bloc partial or total vertebrectomy for T4 lung tumours [42]. However, 5-year survival was only 14%. The same year, Fadel et al. from the Marie Lonnelongue Institution in Paris [43] reported 20% 5-year survival in 17 patients and Deslauriers et al. reported 40% in 19 patients with no operative mortality [44]. The most impressive report has come from the Toronto group in 2009 who described the outcome of 23 patients undergoing radical vertebral resection for NSCLC after non-concurrent induction chemoradiation with a 3-year survival of 58%; however, patients with complete or almost complete response showed an impressive 92% survival at 3 years [45].

The technique of vertebral reconstruction has significantly evolved with posterior fixation and the use of expandable titanium cages to replace the vertebra. These cages are fast and easy to insert, they can be tailored to the patient's anatomy and they may be filled with bone chips to facilitate bony fusion [46, 47].

Summary

Extended resections for T4 lung cancer can be safely performed even after induction therapy and, even though they are technically demanding, good results can be obtained at high volume centres in well-selected patients. Thorough pre-operative staging and planning is required before attempting resection to select appropriate patients and ensure optimum results.

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Chapter 17

Management of Ground Glass Nodules

Susannah M Love & Julius Asante-Siaw

"Aequam memento rebus in arduis servare mentem"

Introduction

The management of lung cancer has evolved over the past few decades from a nihilistic approach to one of aggressive, radical treatment of advanced tumours including those with metastatic disease at presentation. The curative playing field has grown, supported by lung cancer multi-disciplinary team (MDT) meetings, advances in both surgical and oncological treatments, accurate clinical staging and improved data capture. These developments are evidenced by the updates to the Union for International Cancer Control (UICC) TNM staging system, now in its 8th edition, which help MDTs stratify their patients to determine appropriate treatment and prognosis.

Whilst lung cancer MDTs have been enhanced by these improved resources, frequently they create new and complex clinical dilemmas which may or may not have robust evidence to guide management decisions. One of these is the management of ground glass nodules and this chapter seeks to explore this radiological anomaly further.

Pulmonary Nodules

Pulmonary nodules can be either solid or subsolid. A solid pulmonary nodule is a focal, rounded opacity ≤3cm diameter, mostly surrounded by aerated lung [1]. A subsolid nodule can either be a part-solid nodule or a ground glass nodule. A part-solid nodule (PSN) is a focal opacity that has both solid and ground glass components ≤3cm diameter. A ground glass nodule (GGN) is a hazy opacity ≤3cm diameter which does not obscure the underlying pulmonary vessels or bronchial structures [2].

A GGN can have a benign or malignant aetiology such as areas of focal haemorrhage, fibrosis, inflammation, minimally invasive (MIA) or invasive adenocarcinoma or its precursors, such as atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS)[3]. Atypical adenomatous hyperplasia typically correlates to a CT finding of a GGN <5mm, AIS correlates with a GGN ≥5mm up to 30mm, MIA correlates to PSN with a solid area <5mm and invasive adenocarcinoma presents as a larger PSN or solid nodule [1].

Whilst there is an association with malignancy, not all GGNs are malignant and many can spontaneously regress and disappear suggesting an inflammatory cause. A study by Oh et al. found that 37% of pure GGNs and 48% of mixed GGNs regressed and disappeared within 3 months [4]. Ground glass nodule with an ill-defined border can suggest an inflammatory origin and therefore this is a predictor of spontaneous regression [5]. Kobayashi et al. found that initial large size and a smoking history were predictors of growth [6]. Lee et al. reported that initial size more than 10mm, presence of a solid portion, male sex and age over 65 years were risk factors for future growth [7].

Improved resolution of CT imaging and introduction of CT screening for lung cancer, which followed the reported decrease in mortality as a result of low dose CT screening by such trials as the National Lung Screening Trial (NLST), have led to the increased detection of GGNs [8]. When presented with an incidental finding of solitary or multiple GGNs, clinicians need to decide the likely aetiology and how to manage them with either radiological follow up, tissue sampling or surgical resection. A standardised MDT approach to the management GGNs requires an awareness of the International Association for the Study of Lung Cancer (IASLC) classification of lung adenocarcinomas, applying the IASLC classification of lung nodules and following guidance on the management of pulmonary nodules provided by societies such as the British Thoracic Society or the Fleischner Society.

Classifications and Guidelines

IASLC Classification of Lung Adenocarcinoma

The classification of adenocarcinoma was redefined in the IASLC guidelines published in 2011[9]. The purpose of the reclassification was to provide an integrated clinical, radiological, molecular, and pathologic approach to classification to help define distinct characteristics of tumours. Subsequently, this information could be used to identify prognostic and predictive factors as well as therapeutic targets. The guidelines classified adenocarcinomas as pre-invasive lesions, AAH and AIS, minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma.

IASLC Classification of Lung Nodules

The IASLC advised that lung nodules should be classified based on the findings of thin-section CT as either pure GGN, part-solid or solid nodule [10]. The extent of the solid component in a part-solid nodule can be described using the consolidation to tumour ratio which is the ratio of the maximum diameter of consolidation to the maximum tumour diameter. The significance of these descriptors is that studies have shown that the ground glass element correlates with pathological lepidic growth whereas consolidation represents pathological invasiveness. A consolidation to tumour ratio of 0.5 or less indicates a pathologically less invasive lung cancer compared to those with a higher ratio [11].

