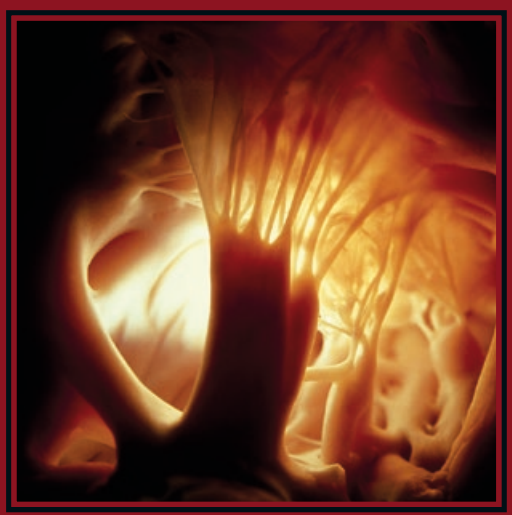
Society for Cardiothoracic Surgery in Great Britain and Ireland

Perspectives in Cardiothoracic Surgery

The SCTS Ionescu University Volume IV



Series Editor
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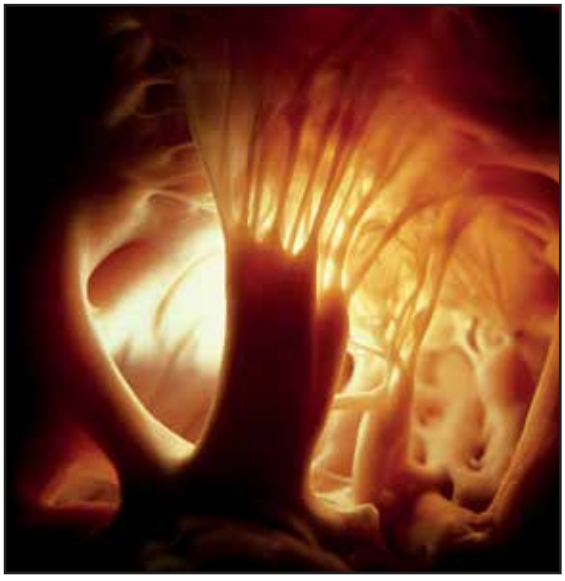

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Perspectives in Cardiothoracic Surgery

The SCTS Ionescu University
Volume IV

Edited by Paul Modi

Invited Editor Marian Ion Ionescu

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Section II: Thoracic Surgery

Guest Editor *Steven Woolley, Liverpool, UK.*

Society for Cardiothoracic Surgery
in Great Britain and Ireland

SCTS Ionescu UNIVERSITY

Preface

"An nescis, mi fili, quantilla prudentia mundus regatur"

Axel Oxenstierna (1583-1654)
In a letter to his son, 1648

As you will see from this beautifully written and presented book, the SCTS Ionescu University goes from strength to strength. This current work summarises the presentations made at the 2018 meeting in Glasgow, which once again had a record attendance. Delegates were privileged to hear presentations from experts from all over the world on all the current controversial areas of practice in our speciality. We are grateful to all the speakers who made the meeting such a great success. Indeed, the main problem for the organisers is to fit everything in to one day. The feedback was, as always, excellent and we look forward to the next SCTS Ionescu University in London. This will be the 10th anniversary since its inception, and it is fitting to recognise at this time the inspiration of Ian Wilson, whose vision when he organised the University in 2010 has led to what you all see today – one of the best educational events in cardiothoracic surgery anywhere in the world.

This latest volume of "Perspectives" is one of the largest yet and is a very worthy addition to any cardiothoracic surgeon's bookshelf. In these days of electronic publications, it is always a pleasure to have an actual printed book to browse through. We would like to thank all who have contributed to the detailed and well-referenced chapters, and the editors for bringing it all together. Steven Woolley has for many years been the guest editor for thoracic surgery and, as always, has done a great job. It is a pleasure to welcome and thank Bil Kirmani as guest cardiac surgery editor. Particular thanks go to Paul Modi who has been the lead editor since "Perspectives" first emerged as a record of the SCTS Ionescu University in 2015. As anyone knows who has done this sort of thing, Paul has done a truly fantastic job in what is a very difficult task – coordinating presentations and submissions from authors in many parts of the world and bringing it all together in the great work you have in your hands as you read this. Paul will be handing over the lead editor role to Bil for the next publication and we wish him a well-earned break, although I know Bil and Steve will be reassured that they will be able to draw on his expertise in the future.

Finally, on behalf of the whole SCTS, we would like to thank Mr Marian Ionescu for his unstinting support for our Society, not only for the SCTS Ionescu University and his help with the production and publication of Perspectives, but for all he does for SCTS Education. We are very lucky to have him as our colleague.

Richard Page
President 2018-20

Simon Kendall
President elect 2020-2022

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"Non fumum ex fulgore, sed ex fumo dare lucem Cogitat, ut speciosa dehinc miracula promat"

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Ars Poetica V 143

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In Search of the Mythical PHOENIX

Every four hundred years
a stupendous bird
arises from its ashes

From the Song of Miracles XVI

'Once upon a midnight dreary, while I pondered, weak and weary,

Over many a quaint and curious volume of forgotten lore –

While I nodded, nearly napping.....'

I gently glided into a dream about the old legend of the mythical immortal bird.

Very shortly, this year, there will be four centuries since the last rebirth of the Phoenix. The legend says that the immortality cycle will continue for evermore. Even within a dream one could make the wish to celebrate two significant events at the same time. The discovery of the place where Phoenix rises from his ashes every 4 centuries and the publication of volume IV of Perspectives in Cardiothoracic Surgery. I have to make haste, to wing my way in search of the unknown place where the miracle may happen. From there, the re-born Phoenix, in its colourful, brilliant splendour will fly away towards its own dreamland, away and out of human sight.

As in most man-made dreams the classic rules of theatre can be ignored. Time has already been bent mathematically, space has been altered at the whims of glorious emperors and unscrupulous dictators, and even History itself has been greatly damaged. Therefore, in this dream I will also take license to ignore the historic real time. This will make the dream appear incoherently fragmented and separated, but it will contain a large number of widely shared memories, awareness and experiences. It will also make it a black-powder mix of history, witchery and imaginary thoughts. Dreams are like this.

A vehement entreaty of my need for help in this enterprise was unexpectedly answered. The gentle Favonius blew the clouds apart and the heavy gates of the upper world opened. The miracle began. I saw descending with the sunrays through the gap between the clouds three Spectres from the glorious past of mankind.

Walking down the huge monumental staircase of the Walhalla, the temple on the Danube of the great German spirits of the past, was Alexander von Humboldt, the 'Inventor' of Nature, coming to help me in the search. From the National Maritime Museum in Greenwich, advanced with a steady step, Isaac Newton, the 'Inventor' of the Firmament and its laws. From the bridge of his beloved Beagle, Charles Robert Darwin the 'Inventor' of Evolution and its explanation descended to join us. The three giants of science and knowledge granted the immense favour of adopting me. What is more, they liked and embraced the idea of discovering the place of the bird's rebirth. I shall call them, during the

time of our travels, 'The Three Great Magi'. They had the spirit, the will and the courage to tear away the veil which covered the unconsciousness of nature. I shall always see them in the inner mirror of my dreams yclad with their long robes walking together and fading away in the crepuscular purple of history.

Many followed in their footsteps of discovery and invention and many before them opened other avenues of search and knowledge. If man did not have the genius of creation and used it in a continuous stream towards the spiral of progress, the obscurity around past centuries would have caught fire.

Our discussion about where to start our search was simple. We knew nothing of the subject therefore we started from the North with Newton guiding us there by the stars. As we approached that land we could smell the dampness of abandoned bricks and stone. The air was brewing dark as tea. There, long ago, the world had drawn the curtains back. The sky lay shattered to the ground. The gates of heaven hung useless by the side and shards of the last rainbow were mixed with splinters from the crumbling walls. We found tall ruins robed in ivy folds, derelict crumbling city walls, deserted palaces lying in slumber surrounded by desolate gardens. The emptiness was hard and cold. There, I realised that from under each ruin flowed a river of melancholy and regrets, as Lucian Blaga would say. The last footprints of the gods had disappeared. 'Sic transit Gloria mundi'. Surprisingly we did not find anything resembling a parliament house in the ruins. Isaac Newton calculated that our visit North might have taken place around the year 2050AD. We have readily turned our backs on the crumbling future where we have not learned anything about our goal.

Always believing that we may find somewhere, someone to help with our endeavour, we thought to visit the studio at 11 Impasse Ronsin in Paris where Constantin Brancusi was creating a new world of sculpture. We visited there in the years between the two Great Wars. The Romanian coryphaeus was a pioneer of Modernism, the most influential sculptor of the 20th century, called the patriarch of modern sculpture. His series of the miraculous bird, golden bird and the many 'Bird in Space' remains in the centre of his masterpieces. We must visit him. He may know something of miraculous birds. We were politely received by the Master and by some of his friends in his Atelier. We were elated to encounter them. Our surprise however was great when we realised that none of these masters and artists knew about our immortal bird.

We left, happy to have met so much talent and genius in one small place but our parting had something of the sad perfection of a sonnet. Incidentally, one of that group mentioned La Fenice.

During our long walk across the Alps, towards Venice, Humboldt began to describe what Serenissima represented for civilisation. He was a very learned man, dripping with history and the gift of storytelling. He opened the treasure of his memory, rich with the most noble fruits taken from the literary orchards of many nations. He spoke and the yarn he spun wove a tapestry of enthralling fantasies and historical facts at the back of our eyes. Venice, he started, is a colourful dream suspended between sky and sea. It remained the most powerful sea empire for centuries and a republic which perdured over a thousand years. These were the pillars which supported an immense cultural and artistic creative edifice. It is a city of a thousand mirrors which reflect our most daring dreams. It is the most mysterious and nostalgic place, blessed by all the Muses. It is a unique open-air museum built with the most exquisite mineral lace of stone and marble. Despite the vicissitudes of times past, the Serenissima remains proud, haughty, arrogant and majestic in its luxury

and melancholy. At sunset, the ripples on the canals became liquid silver and the air a glittering powder of gold.