British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules

The British Thoracic Society (BTS) offers a comprehensive review of the literature and expert opinion on the management of pulmonary nodules of unknown aetiology [1]. The guidelines include a subsection on the management of subsolid nodules such as GGNs which are summarised in Table 1.

Table 1: British Thoracic Society guidelines for management of subsolid nodules

Initial nodule size	
<5mm	Patient can be discharged
≥5mm	No previous imaging • Repeat CT in 3 months
	Previous imaging • Nodule stable for >4 years, discharge • Nodule stable for <4 years, further surveillance, and malignancy risk assessment with Brock model
Appearance on repeat CT at 3 months	
Lesion resolved	Discharge
Lesion stable	Assess malignant risk using Brock model, patient fitness and patient preference • <10% malignant, repeat CT at 1, 2 & 4 years from baseline • >10% malignant, discuss options with patient and advise repeat CT, biopsy, or surgical resection/non-surgical treatment
Lesion has grown/ altered morphology	Surgical resection/non-surgical treatment is advised

The Brock model, also known as the PanCan model, is a multivariable calculation that estimates the risk that a pulmonary nodule on a CT scan is a lung cancer [12]. It combines predictors of lung cancer which include age, female sex, family history of lung cancer, emphysema, nodule size and location, PSN type, lower nodule count and spiculation. The result from the calculation can be used to determine appropriate follow-up and management of CT-detected lung nodules.

The Fleischner Society Guidelines for the Management of Incidental Pulmonary Nodules Detected on CT Images

The Fleischner Society published their 'Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images' in 2017, which are summarised in Table 2 [13].

Table 2: Fleischner Society guidelines for the management of sub-solid nodules

Ground glass nodule	
<6mm	No follow up
≥6mm	CT at 6-12 months to confirm persistence
	• If stable, CT every 2 years until 5 years
	• If growth or solid component develops, consider resection
Part solid nodule	
<6mm	No follow up
≥6mm	CT at 3-6 months to confirm persistence
	• If unchanged and solid component remains <6mm, annual CT for 5 years
	• If nodule changes, either via growth or solid component increases to >6mm, resection is advised
Multiple nodules	
<6mm	CT at 3-6 months
	• If stable, consider CT at 2 and 4 years
≥6mm	CT at 3-6 months
	• Subsequent management is based on the most suspicious nodule

Risk Factors for Malignant Lung Nodules

The Fleischner Society guidelines describe various risk factors which are associated with malignancy which echo the components of the Brock model. Awareness of these risk factors can assist in identifying potentially high-risk nodules which can guide the MDT decision-making process. Also, this understanding enables a patient to be fully informed when making the final decision regarding radiological follow-up or interventions based on their individual risk profile.

Larger nodule size, hence the stratification of the guidelines on size criteria, and marginal spiculation have both been associated with an increased risk of malignancy [12, 14]. Lung cancers more frequently occur in the upper lobes, mainly on the right side, as confirmed by the PanCan trial which found upper lobe location to be a risk factor for lung malignancy with an odds ratio of 2.0 [12].

The NELSON trial reported an increased risk of primary lung cancer as the number of nodules increased from 1 to 4 but a decreased risk if there were more than 5 nodules which mostly likely represented a previous granulomatous infection [15]. The PanCan trial reported that multiple nodules were associated with a reduced risk of lung cancer compared to the risk of a solitary nodule [12].

The presence of emphysema on a CT scan is an independent risk factor for lung cancer, likely due to its frequent correlation with smoking [16]. Subgroup analysis in the NLST trial found an incidence of 25 instances of cancer per 1000 screened patients with emphysema, compared to 7.5 instances of cancer per 1000 screened patients without emphysema [17].

Age is a well-established risk factor for lung cancer, it is rarely seen in those under 35 years old but for each additional decade of life, the incidence of lung cancer progressively increases [18]. A family history of lung cancer, irrespective of whether the patient in question has a smoking history or not, increases their risk of lung cancer [19]. Race is also a risk factor for lung cancer, with a significantly higher incidence in black men [20].

Cigarette smoking is the major risk factor for lung cancer but it has been reported that its relationship with adenocarcinoma, which accounts for the majority of GGNs, is weaker than its association with squamous cell and small cell carcinoma [21]. However, the validity of this conclusion remains one of much debate and the association could be much stronger than previously reported especially among heavy smokers [22]. The Fleischner guidelines recommend that the management of GGNs should be decided independently of whether a smoking history is present.

Surgical Considerations

Once the decision has been made that a lesion meets the criteria for surgical resection or if it is the patient's preference for resection, the MDT face further dilemmas such as whether the nodule should be biopsied beforehand, the extent of surgical resection, lymph node evaluation and the management of multiple GGNs.

Pre-operative biopsy

The decision to perform a pre-operative biopsy should be made using similar protocols to managing any type of lung nodule. There is evidence that there is a high correlation between suspicious CT findings and pathological findings which supports a policy of proceeding directly to surgical resection [23]. Also, the lower rates of complications and morbidity conferred by minimal invasive thoracic surgery can make surgical resection a more appealing, definitive option. It has been reported that GGNs that meet Fleischner Society criteria for tissue sampling that underwent surgical resection without previous biopsy were found to be malignant in 95% of cases [24].

Extent of resection

The standard surgical treatment of early lung cancer is an anatomical lung resection with mediastinal lymph node evaluation as established by the Lung Cancer Study Group in 1995 [25]. However, whether it remains an appropriate recommendation in view of the improvements in clinical staging techniques over the last two decades and with reference to small, peripheral early lung cancers is a topic of frequent debate. Studies comparing 5-year survival of cT1N0M0 treated with either sublobar (wedge or segmentectomy) versus lobectomy found no significant difference, nor a difference in recurrence rate [26, 27]. Also, postoperative lung function was significantly better in patients who underwent sublobar resection [26, 28].

As pure GGNs are likely to be AAH or AIS, then a lesser resection could be argued to be sufficient. Investigating GGNs specifically, several institutes have reported similar 5-year overall survivals and recurrence-free survival irrespective of whether a GGN is resected via wedge, segmentectomy or lobectomy [29]. However, so far this has only been recommended for GGNs with a solid component of less than 25%.

Multiple GGNs

One-third of patients with a GGN will have more than two other simultaneous GGNs. Genetic analysis of multiple GGNs has found a discordance in their mutations which suggests that they are multifocal in origin rather than metastases [30]. In view of that, it has been suggested that the management of multiple GGNs should be guided by the behaviour of the dominant lesion with a parenchymal-sparing surgical technique to maximise potential future options to treat newly evolving GGNs [31, 32].

Intra-operative identification of GGNs

Surgeons should be aware that GGNs can be impalpable at the time of surgery and plan appropriately for this potential intra-operative predicament. One option is to perform a lobectomy if the nodule is impalpable or to arrange for an intra-operative frozen section to identify if the nodule is contained within a wedge resection specimen. Pre-operatively, nodule marking techniques can be utilised such as metallic hook localisation under CT guidance, microcoil, barium, coloured collagen or radioactive dye injection with human serum albumin labelled with technetium-99m (99mTc-HSA) [33, 34]. Intra-operative ultrasonographic localisation of GGNs has also been described [35, 36].

Mediastinal Lymph Node Evaluation

As the majority of malignant GGNs are early stage lung cancers, the value of performing mediastinal lymph node evaluation (MLE) could be questioned. Several studies have reported a zero incidence of mediastinal lymph node metastasis in patients with pure GGNs [37, 38]. This is in stark contrast with a reported rate of up 20% of unexpected lymph node metastasis found in semi-solid or solid tumours [39]. Moon et al. reported no cases of mediastinal lymph node metastasis in GGN predominant tumours [40]. In addition, they reported no difference in the survival of patients with GGNs irrespective of whether MLE was or was not performed.

Conclusion

The management of GGNs has been clarified over recent years due to extensive research which has led to clear definitions, identification of risk factors, establishment of correlations between CT and pathological findings and prediction of surgical outcomes. Based on this evidence, clear guidance has been issued by several societies which can be utilised by MDTs to ensure that patients are managed appropriately and in accordance with their own risk profile.

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Chapter 18

Does the manner of follow-up after lung cancer surgery improve survival?

Elizabeth Belcher, Jenny Mitchell, Rachel Benamore & Fergus Gleeson

"Suaviter in modo, fortiter in re"

Introduction

Following resection of early stage lung cancer, patients are at risk of both recurrent disease and the development of new primary lung tumours. Observational studies show a risk of recurrence for early lung cancer survivors of up to 10% per year in the early years declining to 2% thereafter [1]. The risk of metachronous tumours is 1-6% per year and persists over time. Whilst these risks are well documented and follow-up is advocated, the optimal imaging program, both modality and frequency is yet to be determined. Historically, the mainstay of follow-up has been clinical examination and the chest radiograph (CXR). In the era of modern imaging, the role of Computed Tomography (CT)-based follow-up is attractive. Given that CT is known to be significantly more sensitive than the CXR in thoracic disease detection, and that the weight of evidence suggests asymptomatic recurrence has significantly better outcomes than symptomatic recurrence [2-5], and that screen-detected lung primaries are associated with improved survival [6], then it is logical that CT follow-up of lung cancer patients who have undergone curative intent resection may improve survival.

The advent of newer treatments, such as stereotactic ablative radiotherapy (SABR), percutaneous thermal ablation (microwave and radiofrequency), and modern surgical techniques (video assisted thoracoscopy surgery – VATS), allow minimally invasive treatment not previously available. These techniques may be applicable to detected recurrent disease as well as at initial presentation, and are likely to play a significant part in improving outcomes in early detected disease recurrence. There is also a trend in oncology to aggressively treat oligometastatic disease, at both presentation and follow up, and this may well become prevalent in lung cancer, necessitating CT follow-up.

Current Recommendations

Current recommendations for the follow-up of surgically treated early stage lung cancer patients are summarized in Table 1 opposite. UK-based recommendations stipulate follow-up of radically treated patients, but do not specify the imaging modality or frequency. International guidelines all recommend CT based follow-up. There is lack of consensus regarding the use of contrast enhancement and the interval of imaging.

Evidence for CT follow-up of surgically treated lung cancer patients

The proposed benefits of CT based follow-up of patients following resection of early stage lung cancer are predicated on the suggestion that CT detects more tumours at an earlier stage than chest x-ray and that asymptomatic recurrence has a better survival rate than symptomatic recurrence (Figure 1 overleaf).