But our centre of interest was La Fenice, the famous lyric theatre which had been burned to the ground three times during the centuries and rebuilt more beautiful each time. We were allowed inside the superb gilded structure. No-one there knew anything of interest to us. On leaving the place, an old man whispered to us: Go to the Island of Torcello at sunset to meet the great wizard in the graveyard behind the church. While sailing to Torcello Newton, who knew something of scientific magic, told us his views on witchery. He started with a question. What do we know about wizards except that they live in the present moment and travel on the wings of the wind? They do not cast a shadow in daylight and leave no tracks in the dark. Their perpetual diaspora in ubiquity represents their certitude, their transcendent homeland, a universe without roots, like its inhabitants, as far from this life on the ground as that of angels and phantoms. Although attached to this world they do not seem to be part of it. There is something unearthly in their walk on this planet. They must have witnessed, in a distant past, a display of beatitude of which they guard a nostalgic souvenir. And what could they have seen in the twilight of time that escapes our perception? I still wonder, what do they contemplate in their longing for the land of their memories. And which land is that? And in what seasons did it happen? And what if their souvenirs are but feathers left forgotten in empty nests?

Newton was right. We watched a medieval incantation by the great wizard that ended with: All signs point to the South, Follow Al Abiad to the mountains. Is it that some restless spirit of older times has spoken through the wizard's voice? At first, we were downcast, almost depressed, sad as a Sunday afternoon, when suddenly Darwin understood what the wizard meant. We regained confidence and hope although there is folly to bring hope into logic.

We started our journey South full of elan and excitement, on land alongside the Nile or on water on feluccas when the fellahins sailed up the river. We passed Khartoum and advanced on the al Abiad up to the little town of Faguir from where we followed the Al Abiad al Jabal on the Mountain Nile. Beyond Bahr al Jabal we were almost sucked into a valley called by the local tribes Ouadi al Shaitan al Mothlim. In this devil's sombre valley, we advanced slowly and carefully. Menacing clouds descended over the place. The air became heavy and dense with the mist which enveloped everything, it smelt of tar and burnt feathers. The sky became even darker, it looked like a nightfall which carries something of the beauty of a hallucination. Lightening came down with black and silver arrows; the dying stars cast their feeble amber light upwards towards a transparent firmament. The waterfalls, still shining in the sombre valley were silent like petrified light. We felt like we were in Hell. I remembered Churchill's advice that when you reach Hell, don't stop, keep going. And so we did.

Soon the nightmare vanished as we came to an open space which looked like a huge lake. As we approached, it became a sea of sand, a desert, perhaps the place we searched for. As it is unknown to the world I named it Sahra al Hakim al Nairam *. We settled for the freezing night as well as we could. Cold nights in the desert bring the stars closer to us. The morrow came with a strange light in the west. It could have not been the sun rising. It grew bigger and brighter as it came closer to us. It was a ball of fire, a multitude of colourful strings in flames, an explosion of light, a joy of a myriad of sparks around an astonishingly marvellous bird. The miracle of the rebirth of the Phoenix from its ashes happened before our very eyes. The Phoenix fluttered its exquisite majestic plumage and took to the air. It circled around us once before darting away towards another dream.

The time for separation and departure was upon us. The word Namaste was uttered by all four of us. The three Great Magi walked away on a pathway of thistle but, as always, their feet did not touch the ground. In the distance, the horizon bled in all colours of the rainbow before sinking slowly into the crepuscular majestic gold and purple for the three Great Magi to fade away solemnly into history.

Alone in the desert, I had to think of my return home. I had to put the last few words on volume four of the Perspectives in Cardiothoracic Surgery. I shall have to ask the Keeper of the Tower of London to send me two large ravens to help me with the return.

Marian Ion Ionescu
Monaco, Summer 2018

**The desert of the Doctor Marian*

Section 1

Cardiac Surgery

Bilal Kirmani

"Non nobis solum nati sumus"

Marcus Tullius Cicero (106BC-43BC)

SECTION 1 CARDIAC SURGERY

Coronary Artery Surgery

"Sic transit gloria mundi"

Used between 1409 and 1963 at papal coronations

Chapter 1

Debate: The Optimal Strategy for High-Risk Coronary Patients

Conventional On-Pump:

Mustafa Zakkar and Alan Bryan

Off-Pump:

Umberto Benedetto and Gianni D Angelini

Robotic Hybrid Revascularisation is the Future:

Bob Kiaii, Ali Hage, Michael WA Chu, Kumar Sridhar, Christopher C Harle and Patrick Teefy

"Espice, adspice, prospice"

Conventional On-Pump

Mustafa Zakkar, Alan J Bryan

"Consuetudinis magna vis est"

Introduction

Coronary artery bypass grafting (CABG) with conventional cardiopulmonary bypass (ONCABG) has been the standard surgical technique for patients requiring CABG since its development more than 50 years ago. It is recognised that the use of cardiopulmonary bypass (CPB) is associated with a range of potentially deleterious effects which include the activation of different inflammatory and coagulation cascades due to the contact of blood with the non-physiological surface of the bypass machine. Additionally, there is a significant degree of anticoagulation and haemodilution of the patient's circulating volume (from the prime volume in the pump) with CPB, as well as considerable manipulation of the aorta (e.g. from cannulation) [1,2]. These factors can result in an increased risk of post-operative adverse events such as bleeding, increased use of blood products and a theoretical increase in the incidence of stroke. Off-pump CABG (OPCABG) was introduced more than three decades ago in an attempt to avoid the detrimental effects of CPB as well as to reduce aortic manipulation with a potential reduction in the risk of neurological events. Whilst, in theory, avoidance of cardiopulmonary bypass should result in a reduction in the incidence of a range of adverse outcomes and mortality, in practice these benefits have been hard to demonstrate convincingly. Indeed, OPCABG has presented a set of specific problems related to this technique such as haemodynamic instability during exposure of the coronaries, impaired quality of the anastomoses and consequent reduced graft patency as well as the risk of incomplete revascularisation [3]. Thirty years later and after a colossal amount of retrospective series, randomised trials and meta-analyses, there is still no clear answer with respect to the superiority of one technique over the other.

In cardiac surgical centres across the world, the situation with respect to the use of OPCAB is now relatively stable with a minority of CABG operations being undertaken without CPB (15-20%) in most Western countries, albeit much higher proportions in countries such as India. Uptake of OPCAB is generally related to the preference of a particular cardiac surgeon (as we have noted over the years at the Bristol Heart Institute) rather than the specific application of it in a particular situation (Figure 1).

In the current era, where surgeons are expected by their patients to deliver the highest levels of care and outstanding early and late outcomes, CABG remains the benchmark treatment for most patients requiring multivessel revascularisation particularly those with a higher risk profile such as diabetics and those with poor LV function. Our primary aim is to achieve complete revascularisation and the secondary long-term prognostic benefit that will accrue from this while minimising adverse outcomes in the perioperative period.

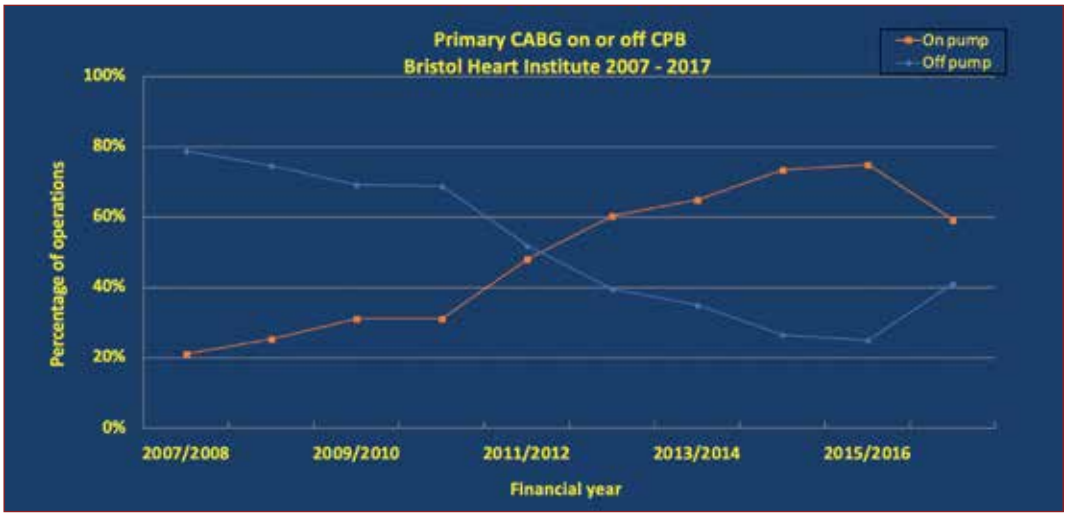

Figure 1: Data from the Bristol Heart Institute demonstrating the changing trends in CABG over the years with a steady rise in the number of cases being done on-pump mirrored by a fall in the number of off-pump cases.

Complete revascularisation offers superior outcomes to incomplete revascularisation, with better long-term survival and a lower rate of reintervention especially in this high-risk cohort [4-6]. On this basis we believe that ONCABG should remain the gold standard treatment for patients requiring surgical revascularisation, regardless of risk profile, based on currently available evidence.