Survival of asymptomatic vs symptomatic recurrence

Several reports indicate that recurrence identified in asymptomatic patients may be associated with significantly longer survival [2-5]. These studies consistently show that asymptomatic recurrence is associated with 2 to 3-fold longer survival than those patients with symptomatic recurrence [2, 3]. Westeel et al. found 3-year survival from the date of recurrence was 31% in asymptomatic patients, versus 10% in symptomatic patients [2]. Similarly, Gourcerol et al. found median overall survival from time of recurrence was

Table 1: Current Recommendations for the follow-up of Radically Treated Lung Cancer Patients

Organisation	Who should be followed-up?	Which imaging modality?	When should imaging be carried out
European Society for Medical Oncology (ESMO) [7]	NSCLC patients treated with radical intent	Contrast enhanced chest CT	Every 12 months
	Patients who are suitable for salvage treatment	Contrast enhanced chest CT	Every 6 months for 3 years, then annually
American Association for Thoracic Surgery (AATS) [8]	Patients who have had surgical resection of stages 1A to IIIA NSCLC	High-resolution CT	Every 6 months for 2–3 years, then annually to year 4
		Low dose CT chest	Annually from year 5 onwards
American College of Chest Physicians (ACCP) [9]	Patients who have undergone curative intent surgical resection of NSCLC	Chest CT	Every 6 months for 2 years, then annually
National Institute for Health and Clinical Excellence (NICE) [10]	Protocol driven follow-up with a clinical nurse specialist for patients with a life expectancy of more than 3 months	No recommendation	No recommendation
National Comprehensive Cancer Network [11]	Patients with radically treated stage I-II disease	Chest CT with or without contrast	Every 6–12 months for 2 years
		Low dose non-contrast enhanced chest CT	Annually

significantly higher in asymptomatic patients than in symptomatic patients (15.5 months versus 7.2 months) [5].

Such identification of asymptomatic patients and their apparent increased survival may be subject to biases including lead time and length time bias. Lead time bias is the apparent benefit conferred by detecting disease early when in fact there has been no benefit, rather just increased time knowing the disease is present. Length time bias is the apparent benefit of disease detection and consequent treatment increasing survival, when in fact, the benefit is artefactual and relates to indolent disease that would not have been of significance to the patient. These biases may account for survival differences in screening studies, but logically should not have a significant effect in detected disease recurrence in lung cancer

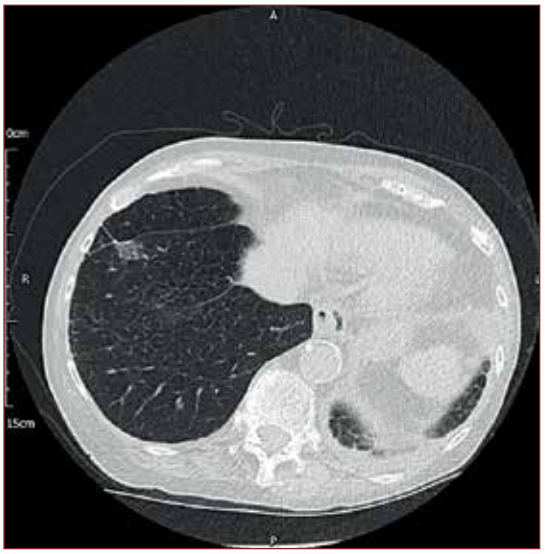

Figure 1: Metachronous adenocarcinoma of right lower lobe diagnosed during CT following earlier resection of left upper lobe T3N0M0 NSCLC 5 years previously. Patient underwent radical treatment via VATS resection and has entered further CT follow-up program.

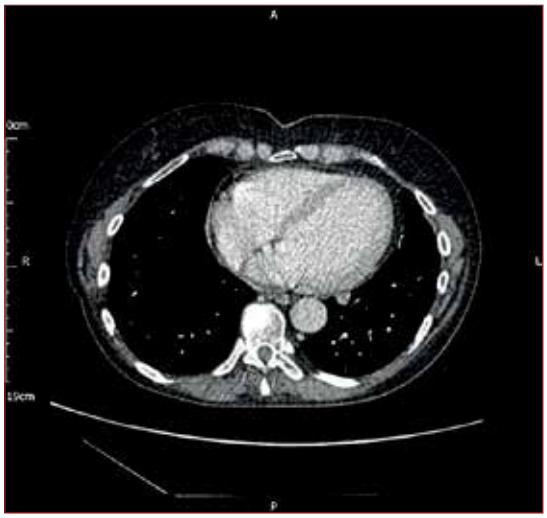

Figure 2: Left lower lobe lesion diagnosed during CT follow-up in patient having undergone right upper lobectomy of cTN0M0 adenocarcinoma of the lung 1 year previously. Patient underwent radical treatment via VATS resection of typical carcinoid and continues in CT follow-up program.

patients already treated for cure. Whilst slowly growing, new primary tumours such as adenocarcinoma in situ or minimally invasive adenocarcinoma may be subject to such bias, recurrence is unlikely to exhibit these characteristics. The degree to which length time bias may be observed in CT follow-up will depend on the relative proportion of recurrence versus indolent new primaries, although the evidence from screening trials suggests that new lung cancers detected at incidence screens, which are the equivalent of new cancers detected on CT follow up, have shorter doubling times and are less likely to be indolent adenocarcinomas [12-14].

As would be expected, both studies found no difference in disease-free interval between asymptomatic and symptomatic patients and concluded lead time bias could not explain the survival advantage observed in patients who were asymptomatic at the diagnosis of recurrence (Figure 2) [2, 5].