There are three frequently cited randomised clinical trials: Randomized On/Off Bypass (ROOBY) [7], CABG On or Off Pump Revascularization Study (CORONARY) [8], and the German Off-Pump CABG in Elderly (GOPCABE) trial [9] which have attempted to address the superiority of on- or off-pump CABG in a broad range of essentially low risk patients.

a) The ROOBY trial demonstrated no significant difference between OPCABG and ONCABG in the rate of a 30-day composite outcome (reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure) before discharge or within 30 days after surgery (7.0% and 5.6%, respectively, p=0.19). A careful review of the ROOBY trial shows that the proportion of patients with fewer grafts completed than originally planned was higher with OPCABG than with ONCABG (17.8% vs. 11.1%, p<0.001). Moreover, at 1 year, the rate of the composite outcome was higher for off-pump than for on-pump CABG (9.9% vs. 7.4%, p=0.04). Follow-up angiograms in 1371 patients who underwent 4093 grafts revealed that the overall rate of graft patency was lower in the OPCABG group than in ONCABG (82.6% vs. 87.8%, p<0.01) which was mainly related to a lower rate of patency of saphenous vein grafts in the OPCABG group (76.6% vs. 83.8%, p<0.01). More patients in the OPCABG group had at least one occluded graft (36.5% vs. 28.7%, p<0.01). For patients with no occluded grafts, the rate of the primary 1-year composite outcome was higher in the OPCABG group (6.4% vs. 3.3%, p=0.03) which was attributed to less complete revascularisation. Admittedly, this trial was criticised by many because patients enrolled were almost exclusively males, there was a trend toward enrolling lower-risk and excluding higher-risk patients

and the conversion rate to CPB was 12% which brought some scepticism with respect to the level of off-pump 'expertise' of the surgeons involved in the study.

b) The CORONARY trial has been considered an improved version of the ROOBY trial – it showed no significant difference in the rate of the primary composite outcome of 30-day rate of death, myocardial infarction (MI), stroke, or renal failure requiring dialysis between OPCABG and ONCABG (9.8% vs. 10.3%; hazard ratio (HR) for OPCABG 0.95, p=0.59) or in any of its individual components. Off-pump CABG was, however, associated with an increased rate of early repeat revascularisations (0.7% vs. 0.2%; HR 4.01, p=0.01).

c) Once again, in the German Off-Pump CABG in Elderly (GOPCABE) study, there was no significant difference between patients who underwent off-pump surgery and those who underwent on-pump surgery in terms of the composite outcome (7.8% vs. 8.2%; Odds Ratio (OR) 0.95, p=0.74) or four of the components (death, stroke, MI or new renal replacement therapy) at 30-days after surgery. Repeat revascularisation occurred more frequently after off-pump CABG than after on-pump (1.3% vs. 0.4%; OR 2.42, p=0.04). At 12 months, there was no significant between-group difference in the composite endpoint (13.1% vs. 14.0%; HR 0.93; 95% CI, 0.76-1.16, p=0.48) or in any of the individual components. A more recent exploratory post-hoc analysis that investigated the impact of surgical aortic manipulation on the rate of stroke showed that there was no significant difference in the rate of stroke within 30 days after surgery between both groups (OPCABG 2.2% vs ONCABG 2.7%; OR 0.83, p=0.47). Additionally, within the off-pump group, different degrees of aortic manipulation did not translate in to significant differences in stroke rates.[10]

An aggregate analysis including more than 10,000 patients from the four most recent major trials also yielded comparable stroke rates for on- and off-pump CABG (OPCABG 1.4% vs ONCABG 1.7%, OR 0.87) suggesting that off-pump CABG did not result in lower stroke rates. The possible intrinsic benefit of off-pump CABG may be offset by the complexity of the operative technique as well as the complex pathophysiology involved in perioperative stroke.

It is important to note that these trials included a mix of patients and were not focussed on outcomes for high risk patients, which can present an interesting subset of patients with unique considerations. When looking at the high-risk cohort of patients, we can look at OPCABG vs. ONCABG in terms of both short and long-term outcomes.

Short-Term Outcomes in High Risk Patients

Moller et al., in the Best Bypass Surgery Trial, randomly assigned 341 patients with a Euroscore ≥5 and 3-vessel coronary disease to undergo coronary artery bypass grafting without or with cardiopulmonary bypass [11]. The primary outcome was a composite of adverse cardiac and cerebrovascular events (all-cause mortality, acute MI, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention). There were no significant differences in the composite primary outcome (15% versus 17%, p=0.48) or the individual components at 30-day follow-up. This trial showed that the mean number of grafts per patient did not differ significantly between groups (3.22 in OPCABG group and 3.34 in ONCABG group, p =0.11), however, fewer grafts were performed to the lateral part of the left ventricle territory during OPCABG surgery (0.97 versus 1.14 after on-pump surgery, p=0.01). At three years follow up, the composite outcome occurred in 69 (40%) patients undergoing OPCABG versus 54 (33%) in

the ONCABG group (HR 1.22, p=0.26). There were no differences in MI detected between groups (7% vs 14%; HR 0.53, p=0.06). Interestingly, no difference in stroke (HR 1.43, p=0.36) was noted and the incidence of stroke within the first 30 days postoperatively was 4% in both groups [12].

Lemma et al., in the On-Off Study, a multicentre prospective randomised parallel trial, enrolled patients for elective or urgent isolated coronary artery bypass grafting with an additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 6 or more [13]. The composite primary endpoint included operative mortality, MI, stroke, renal failure, reoperation for bleeding and adult respiratory distress syndrome (ARDS) within 30 days after surgery. The interim analysis included 411 patients (203 ONCABG and 208 OPCABG) and, according to the intention to treat analysis, the rate of the composite primary endpoint was significantly lower in the OPCABG (5.8% vs 13.3%, p=0.01) suggesting that OPCABG reduced early mortality and morbidity in high-risk patients. A more detailed review of this study reveals that there were actually no differences between on- and off-pump with regards to operative mortality (3.4% vs 1.9%, p=0.379), MI (3% vs 1.9%, p=5), stroke (0.5% vs 0%, p=0.99), renal injury (4.9% vs 2.4%, p=0.149), reoperation for bleeding (3.4% vs 1.4%, p=0.115) and ARDS (0% vs 0.5%, p=0.995). In fact, this study demonstrated that both are associated with excellent outcomes but with a significantly lower mean number of distal anastomoses per patient in the off-pump group (p=0.001).

Polomsky et al., in a retrospective review of the STS National Adult Cardiac Database, analysed 876,081 patients who underwent coronary bypass grafting [14]. Operative mortality, stroke, acute renal failure, mortality or morbidity, and prolonged postoperative length of stay were analysed. Off-pump CABG was associated with reduced adverse events compared with ONCABG after adjustment for 30 patient risk factors. This study was limited by its retrospective, observational nature. Although the group adjusted for the different preoperative factors, as well as surgeon and hospital factors, there was the potential for residual confounding from variables not captured in the STS Database. Another major limitation of this study was related to selection bias in the choice of OPCABG versus ONCABG and potential under-reporting of unplanned conversion from off-pump to on-pump.

Kowalewski et al., in another meta-analysis, assessed the benefits and risks of OPCABG versus ONCABG [15]. The endpoints assessed were all-cause mortality, MI, and stroke occurring within 30 days of the surgical procedure. There was no difference between the two techniques with respect to all-cause mortality and MI. Off pump CABG was associated with a significant reduction in the risk of stroke. A significant relationship between patient risk profile and benefit from OPCAB was found in terms of all-cause mortality and stroke. This analysis included a range of different studies over a long period of time. Results in this study were analysed at the trial level and not at the patient level which means that clinically relevant differences may have been missed. Moreover, the criteria for patient inclusion in the studies were different as was the level of experience of the surgeons.

Another recent systematic review and meta-analysis including 16,261 patients by Dieberg et al. investigated post-operative atrial fibrillation, MI ≤30 days, mortality, stroke and hospital stay [16]. Off-pump CABG led to a significantly lower incidence of post-operative atrial fibrillation (p=0.01), but no differences in either MI (OR 0.98, p=0.77) or 30-day mortality (OR 0.85, p=0.16). Furthermore, there was no significant difference in the incidence of stroke (OR 0.77, p=0.05). There were, however, significant differences in hospital length of stay favouring OPCABG.

A study by the Bristol group, where 250 patients (median age 65 years) with a preoperative LVEF <30% were identified and early and midterm clinical outcomes analysed (74 off pump; 29.6%), found that patients undergoing ONCABG were more likely to have more extensive coronary artery disease and to require more grafts than those undergoing OPCABG surgery. The only in-hospital outcome to show a significant difference after adjustment was the need for intraoperative inotropic support, which was higher in the ONCABG group (OR 5.1, p<0.001) [17].

Traditionally, ONCABG is carried out with a conventional CPB circuit and the heart is arrested. An alternative technique is to carry out CABG on-pump but with a beating heart (ONBH CABG) as a hybrid between off- and on-pump, especially for high risk patients. A meta-analysis of studies comparing the clinical outcomes of ONBH CABG with conventional arrested heart ONCABG showed that ONBH CABG provided a 45% lower risk of early mortality compared with conventional ONCABG (OR 0.553, p=0.003). There was significantly lower perioperative morbidity associated with ONBH CABG, including MI (OR 0.294, p=0.001), renal failure (OR 0.362, p<0. 001) and low output syndrome (OR 0.330, p<0.001) [18].

When investigating the early clinical outcomes of ONBH CABG versus OPCABG in patients with severely impaired LV function, Xia et al. studied 216 consecutive patients with LVEF≤35% undergoing non-emergent primary isolated CABG (ONBH CABG, n=88; OPCABG, n=128) [19]. Patients in the ONBH CABG had a significant higher early postoperative LVEF compared to OPCABG (35.6±2.9 vs. 34.8±3.3%, p=0.034) despite having a similar baseline LVEF (31.0±2.8 vs. 31.0±2.9%, p=0.930). Moreover, patients in the ONBH CABG group received a greater number of grafts (3.7±0.8 vs. 2.8±0.6, p<0.001). Interestingly, logistic regression analysis showed that surgical technique had no independent influence on in-hospital mortality or major postoperative morbidity in patients with a preoperative LVEF of 35% or less.

To overcome the potential adverse effects of traditional CPB, miniature CPB circuits were developed and introduced in to practice. These had the potential advantages of a reduction in the deleterious effects of traditional CPB, patient-derived volume addition, and better physiological compatibility. When comparing ONBH CABG to OPCABG using mini-CPB, Skancke et al. performed a retrospective analysis of 756 patients who underwent beating heart CABG using mini CPB (BHOP n=60) versus OPCAB (n=696) [20]. Multivariate regression analysis showed a protective effect on three- and six-year mortality for BHOP (OR 0.325, p=0.035; OR 0.323, p=0.031, respectively) and two (OR 0.385, p<0.001; OR 0.539, p=0.018) and three (OR 0.154, p<0.001; OR 0.315, p<0.001) vessel revascularisation, suggesting superiority to OPCAB.

Long-Term Outcomes in High Risk Patients

Complete revascularisation has been shown to be a predictor of better long-term survival [4-6]. The importance of complete revascularisation is clear in high risk patients, as demonstrated by a meta-analysis of 28 studies including 83,695 patients with 4.7±4.3 years of follow-up showing a reduced mortality and risk of MI [5]. It is, thus, logical that the main aim of surgery should be to achieve complete revascularisation. Although there is some debate with regards to early outcomes, it is clear that OPCABG is associated with more incomplete revascularisation when compared to ONCABG. It is hard to accept that this will have anything other than a negative impact on long term outcomes. In fact, the ROOBY trial at 5 years demonstrated a rate of death of 15.2% in the OPCABG group versus

11.9% in the ONCABG group (Relative Risk (RR) 1.28, p=0.02). Similarly, the rate of major adverse cardiovascular events at 5 years was 31% in the OPCABG group versus 27.1% in the ONCABG group (RR 1.14, p=0.046) (Figure 2) [21]. Furthermore, in high risk patients, the 3-year follow up of the Best Bypass Surgery Trial revealed that all-cause mortality was significantly increased in the OPCABG group (24% vs 15%; HR 1.66, p=0.04) (Figure 3) [12].

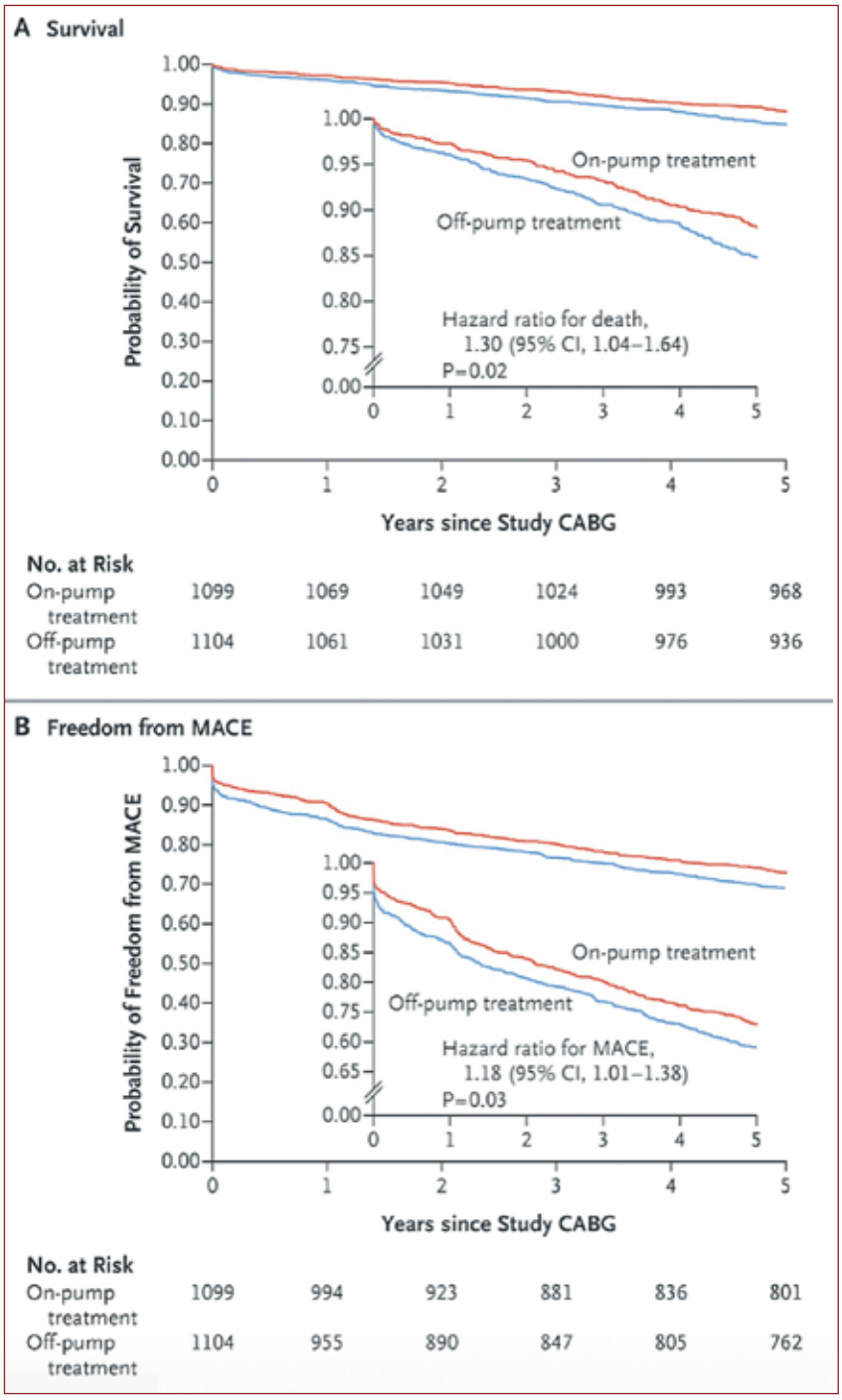

Figure 2: Kaplan–Meier Estimates of Rates of Survival and Major Adverse Cardiovascular Events (MACE) at 5 Years after Surgery from the ROOBY trial (reprinted with permission).

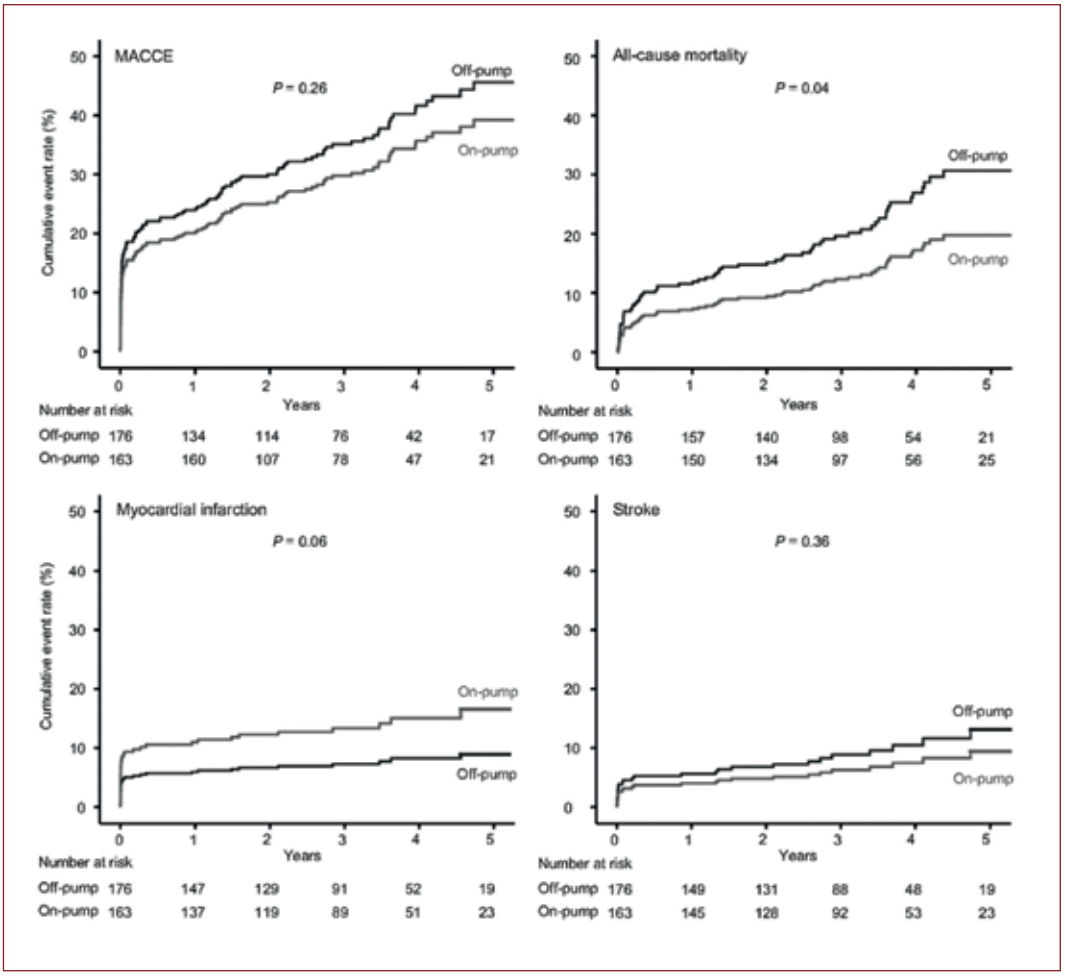

Figure 3: Intention-to-treat Cox regression analysis of major adverse cardiac and cerebrovascular events (MACCE: all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, or coronary reintervention) in the off-pump coronary artery bypass grafting (CABG) group (off-pump) versus the on-pump CABG group (on-pump) from three-year follow-up in a subset of high-risk patients randomly assigned to off-pump versus on-pump coronary artery bypass surgery: the Best Bypass Surgery Trial (reprinted with permission).