CT detects recurrence and new primary tumours at an earlier stage

Several studies suggest CT detects recurrence and new primary tumours at an earlier stage, with some demonstrating significantly longer survival. Hanna et al. studied a predominantly early-stage non-small cell lung cancer (NSCLC) population (79% stage I) that underwent surveillance with simultaneous CXR and minimal-dose CT at 3, 6, 12, 18, 24, 36, 48, and 60 months and found that minimal-dose CT was more sensitive (94% vs 21%; p<.0001) and had a higher negative predictive value (99% vs 96%; p = 0.07) than CXR for the diagnosis of new or recurrent lung cancer [15]. They also demonstrated that patients whose successive malignancies were detected asymptomatically had a markedly greater rate of curative-intent treatment (75%) compared to symptomatic patients, and that those treated with curative intent had improved median survival compared to those treated palliatively (69 months versus 25 months p<0.0001).

A retrospective study utilising Surveillance, Epidemiology, and End Results-Medicare data (1995-2010) examined the survival of surgically resected patients, with stage I and II non-small cell lung cancer (NSCLC), categorized by imaging received during the first 4-8 months following resection. Five-year survival by initial surveillance imaging was 61% for CT, 58% for chest radiography, and 60% for no imaging. CT was associated with a lower overall risk of death for stage I patients (HR, 0.85; 95% CI, 0.74-0.98), but not for stage II (HR, 1.01; 95% CI, 0.71-1.42). Overall, initial CT was not associated with improved overall survival (HR, 1.04; 95% CI 0.96-1.14). Stage I patients with early follow-up may represent a subpopulation that benefits from initial surveillance [16].

A meta-analysis of nine studies that examined the role of more intensive follow-up for 1669 patients with treated stage I-III lung cancer including those with CT based follow-up showed asymptomatic recurrence was associated with increased survival (HR 0.61 (0.50-0.74) (p<0.01.). The analysis included heterogeneous studies of varying disease types, stage, radically and palliatively treated patients managed using various follow-up regimens. A nonsignificant trend for intensive follow-up to improve survival was identified for the curative intent treatment subgroup (HR: 0.83; 95% confidence interval: 0.66-1.05) (Figure 3) [17].

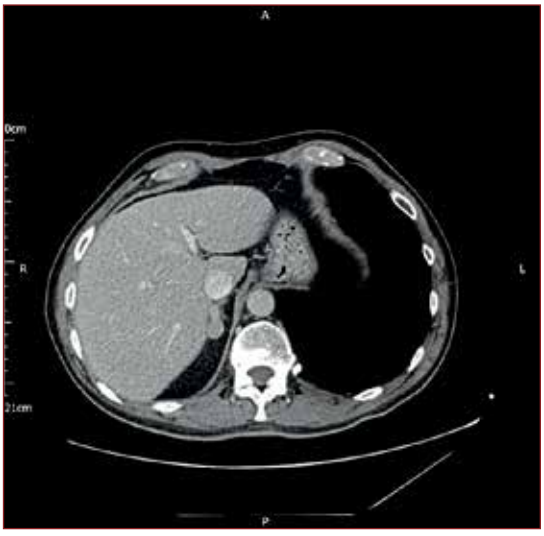

Figure 3: Right adrenal metastasis identified during CT follow-up 1-year post resection of pT3N0M0 adenocarcinoma of the lung. Patient underwent adrenalectomy and continues in CT follow-up program.

Evidence against CT follow-up of surgically treated lung cancer patients

There is inconsistency with regards to the results of studies demonstrating earlier detection of lung cancer and resultant improved survival. Several studies have shown no difference in survival comparing CT based follow-up to CXR or less intensive methods. A retrospective analysis of patients managed according to surgeon choice showed CT follow-up of stage I lung cancer was associated with earlier diagnosis of successive malignancy compared to CXR, although no difference in survival was demonstrated. The study excluded 586 of 1140 patients for various reasons. This reduced its ability to detect survival differences of less than 29% [18]. Nakamura et al. [19] reported similar survival for 1389 stage I patients utilising surveillance with CT and CXR vs. CXR alone, whilst Younes et al. [20] demonstrated that routine follow-up with CT did not improve survival compared to symptom-based follow-up in 130 patients with stage I-IIIB previously treated disease. Similarly, Benamore et al. [21] found that in patients previously treated for stage IIB-III lung cancer, CT offered earlier detection of successive malignancy but did not result in improved survival compared to chest radiograph follow-up. These studies vary in their power to detect survival differences and in initial stage of lung cancer patients entered into follow-up programs.

Does CT follow up detect recurrence or is it screening of a super risk population for new primaries?

The precedent of utilising CT in high risk groups to identify primary lung cancer and consequently reduce mortality has been set by trials of CT screening in high risk patients. The National Lung Screening Trial (NLST) [6] examined the use of routine low-dose CT scans in patients at high risk for developing a first primary lung cancer compared to routine chest radiograph. Identification of lung cancer was around 0.6% per person-year. They demonstrated a 20% relative reduction in mortality for lung cancer. The risk of new primary tumours in the population of patients with prior radically treated lung cancer is approximately 10-fold higher than the risk of identifying lung cancer in a high-risk group of smokers who are lung cancer naïve. An extrapolation of the survival benefit from the lung cancer naïve screened population to the post-resection population may be an oversimplification due to the added risk of recurrence in this latter group. Any survival benefit of screening such a population for metachronous lesions may be masked by the risk of recurrence in this group with its attendant poor prognosis (Figure 4).

Does CT follow up produce significant false positive results?

The rate of false positive disease detection is of concern in any CT based imaging program. This is likely to be similar or less than the incidence false positive rate in lung cancer screening programmes, and may be managed in a similar manner. In a review of lung cancer screening studies, major complications secondary to invasive investigations in those with false positive scans were uncommon [22]. The overall rates of abnormal or indeterminate surveillance CT which required additional testing that did not result in a diagnosis of recurrence or second primary cancer were 25% with an invasive diagnostic rate of 4-5% in a study of CT based follow up [1, 18]. The complication rate as a result of subsequent invasive diagnostic procedures was 0.3% [1, 23, 24]. Surgical intervention for benign disease was rare (0.24%) [23].

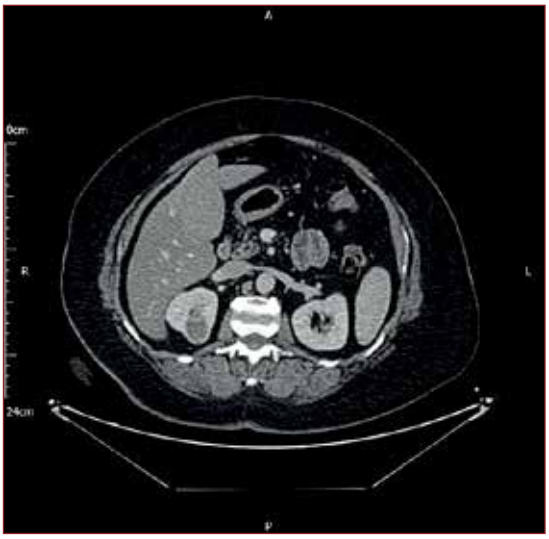

Figure 4: Right renal primary tumour identified during CT follow-up 1-year post resection of pT1aN0M0 adenocarcinoma of the lung. Patient underwent right partial nephrectomy with curative intent and continues in CT follow-up program.

What is the correct imaging protocol, imaging frequency and risk of radiation exposure?

The extent to which resected lung cancer patients are cumulatively exposed to radiation during the period of a follow-up program will depend on the exact protocol chosen by each institution. It is possible to perform a range of examinations, from low dose chest CT (LDCT) to whole body contrast-enhanced CT. These result in a range of radiation exposures. There are several population-based factors that need to be considered in the context of radiation exposure in patients with a prior history of lung cancer. It is important to remember that radiation exposure is not of relevance to patients with incurable recurrence, and almost certainly not in patients with potentially curable recurrence, as they would need to be worked up to exclude metastatic disease prior to radical treatment. The median age of presentation in patients with surgically treated lung cancer is 73 years, and radiation exposure in this patient age group is of less significance than the young. The additional risk of cancer secondary to radiation from a CT is 1 in 1,820 for a 10mSv exposure, expressed over 20 years, whereas the risk of developing a second lung cancer is between 1 in 100 and 1 in 20 patients per year post resection.

Which scanning protocol to use has not been determined. The AATS recommends annual LDCT screening to be offered to all surgically treated NSCLC survivors who have completed 4 years of radiologic surveillance without evidence of recurrence [8]. A low dose CT scanning program involving 7 scans over 5 years will expose the patient to a total of approximately 14 mSv dose. This will allow detection of pulmonary recurrence and new cancers but will not allow detection of nodal disease or other sites of metastatic disease.

Whether patients are ultimately discharged from follow-up at 5 years will depend on a normal scan at this time point, patient anxiety at the prospect of discharge and the institutional protocol. Identification of a second primary remains stable over time, at 3% to 6% per person-year [1] and therefore beyond 5 years, ongoing scanning will tend towards screening of a very high-risk population rather than identification of recurrence. Should surgically resected lung cancer patients be treated as a high-risk screening cohort without discharge? Analysis of nuclear worker cohort studies and atomic bomb survivor studies

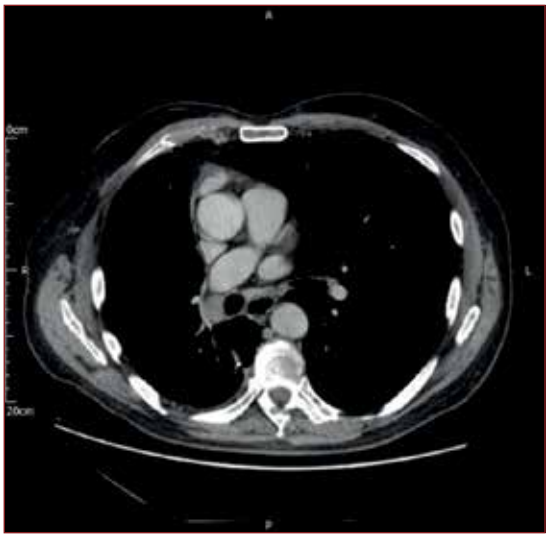

Figure 5: Intrathoracic nodal recurrence identified during CT follow-up 6 months post resection of pT3N0M0 adenocarcinoma of the lung. Tissue confirmation obtained at EBUS.

suggests that a lung screening participant may experience a cumulative radiation exposure of up to 280 mSv over a 20-year period and 420 mSv over 30 years [25]. Although these levels can independently increase the risk of lung cancer, most lung cancer survivors will not experience such levels given the average age of lung cancer patients is 73 years at diagnosis.