The most recent meta-analysis comparing OPCABG and ONCABG, where 104 trials were included, representing 20627 patients (OPCABG n=10288; ONCABG n=10339) with a weighted mean follow-up time of 3.7 years (range 1-7.5 years), revealed OPCABG was associated with a higher risk of mortality at follow-up (p=0.05). The difference was significant only for trials with mean follow-up ≥3 years and for studies with a crossover rate of ≥10%. There was a trend toward lower risk of perioperative stroke and higher need for late repeat revascularisation in the OPCABG arm [22].

Another recent meta-analysis by Smart et al. concluded that OPCABG was associated with an increased risk of long-term mortality (OR 1.16; p=0.03) [23]. In contrast, there were no differences in the incidence of MI (OR 1.06, p=0.45), need for revascularisation (OR 1.15, p=0.16), or the incidence of stroke (OR 0.78, p=0.16).

Takagi et al. performed a meta-analysis of adjusted observational studies and randomised controlled trials, enrolling a total of 104,306 patients and demonstrated a statistically significant 7% increase in long-term all-cause mortality with OPCABG (HR 1.07, p=0.0003) in the pooled analysis of all 22 studies [24].

An interesting study by Li et al. investigated the influence of OPCABG on early- and long-term mortality and morbidity in a consecutive series of elderly patients and showed that patients undergoing OPCABG had a higher incidence of stroke (HR 2.611, p<0.001), hospital readmission (HR 2.0, p<0.0001) and major adverse cardiac and cerebrovascular events (HR 1.764, p<0.001) [25].

Finally, a historical study by the Bristol group on the impact of surgical technique on outcomes in patients with impaired LVEF demonstrated that 3-year survival was higher in the ONCABG group (87%) compared to OPCABG (73%) but this difference did not reach statistical significance after adjustment for prognostic variables (HR 0.54, p=0.16) [17].

Conclusions

Current evidence from randomised controlled trials demonstrates that OPCABG does not offer any substantial advantages over ONCABG in term of major early health outcomes. However, there is a reduction in postoperative bleeding, blood transfusion and time on mechanical ventilation in patients undergoing OPCAB, but this is achieved at the expense of a reduced mean number of grafts and higher rate of incomplete myocardial revascularisation, which may explain the worse long-term outcomes. The message is clear: CABG should be performed using CPB, especially in higher risk patients where complete revascularisation is the key to achieving optimal long-term outcomes.

There is no doubt that the avoidance of CPB and aortic manipulation is essential in certain situations such as porcelain aorta and OPCABG, among other options, can be considered as it may potentially result in a reduced risk of aortic emboli or stroke. Off-pump CABG, like any other surgical technique, requires dedication, infrastructure, and expertise to achieve proficiency and good results. It perhaps should be considered as a sub-specialised technique, such as mitral or complex aortic surgery, considering that experienced surgeons and teams can achieve outstanding results - but it may not be for all surgical teams [26].

Finally, it is paramount to point out that we have to be very careful in our interpretation of meta-analyses on face value. There is nothing magical about a meta-analysis which is a form of observational study where a mathematical method is utilised to combine data which is weighted by the quantity but not the quality of the observations. Designing proper meta-analyses requires the presence of a certain number of events to achieve meaningful results. This is an issue when looking at outcomes after CABG as, in general, it is associated with excellent outcomes and isolated adverse events are small in number [27]. Appropriate scepticism is therefore required and justifiable in accepting new conclusions resulting purely from meta-analyses.

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Off-Pump

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"Qui audit adipiscitur"

Introduction

The efficacy of coronary artery bypass grafting (CABG) is well established worldwide and, compared to medical therapy, not only improves quality of life, but also prolongs life in selected subsets of patients. Conventional coronary artery bypass grafting (CCABG) using cardiopulmonary bypass (CPB) with cardioplegic arrest and aortic cross-clamping has been the standard procedure for surgical revascularisation and is associated with excellent early and late outcomes.

However, coronary patients requiring surgical treatment are frequently elderly, with a high frailty index, a high predicted risk of mortality, and have complex three vessel disease [1]. Off-pump coronary artery bypass grafting (OPCAB) has attracted the interest of an increasing number of surgeons, particularly for high-risk patients, and has assumed an increasing role in surgical practice. Off-pump techniques may help avoid the organ damage caused by CPB, and reduce the systemic inflammatory response, blood component damage and haemodilution, and this may be especially important in high-risk patients [2]. Moreover, OPCAB minimises or completely avoids aortic manipulation which can ultimately result in lower rates of postoperative stroke and neurocognitive dysfunction, especially in elderly patients [3].

However, the potential advantages of OPCAB compared with CCABG remain a source of controversy. While large observational series suggested that OPCAB is associated with a lower operative mortality and incidence of stroke [4,5,6], the anticipated benefits from OPCAB have never been confirmed in a single randomised controlled trial (RCT) [7,8].

Summary of the Evidence

First, the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial found no significant difference between OPCAB and CCABG in the rate of the 30-day composite endpoint of death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure [7]. Similarly, the largest experience to date, the CABG Off or On Pump Revascularization Study (CORONARY), which randomised more than 4700 patients to OPCAB and conventional CABG, showed no significant difference between these two techniques in terms of 30-day mortality, myocardial infarction, stroke, or renal failure requiring dialysis [8].

The most up to date meta-analysis of fifty-four studies (n=16,261 participants) showed no differences in either myocardial infarction or 30-day mortality. There was a strong trend towards a reduced incidence of stroke, but this did not reach statistical significance [9].

The apparent contradiction between the available registry data that report a significantly decreased incidence of mortality and stroke with OPCAB compared to the apparent lack of

benefit in RCTs may be explained by the fact that the RCTs excluded high-risk patients [7,8]. As a consequence, operative mortality and stroke were relatively rare entities in the selected low risk populations enrolled and even the largest randomised studies were underpowered to demonstrate a possible advantage of one technique over the other. Only a small number of RCTs have selectively enrolled high-risk patients (Table 1). Most of these studies were largely underpowered to detect significant difference between the two groups, different definitions for high risk patients were adopted and results were therefore inconclusive. Moreover, despite the adoption of standardised definitions of high-risk patients based on validated risk scores, such as EuroSCORE ≥ 6, "truly high-risk" patients referred to surgery in the real world clinical practice are often excluded from randomised comparisons.

Thus, a comparison of the RCT data with the registry data may play an important role in clarifying the true differences between the two procedures and/or the actual benefits of OPCAB. Retrospective registries have the advantage of including a large number of high-risk patients, thus making possible the detection of significant differences between the two groups and reflecting real world practice. A retrospective analysis of the Society of Thoracic Surgeons National Cardiac Database[1], including 210,469 patients who underwent surgery at participant "high-volume sites" (those that had performed more than 300 off-pump and 300 on-pump coronary artery bypass operations during the 6-year study period) showed that OPCAB was associated with reduced adverse events compared with on-pump surgery and that patients with higher predicted risk of mortality had the largest apparent benefit.

Table 1: Randomised trials comparing off-pump vs. on-pump CABG in high risk patients.

Trial	n	Definition of high-risk patients	Primary endpoint	Findings
Carrier M et al. Heart Surg Forum. 2003;6(6):E89-92.	65	3 of the following criteria: age > 65 years, hypertension, diabetes, serum creatinine >133 mol/L, LVEF<45%, chronic pulmonary disease, unstable angina, congestive heart failure, repeat CABG, anaemia, and carotid atherosclerosis.	Composite of death, neurological injury, renal failure, respiratory failure, and operative myocardial infarction after CABG	Two off-pump (7%) compared to 11 on-pump (30%) patients had composite end-point (p =0.02).
Møller CH et al The best bypass surgery trial. Circulation. 2010 Feb 2;121(4):498-504.	341	EuroSCORE ≥ 5 and triple vessel coronary disease	Composite of all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/ cardiogenic shock, stroke, and coronary reintervention	No significant differences in the composite primary outcome (15% versus 17%, p=0.48)

Lemma MG et al. On-off study. J Thorac Cardiovasc Surg. 2012 Mar;143(3): 625-31.	411 interim analysis	EuroSCORE ≥6	Composite of operative mortality, myocardial infarction, stroke, renal failure, reoperation for bleeding and adult respiratory distress syndrome within 30 days after surgery.	The rate of the composite primary endpoint was significantly lower (unadjusted p=0.009, adjusted p=0.01) in the off-pump group (5.8% vs 13.3%).
Østergaard B et al. Eur J Cardiovasc Nurs. 2016 Apr;15(2):126-33	120	Elderly patients >70 years	Medical Outcome Study Short Form 36 (SF-36) and Major Depression Inventory diagnostic scale for self-reporting of HRQoL.	HRQoL SF-36 scores seemed to improve more in patients undergoing on-pump CABG. No long-term clinically relevant difference between the groups could be demonstrated.
Hlavicka J et al. PRAGUE-6 trial. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016 Jun;160(2):263-70.	206	Additive EuroSCORE ≥ 6,	Combined endpoint of all-cause death, stroke, myocardial infarction, or renal failure requiring new haemodialysis, within 30 days and 1 year after randomisation.	Higher incidence of primary combined endpoint in on-pump group (20.6% vs. 9.2%, p=0.028, HR 0.41, 95% CI 0.19-0.91) in the first 30 days, but not after 1 year (30.8% vs. 21.4%, p=0.117, HR 0.65, 95% CI 0.37-1.12).

Diegeler A et al. GOPCABE Study Group. N Engl J Med. 2013 Mar 28;368(13): 1189-98	2539	Patients ≥75 years of age	Composite of death, stroke, myocardial infarction, repeat revascular-ization, or new renal-replacement therapy at 30 days and at 12 months after surgery.	No significant difference between off-pump vs. on-pump groups in the composite outcome at 30 days (7.8% vs. 8.2%; p=0.74) and at 12 months (13.1% vs. 14.0%; p=0.48.