Lung cancer follow-up studies and programs have generally utilised non-contrast CT chest. The use of contrast CT chest, on the basis that the identification of hilar or mediastinal lymph node metastases, as well as liver metastases, is an important component of post-surgical follow-up has been advocated by others. Indeed, Lou et al. found 74% of patients had some degree of extra-thoracic disease [1]. Our institution utilises a contrast-enhanced CT chest, abdomen and pelvis with cumulative exposure of around 100 mSv over 5 years. Whether CT chest will suffice and what the added benefits of inclusion of the abdominal and pelvic areas are is still to be determined. The additional independent radiation-induced cancer risk to patients is approximately 1.5%, however when corrected for the average age of lung cancer patients represents only 0.02% additional risk. In reality, the additional radiation exposure of contrast CT chest, abdomen and pelvis versus non-contrast CT chest in this already high-risk of cancer group may prove negligible.

Costs

Clearly the establishment of CT-based follow-up has significant cost implications and cost benefit estimations are calculated in terms of cost per year life gained (LYG). Cost per life year gained calculations for follow-up for resected NSCLC patients range from approximately £25,000-£70,000 [5, 26] with suggestions that more intensive follow-up is associated with reduced cost per LYG. Gourcerol et al. [5] found the cost per LYG was $32700 (Euros 22397, £26,300). In one study in which patients underwent physical examination and chest radiography every 3 months, and CT chest, bronchoscopy, abdominal ultrasound, brain CT and bone scan every 6 months for 3 years, then every year over the following 2 years the cost per LYG was approximately £25,000. Whilst these costs might be considered acceptable, the authors suggest that costs could be further reduced to under £20,000 by omitting the bone scan which did not diagnose curable recurrences. Interestingly, even when the full costs of such an intense follow-up program are considered, the cost per LYG

appears to be considerably less than a clinic and chest radiograph based protocol. A Swiss study found it cost over £70,000 per additional life year when costs of a chest radiograph protocol were examined. The protocol included 3 monthly chest radiographs for 2 years then 6 monthly up to 5 years and then yearly for 10 years. Second curative treatment was performed in 4.1% of patients with 17 additional life years gained [26]. Older studies may underestimate the true cost of screening in terms of LYG due to higher recurrence rates in studies performed before the current era of accurate pre-operative staging. Such studies are notable for their significant number of stage III patients, high pneumonectomy and recurrence rates [2, 20] (Figure 5).

Does one size fit all?

Most current follow-up programs and studies have assessed the role of CT in a heterogeneous post-resection follow-up group. Having been deemed suitable for resection, the grouping of these patients together into a single follow-up protocol may not ultimately be the optimal approach for all. This one size fits all approach may require amendment to account for pT1a tumours versus those with large tumours or nodal disease who have undergone adjuvant chemotherapy. Saweda et al. in a retrospective review of practice, recommended pathways based on risk of recurrence [27]. Pathways included recommendations for frequency of physical examination, blood tests, chest radiographs and chest CT. Of note the recommendation for frequency of CT was 6-monthly for 2 years and then yearly to 5 years with the exception of the low risk pathway pertaining to minimally invasive adenocarcinoma and adenocarcinoma in situ [27].

Evidence for PET-CT

Toba et al [28] utilised PET-CT as part of a follow up protocol which also included CXR, CT chest and MRI brain. Patients underwent alternate PET-CT or chest CT every 6 months for 3 years and then annual PET-CT for the next 2 years. They found high sensitivity, specificity, positive predictive value, negative predictive value and accuracy (94.4%, 97.6%, 89.5% 98.8%, 97.0% respectively). However, most patients underwent only one or two PET scans during their follow-up period and therefore the role of PET-CT in the routine follow-up of patients over time is yet to be determined [28]. In a study utilizing 6-monthly CT with additional annual PET-CT post resection of lung cancer, FDG-PET-CT identified some recurrences not identified by chest CT. However, FDG-PET-CT was less sensitive than CT in the detection of small adenocarcinomas and ground-glass lesions [29]. In a subgroup of patients with recurrence who had undergone both PET-CT and chest CT, 37% were detected by PET-CT only, 51% were detected by both PET-CT and CT, 12% detected by CT only. Some studies of the use of PET-CT in surveillance may suggest additional value over CT, however, it must be considered that most series compare PET-CT with chest CT. Our experience of CT of the chest, abdomen and pelvis in the follow-up of lung cancer patients has also identified a significant number of recurrences (>10%) which would not have been identified on a chest CT alone, and the role of PET-CT versus chest CT or CT chest, abdomen and pelvis needs to be evaluated. Issues with PET-CT include its significantly greater cost (5-10 times that of a CT of the chest, abdomen and pelvis) and greater radiation exposure (2-3 times that of CT) [30]. Given the current data, most guidelines specifically do not recommend a role for PET-CT in the follow up of resected lung cancer patients [7, 9, 31].