A recent analysis of the Nationwide Inpatient Sample (NIS) database from 2003–2011, including 34,117 patients aged ≥80y, showed that OPCAB was associated with lower risk of stroke and atrial fibrillation in octogenarians [5]. An analysis of the CREDO-Kyoto Registry (a registry of first-time percutaneous coronary intervention and coronary artery bypass graft patients in Japan) including 1377 patients receiving CCABG and 1091 receiving OPCAB, showed that OPCAB was associated with short-term and long-term benefits in stroke prevention in patients at higher risk, as estimated by EuroSCORE [6]. We recently published a comparison between off-pump vs on-pump in 3424 high risk patients (EuroSCORE ≥6) who underwent coronary bypass surgery at Bristol Heart Institute from 1996 to 2015. Off-pump CABG was performed in 1670 patients and on-pump in 1754 patients [10]. Propensity matching was used to selected 1199 pairs with comparable baseline characteristics as shown in Table 2 (standardised mean difference <0.10). In the matched sample, OPCAB was found to be significantly associated with reduced risk of in-hospital mortality (Odds Ratio (OR) 0.61; 95% Confidence Interval (CI) 0.39-0.95) (Table 2 overleaf).

Role of surgeon experience

Expertise in OPCAB by individual surgeon and hospital volume has been shown to be an important determinant of outcomes [4]. Available randomised trials that suggested an increased risk with OPCAB have been criticised for failing to account for the major role that surgeon experience plays in determining outcomes. In the ROOBY trial, 53 participating surgeons enrolled on average only 8 patients per year during the study period and had unacceptably high rates of both conversion to on-pump surgery (12%) and incomplete revascularisation (18%) [7]. Poor surgeon experience has been used to explain the increased 5-year mortality observed after OPCAB (15.2% in the OPCAB group vs 11.9% in the on-pump group, p=0.02). In the CORONARY trial, each procedure was performed by a surgeon who had expertise in the specific type of surgery (completion of >100 cases of the specific technique, off-pump or on-pump) and off-pump was associated with comparable late mortality when compared to on-pump surgery [8]. A recent analysis from the Nationwide Inpatient Sample, including a total of 2,094,094 patients undergoing on- and off-pump surgery, showed that while off-pump was associated with increased risk-adjusted mortality when performed by sporadic off-pump surgeons (<19 cases per year) (OR 1.26, 95% CI 1.02 to 1.56), when performed by high volume surgeons (≥48 cases per year), OPCAB was associated with reduced hospital mortality (OR 0.63, 95% CI 0.49 to 0.81) [4].

Table 2: High risk patients (EuroSCORE≥6) undergoing first time isolated coronary artery bypass graft surgery at Bristol Heart Institute from 1996-2015

	BEFORE MATCHING			AFTER MATCHING		
	Off-pump	On-pump	SMD	Off-pump	On-pump	SMD
n	1670	1754		1199	1199	
Mean age (yrs) (SD)	74 (7)	73 (7)	0.158	74 (7)	74 (7)	0.004
Female, n (%)	486 (29.1)	489 (27.9)	0.027	332 (27.7)	336 (28.0)	0.019
NYHA III/IV, n (%)	680 (40.7)	767 (43.7)	0.061	497 (41.5)	506 (42.2)	<0.001
MI within 30 days, n (%)	666 (39.9)	649 (37.0)	0.059	463 (38.6)	474 (39.5)	0.016
Prior PCI, n (%)	91 (5.4)	88 (5.0)	0.019	69 (5.8)	65 (5.4)	0.030
IDDM, n (%)	163 (9.8)	161 (9.2)	0.020	113 (9.4)	121 (10.1)	0.039
Smoking, n (%)	164 (9.8)	177 (10.1)	0.009	115 (9.6)	120 (10.0)	0.014
Creatinine >200mmol/l, n(%)	99 (5.9)	102 (5.8)	0.005	70 (5.8)	65 (5.4)	0.018
COPD, n (%)	254 (15.2)	266 (15.2)	0.001	195 (16.3)	182 (15.2)	0.056
CVA, n (%)	111 (6.6)	126 (7.2)	0.021	77 (6.4)	90 (7.5)	0.033
PVD, n (%)	440 (26.3)	450 (25.7)	0.016	334 (27.9)	311 (25.9)	0.029
NVD, n (%)			0.299			0.092
1	101 (6.0)	44 (2.5)		51 (4.3)	30 (2.5)	
2	416 (24.9)	282 (16.1)		261 (21.8)	197 (16.4)	
3	1153 (69.0)	1428 (81.4)		887 (74.0)	972 (81.1)	
LMD, n (%)	529 (31.7)	545 (31.1)	0.013	392 (32.7)	399 (33.3)	0.005
LVEF<30%, n (%)	237 (14.2)	331 (18.9)	0.126	179 (14.9)	203 (16.9)	0.055
Cardiogenic shock, n (%)	23 (1.4)	67 (3.8)	0.154	20 (1.7)	28 (2.3)	0.006
Preop IABP, n (%)	59 (3.5)	77 (4.4)	0.044	49 (4.1)	54 (4.5)	0.009
Emergency, n (%)	64 (3.8)	139 (7.9)	0.175	53 (4.4)	59 (4.9)	0.037
Mean BMI (SD)	27 (4)	27 (5)	0.092	27 (4)	27 (5)	0.012
YOP (mean (SD))	2006 (4)	2005 (6)	0.328	2006 (5)	2006 (5)	0.051
Trainee performed, n (%)	411 (24.6)	437 (24.9)	0.007	294 (24.5)	293 (24.4)	0.014
Mean log EuroSCORE (SD)	10±7	10±8		10±7	10±8	
In Hospital Mortality, n (%)	54 (3.2)	75 (4.3)	0.11*	36 (3.0)	55 (4.6)	0.03*

SMD: standardized mean difference; NYHA: New York Heart Association; MI: myocardial infarction; PCI: percutaneous coronary intervention; IDDM: insulin dependent diabetes mellitus; COPD:

*Chronic obstructive pulmonary disease; CVA: cerebrovascular accident; PVD: peripheral vascular disease; NVD: number of vessels diseased; LMD: left main disease; LVEF: left ventricular ejection fraction; IABP intra-aortic balloon pump; BMI: body mass index; YOP: year of procedure. * from Doubly robust logistic*

Conclusions

In the current era, an increasing number of patients with a high-risk profile are being referred for surgical revascularisation, and OPCAB surgery represents an attractive strategy to reduce operative morbidity. However, expertise in off-pump surgery by individual surgeons and high hospital volume remain important determinants of outcomes. The unique technical challenges of OPCAB may lead to poorer outcomes when it is performed by inexperienced surgeons. On the other hand, superior outcomes in high-risk patients can be achieved only if off-pump surgery is offered to both high- and low-risk patients alike, and this further emphasises the need for recognition of OPCAB surgery as a subspecialty with its own structured training program. The learning curve in OPCAB can be safely negotiated with appropriate patient selection, individualised grafting strategies, peer-to-peer training of the entire team, and a graded clinical experience.

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Robotic Hybrid Revascularisation is the Future

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"Ignus aurum probat, miseria fortes viros"

Definition and Rationale

Hybrid Coronary Revascularisation (HCR) is defined as the combination of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) to treat multivessel coronary artery disease. It most commonly combines a minimally invasive CABG procedure involving a left internal mammary artery (LIMA) to the left anterior descending coronary artery (LAD) anastomosis with PCI to non-LAD vessels. This technique offers and combines the advantages of both surgical and percutaneous revascularisation, at the same time eliminating the disadvantages of both procedures. In fact, this evolving revascularisation technique utilises the survival benefits conferred by the LIMA to LAD graft while providing patients with complete and truly minimally invasive coronary artery revascularisation with PCI to the non-LAD vessels.

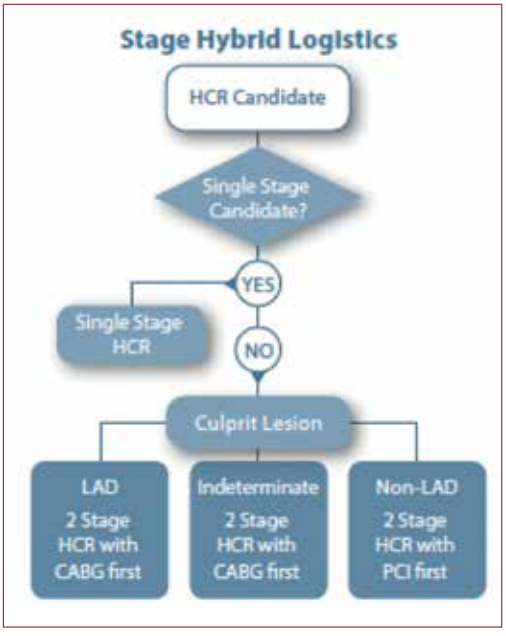

Figure 1: The Sequence of Hybrid Therapy

The sequence and timing of the surgical and interventional component of hybrid therapy can be in three different ways (Figure 1): PCI first followed by surgery; surgery followed by PCI (two stage HCR); or both during the same setting (single stage HCR). In the era of primary PCI for ST segment elevation myocardial infarction, it is probable that those requiring immediate PCI of the right coronary artery (RCA) or circumflex artery as their culprit lesion, may require subsequent surgical revascularisation of a complex LAD or left main lesion at some time in the future. Hence, HCR, by definition, generally refers to a revascularisation strategy which has been strategically planned in a coordinated fashion by both interventional cardiologist as well as the cardiac surgeon.