Pending Randomised Controlled Trials

The results of the IFCT-0302 trial are awaited. This phase III, multicentre, randomised, controlled trial will address the clinical and cost effectiveness of surveillance CT and fibreoptic bronchoscopy and chest radiograph versus chest radiograph alone after complete resection for stage I to IIIa NSCLC. Physical examination and chest radiography every 6 months during the first 2 years then every year over 3 years will be compared with physical examination, a chest radiograph as well as a chest CT scan with sections of the liver and adrenal glands, and a bronchoscopy in some, every 6 months during the first 2 years then every year over 3 years. The primary end-point of the study is overall survival. Whilst this trial will increase our understanding of the role of CT chest versus chest radiograph, further questions will remain including the role of extended CT in identifying distant relapse and oligometastatic disease. Moreover, the role of PET-CT and brain CT will also require evaluation.

Wider benefits of CT based follow-up programs

The development of CT follow-up of resected NSCLC patients has a number of benefits over and above those of purported improvement in survival. Most current CT programs suggest intervals between scans of 6 to 12 months compared to chest radiograph follow-up which have often required patients to attend every 12 weeks. This allows patients to attend the hospital less frequently, saving time, money, and interval anxiety for patients. This also facilities improved overall clinic capacity leading to increased efficiency for the institution. The protocol-driven nature of such programs lends itself to nurse delivered clinics which allows the nurse to become a single point of contact for lung cancer survivors. Moreover, trainees are freed to review only new patients. The benefits of CT reports being available prior to patients attending clinics creates ‘organised’ clinics compared to patients attending for chest radiographs on the day which require later reporting if abnormalities are not recognised prior to reporting by radiologists. Given this knowledge is available prior to the patient attending the clinic, the development of virtual clinics can also be considered for patients who consent to obtaining the results of their scans over the telephone.

Barriers to the development of CT based follow-up programs

A number of barriers need to be overcome to develop a clinical CT follow-up program. Whilst the evidence currently is uncertain, historical precedent and status quo bias may inhibit the development of new programs. Certainly, involvement of chest radiology expertise is the key to the success of any such program. Chest CT based programs appear costlier even when the reduced frequency of CT vs chest radiograph is considered. However, where all costs are included such as reporting time and medical, nursing staff and administration clinic staff time, then the overall costs may not be substantially larger. In particular, entirely CT based programs facilitate the introduction of telephone based follow-up, reducing the institutional footprint with reduction in overall costs. We have developed a virtual clinic at our institution since the introduction of our CT only based follow up.

Conclusion

Whilst higher detection rates of both recurrent and new disease have been demonstrated in some studies of CT vs. chest radiograph follow-up, there is a lack of definitive evidence

for a survival benefit. At present, no prospective randomised study has been completed to evaluate the outcomes of CT based follow-up of radically treated lung cancer patients. The value of screening for second primary cancers seems attractive in light of the results of the National Lung Screening Trial, but it remains less clear whether earlier detection of distant recurrences can lead to improved survival or quality of life. Further understanding will depend on the outcome of randomised, controlled trials to assess survival and patient-centred outcomes.

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Postscriptum

Eheu fugaces, Postume, Postume
labuntur anni, nec pietas moram
rugis et instanti senectae
adferet indomitaeque morti.

Quintus Horatius Flaccus
65 – 8 B.C. from Carmina, II, 14.

In a faraway land, near the end of the earth, where the clouds are low and dark and heavy, where the raging winds pummel the cliffs, between the 'Furries' and Cape Horn, the people of Tierra del Fuego count only one, two and many.

We are very pleased to have reached three! Volume III of the Perspectives in Cardiothoracic Surgery. This book carries from now on the seal of perdurance. It is established as an ongoing yearly publication, a part of the educational programme of our Society. Together with the SCTS University, the Scholarships plan and other educational activities, it became one of the Society's pillars.

The 18 Chapters comprised in this volume pertain to a variety of up to date topics from the advanced edge of our Speciality. They give the reader clear, detailed and well documented descriptions on various subjects. These Chapters were produced by great specialists in their respective fields, specialists who gave gladly their time and experience to contribute to the works of our University and the publication of this volume.

Paul Modi, the Editor in Chief of the 'Perspectives' series, established and guided a small team of guest editors, all specialists in their domains. Together they produced this third volume, a highly scientific and pleasantly aesthetic Book for the use of all students of Cardiothoracic Surgery.

It is obvious that the high quality and diversity of the subjects addressed in the first three volumes of 'Perspectives' is due to the progress made in scientific research in our speciality.

Following my personal dreams, I would have wished to see more surgeons engaged in research. For those who intend to embark on this exciting field, I take the liberty to venture some advice.

One should understand from the beginning that research activity does not always lead to success or happiness or peace. To paraphrase Fernando Pessaro: The gods placed danger and the abyss in the sea, but they also made it heaven's mirror, Nothing is simple or easy! Be prepared, read all if you want to know all, thus you may discover what does not exist

and what should be created. Let yourself be attracted toward the impossible, even toward Utopia and open the window towards thy sky to see the light flowing in waves. Only with sails full-set should you wait for the wind, as good sailors do. But you should also be prepared to travel the circuit between the sublime and the ridiculous unflinchingly. Most scientists know of both from Kipling's 'If-'.

But finally, you may reach the point when success will make you bask in the price of critics and the envy of your colleagues and suffer when your work falls into the wrong hands.

Do not despair, the learned world knows about 'invidia medicorum pessima' and how to disregard it. Please bear in mind also that when you have reached the top of the mountain, then, as the Prophet said, only then do you really begin to climb and I wish that you remember this thought when you have reached the top of your many mountains.

Marian Ion Ionescu

Autumn 2017 – Chamonix