The optimal revascularisation strategy for multi-vessel coronary artery disease (CAD) is still debated. If it is true that recent trials including SYNTAX have helped to establish which anatomic categories are best addressed with traditional CABG versus multi-vessel PCI with drug eluting stents (DES), it is also true that there is still potential for prognostic and symptomatic improvement from coronary revascularisation in certain patients with multi-vessel coronary artery disease [1]. The modality depends on many factors, most important of which is the coronary anatomy itself. Other crucial factors include the clinical setting (emergent, acute or chronic), left ventricular function, the degree of myocardial viability, the presence or absence of comorbidities such as diabetes (assessed through the STS score or EuroSCORE), associated valvular heart disease, the presence of calcification of the ascending aorta which could preclude safe cross-clamping during surgical intervention, age, patient preference, and the availability of bypass conduits. However, CABG is still considered the gold standard treatment for patients with multi-vessel CAD [2-4]. The major therapeutic benefits of CABG arise from grafting the LIMA to the LAD which has been shown to have excellent long term results in term of patency, event-free survival and relief of angina [5,6]. On the other hand, saphenous vein grafts (SVGs) have showed a high incidence of failure as opposed to multi-vessel PCI with DES which have shown lower restenosis rates, lower failure rates than SVG, lower stroke rates compared with CABG, in addition to the fact that PCI is less invasive and has a shorter recovery time [7-9]. Hybrid revascularisation therefore represents a promising revascularisation strategy due to the fact that it offers the advantages of both treatment options, taking advantage of the survival benefit conferred by the LIMA-to-LAD graft while minimising the invasiveness of the revascularisation therapy and providing a complete revascularisation with PCI to the non-LAD vessels. Additionally, the use of the robot for a robotic-assisted minimally invasive coronary artery bypass grafting (RACABG) of the LIMA to the LAD minimises further the surgical trauma.

Several studies have already demonstrated similar results (in terms of mortality, patency and major adverse cardiac event rates) between a hybrid revascularisation strategy and conventional on- and off-pump coronary bypass surgery [10-13]. However, the safety and effectiveness of HCR is still understudied and further studies, especially randomised trials, are necessary before stronger recommendations can be made for this revascularisation therapy.

History of Hybrid Coronary Revascularisation

Hybrid Coronary Revascularisation was first described by Angelini et al. in 1996 [14]. He used the classic minimally invasive direct coronary artery bypass (MIDCAB) procedure, in which the LIMA is harvested by direct vision through a fourth interspace left mini-thoracotomy and then sutured to the LAD on the beating heart. In fact, after the pioneering work of Benetti et al. on minimally invasive CABG, MIDCAB was adopted by several groups in the mid-1990s [15-19]. Hybrid revascularisation evolved as a result of the desire to effectively

treat patients with multi-vessel disease while at the same time lowering procedure-related morbidity by combining minimal access coronary surgery with percutaneous techniques. It was a very innovative and new concept in the field of coronary artery revascularisation, utilising two disciplines, cardiac surgery and interventional cardiology. In fact, interventional cardiologists were progressively more aggressive in their percutaneous treatment of coronary artery disease and surgeons were developing minimally invasive techniques with smaller incisions, avoidance of sternotomy and beating heart surgery. Additionally, throughout the 1990s, endoscopic, video-assisted and finally robotic-assisted LIMA dissection were performed. Successful endoscopic harvesting of the left internal mammary artery (LIMA) has been a crucial step in the performance of minimal access coronary artery bypass surgery through mini-thoracotomy incisions, and video-assisted LIMA takedown has been further facilitated by the use of robotic assistance [20]. In the last 15 years, surgical telemanipulation systems have significantly improved, and currently robotic-assisted coronary artery bypass grafting surgery encompasses utilisation of robotic assistance in varying degrees, from robotic-assisted coronary artery bypass grafting (RACABG) procedures to totally endoscopic coronary artery bypass (TECAB). On the other hand, there has been a continuous improvement of DES performance, and PCI can now provide, in low-risk patients and in those with single vessel disease, comparable short- and mid-term outcomes to CABG [21,22].

Indications for Hybrid Coronary Revascularisation and Patient Selection

According to the 2011 American College of Cardiology/American Heart Association guidelines for coronary artery bypass graft surgery, HCR is a suitable revascularisation strategy for patients with multi-vessel CAD (e.g. LAD and ≥1 non-LAD vessel) and an indication for revascularisation [23]. "Hybrid revascularisation is ideal in patients in whom technical or anatomic limitations to CABG or PCI alone may be present and for whom minimising the invasiveness (and therefore the risk of morbidity and mortality) of surgical intervention is preferred (e.g. patients with severe pre-existing comorbidities, recent myocardial infarction, a lack of suitable conduits, a heavily calcified ascending aorta, or a non-LAD coronary artery unsuitable for bypass but amenable to PCI, and situations in which PCI of the LAD artery is not feasible because of excessive tortuosity or chronic total occlusion)".

Hybrid Coronary Revascularisation: Class of Recommendation (from 2011 ACCF/AHA Guideline for Coronary Artery Bypass Surgery)

Class IIa

Hybrid coronary revascularisation (defined as the planned combination of LIMA-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries) is reasonable in patients with 1 or more of the following (Level of Evidence B):

- Limitations to traditional CABG, such as heavily calcified proximal aorta;
- Poor target vessels for CABG (but amenable to PCI);
- Lack of suitable graft conduits;
- Unsuitable LAD artery for PCI (i.e., excessive vessel tortuosity or chronic total occlusion).

Class IIb

Hybrid coronary revascularisation (defined as the planned combination of LIMA-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries) may be reasonable as an alternative to multi-vessel PCI or CABG in an attempt to improve the overall risk–benefit ratio of the procedure. (Level of Evidence C)

According to the 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery **Guidelines on Myocardial Revascularisation,** *"Hybrid procedures consisting of IMA to LAD and PCI of other territories appear reasonable when PCI of the LAD is not an option, or is unlikely to result in good long-term outcomes, or when achieving complete revascularisation during CABG might be associated with an increased surgical risk"* [24].

"In addition, some patients with complex multi-vessel disease presenting with STEMI initially require primary PCI of the culprit vessel, but subsequently may require complete surgical revascularisation. A similar situation occurs when patients with combined valvular and CAD require urgent revascularisation with PCI. Finally, when a heavily calcified aorta is found in the operating room the surgeon may elect not to attempt complete revascularisation and to offer delayed PCI".

In the Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology/ Canadian Society of Cardiac Surgery Position Statement on Revascularization—Multi-vessel Coronary Artery Disease [25], it is stated that HCR:

1. Is typically performed with minimally invasive incisions,
2. Combines the advantage of the LIMA–to-LAD graft with the less invasive nature of PCI,
3. Studies to date have demonstrated HCR to be safe and effective, but definitive data (e.g. randomised trials) are lacking.

However, the lack of randomised controlled clinical trials does not allow the identification of a HCR target group of patients. Therefore, HCR should be considered as an alternative treatment strategy that should be tailored to the individual patient based on patient anatomy and patient-related variables through a collaborative Heart Team approach. The ideal patient is a patient with multi-vessel CAD with a complex proximal LAD lesion suitable for LIMA-LAD grafting associated with non-LAD lesions suitable for PCI and no contraindication for dual antiplatelet therapy. Careful attention should be focused on quality and size of the LAD, epicardial or intramyocardial LAD course, presence of large diagonal vessels (which can be mistaken for the LAD and inadvertently grafted), complexity of non-LAD vessel lesions for PCI, and the number of stents necessary to effectively treat the non-LAD stenosis. Other important factors in patient selection for HCR are patient variables including clinical presentation, comorbidities, body habitus, chest wall anatomy, and surgeon experience with minimally invasive CABG procedures. Chest wall anatomy, obesity and thoracic size may have a significant impact on the surgical part of the procedure. Patient comorbidities, such as chronic obstructive pulmonary disease and pulmonary hypertension, also have a significant impact. For a robotic-assisted approach, the patient must be able to tolerate single lung ventilation and physiological changes related to carbon dioxide insufflation. Hybrid revascularisation could then serve patients at the two extremities of the risk spectrum: young and relatively healthy patients who prefer to avoid the sternotomy, but do not want to renounce the durability of the LIMA-LAD graft; and elderly and/or high-risk patients who may benefit from a less traumatic, minimally invasive,

but full and complete coronary revascularisation. In the end, it is quite intuitive that the experience of the surgeon is a key factor in the successful outcome of this revascularisation strategy given the challenging nature and the steep learning curve of minimally invasive CABG techniques.

Hybrid Coronary Revascularisation: Single vs Two Stage

Single Stage

The minimally invasive surgical revascularisation is performed first. After the harvest of the LIMA, Biavlirudin (Angiomax) at a loading dose of 0.75mg/kg is administered and then an infusion at 1.75mg/kg/hr. is continued throughout the rest of the procedure including the surgical revascularisation and the PCI. After the surgical revascularisation is completed, the hybrid operating room is reset to cardiac catheterisation configuration. The LIMA graft check is performed. After haemostasis is confirmed with evidence of minimal drainage from the chest tubes, Clopidogrel at a dose of 600mg or Ticagrelor at a dose of 180mg via nasogastric (NG) tube is administered. The PCI is performed to non-LAD targets. The Bivalirudin infusion is continued and overlapped with the clopidogrel or ticagrelor over the next hour. Post-operatively the patient is continued on aspirin and clopidogrel or ticagrelor (Figure 2).

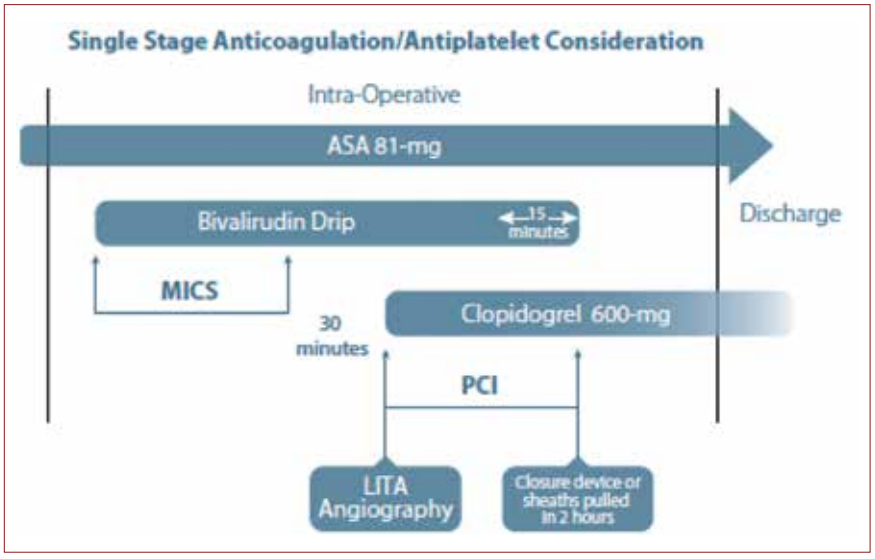

Figure 2: Single stage Anticoagulation/Antiplatelet strategy

Two Stage

Minimally invasive surgical revascularisation is performed as per routine utilising heparin and protamine for reversal. The evening after surgery, the patient is given a loading dose of clopidogrel or ticagrelor and next day the patient undergoes PCI. Post-operatively, the patient is continued on aspirin and either clopidogrel or ticagrelor.

Anaesthetic Considerations

- A paravertebral or intrathecal block with epimorphine is used for pain control.
- Defibrillator pads on the left scapula and inferior and medial to the right breast.
- Perform intubation with a double lumen endotracheal tube (ETT) to deflate the left lung. Alternatively, a single lumen ETT and bronchial blocker may be placed under fibreoptic guidance. Place the proximal end of the balloon approximately 1 to 2-cm below the carina in the left main bronchus.
- Lines are routine and include an arterial line and central venous line (pulmonary arterial catheter if required). If peripheral access is limited, at least a 16-gauge IV should be placed. A triple lumen catheter is placed.
- Warming blanket should be used to avoid hypothermia.
- CO_2 insufflation for intrathoracic pressure 5 to 10mmHg (watch blood pressure).
- Haemodynamic support for OPCAB surgery may be necessary.
- Single-Lung Ventilation.
- Deliver approximately 10 cc/kg of tidal volume prior to and during single-lung ventilation. This may need to be decreased as large tidal volumes can cause shifting of the mediastinum,which may cause the retractor to slip and effect the stabilization.
- Keep the O_2 saturation greater than 90%. If the saturation begins to decrease:
  - Add continuous positive airway pressure (CPAP) of 5cm H_2O to the deflated lung. This can be performed through the bronchial blocker by inserting a 7Fr ETT connector into the barrel of a 3-cc syringe. Insert the syringe tip into the lumen of the bronchial blocker. Attach the 7Fr ETT connector to a CPAP circuit
  - CPAP can be increased, but if it is increased too much, it will cause the lung to inflate and obscure the surgeon's view.

Perfusion Considerations

The need for extracorporeal support is rare. A supported coronary revascularisation would only require a system with a venous reservoir, arterial pump, oxygenator and filter. It is recommended that the extracorporeal support system and devices be on standby.

- The use of a cell saver is recommended
- Percutaneous arterial and venous cannulae are necessary if femoral cannulation is utilised for haemodynamic support

Surgical Technique

A. Preparation, Positioning and Draping

Initial positioning of the patient can have a considerable effect on the operative procedure, as proper positioning minimises interference from internal and external body structures with the robotic equipment. Judicious care at this stage ensures the necessary landmarks for port placement in order to maximise robotic arm manoeuvrability intraoperatively.

The patient is positioned at the left edge of the operating room table. A comfortable support is placed under the distal two-thirds of the left side of the patient's thorax. This support usually takes the form of a rolled-up towel and should elevate the patient thorax 6-8 inches superiorly. The left arm is positioned at the side of the operating table to allow the left shoulder to drop posteriorly. Rotate the table 30º up so the patient is in the partial left lateral position (Figure 3).

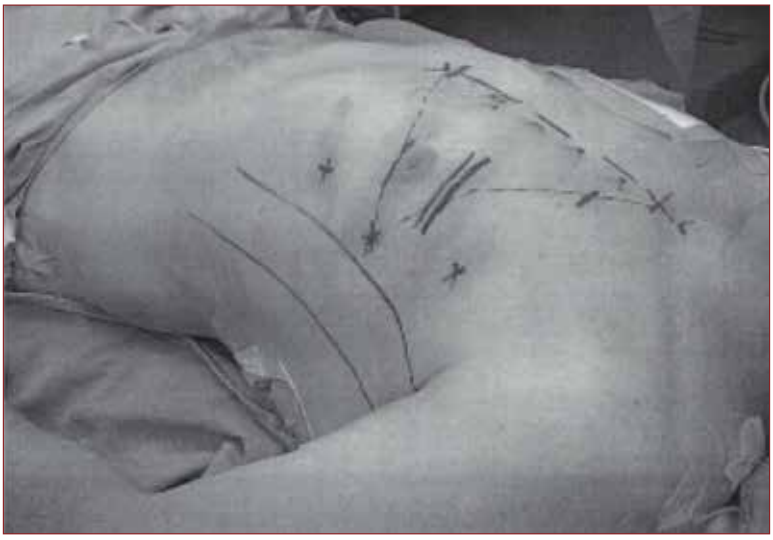

Figure 3: Patient Positioning

Leads and external defibrillator pads are positioned on the patient's chest away from the left lateral and midclavicular areas of the thorax, so as not to interfere with port placement. Place one pad on the right anterolateral thorax and the other on the left posterior thorax. The patient is prepped in a routine manner for conventional CABG and saphenous vein harvesting, safeguarding against the possibility of having to convert the case to an open procedure. The only variation in preparation compared to a sternotomy is exposure of the patient's thorax and axilla on one side for port placement.

B. Direct IMA Harvest

1. Patient Set-up

- Lines/Airway - Double lumen ETT with internal jugular central line.
- Positioning is 30° right lateral decubitus with a roll under left shoulder.

2. Thoracotomy/Incisions

- Perform a 5 to 7cm anterolateral mini-thoracotomy.
- Male patients: over the 5th or 6th intercostal space (ICS), 1/3 medial to the nipple.
- Female patients: inframammary incision in a similar location.
- The medial 2/3 of the window incision is medial to the anterior axillary line.
- While making the incision, deflate the left lung.
- Divide the intercostal muscles laterally to reduce the risk of rib fracture, then divide them medially to avoid damage to the LIMA.
- A soft tissue retractor may be placed in the incision to maximise access.

3. Direct IMA Harvest

- Place a large Kelly clamp with a sponge in the 6th ICS to assist with harvesting the LIMA. Use the sponge to push away tissue for better IMA visualisation.
- Insert the ThoraTrak™ (Medtronic, Minneapolis, MN) retractor system into the ICS incision; then hook the ThoraTrak retractor system to the Rultract Skyhook surgical retractor (Pemco Inc., Cleveland, OH) to facilitate the LIMA harvest.
- In order to prevent crush injury to the LIMA, make sure the superior portion of the retractor is placed and maintained in the lateral aspect of the incision.
- Care should be taken not to fracture a rib.
- The ThoraTrak MICS retractor system should be opened slowly, which allows tissue and bone to acclimate to the change in position in order to minimise the potential for rib fracture and pain.
- Start the LIMA harvest at the 3rd ICS using direct vision through the window incision.
- Use an extended electrocautery instrument, endoscopic forceps, suction, endoscopic clip applier and small clips for the harvest.
- Complete the harvest up to the subclavian vein and down past the left 5th ICS.
- Take care to identify and avoid the phrenic nerve.
- During the LIMA harvest, flexing the table may facilitate access to the superior portion of the LIMA.
- Anchor the pedicle of the LIMA with silk ties to maintain the proper orientation.
- Give intravenous bivalirudin or heparin prior to LIMA division.

C. Endoscopic/Robotic Harvesting of the LIMA and/or RIMA

1. Patient Set-up

- Positioning is 30° right lateral decubitus with a roll under left chest to allow the left shoulder to fall.

2. Port Placement

- This is fundamental to the success of the operation. Placement of each port is centred on constructing an ideal configuration that ensures mobilisation of the IMAs from the 1st rib to the 6th rib with the least amount of impedance to the robotic arms. It is imperative that the surgeon be meticulous with each individual patient taking the necessary time needed to ensure proper completion of port placement prior to moving forward with the operation. Suboptimal port placement can frequently result in dangerous internal and/or external robotic arm conflicts.

The lack of intrathoracic visualisation is the main challenge to determining port placement. Careful review of the coronary angiogram, chest radiograph, and contrast-enhanced chest computed tomography (CT) scan, along with direct examination of the anatomical structures of the individual patient in the operating room, helps to alleviate this problem.

Chest Radiograph

- Evaluate the chest radiograph in an orderly manner. Identify pertinent thoracic landmarks:
  - Supra-sternal notch,
  - Angle of Louis,
  - Xiphoid,
  - 2nd, 3rd, 4th, 5th intercostal spaces (ICS),
  - Left internal mammary artery (LIMA) and right internal mammary artery (RIMA) locations – 1 to 3 cm lateral to the sternum.
- Note the position of the heart in the mediastinum.
- Note the size of the heart in relation to the pleural space on the port access side of the chest.
- Lateral View: Observe the degree of space between the anterior surface of heart and underside of thorax.

Computed Tomography of Chest

- Assess intrathoracic space - the distance from the pleural surface to the mediastinum cannot be less than 1.7 cm at the camera port space which is usually the 5th intercostal space. (Figure 4). A distance less than 1.7 cm will not provide sufficient intrathoracic space for adequate degrees of freedom of the robotic instrument.
- Rule out other anatomical abnormalities such as asbestos plaques (Figure 5).
- Determine the Antero-Posterior (AP) measurement and the transverse (Trv) distance of the chest cavity. If the AP/Trv ratio is less than 45%, it reduces the success of robotic–assisted coronary artery revascularisation[3]. In addition, the vertical distance from the LAD to the chest wall is also a factor in the success of the operation. If this distance is less than 15 mm, there is less chance of being able to perform the operation robotically (Figure 6).
- Assess the location of the coronary arteries if intramyocardial. Access to intramyocardial vessels for revascularisation is challenging and can result in conversion (Figure 7).

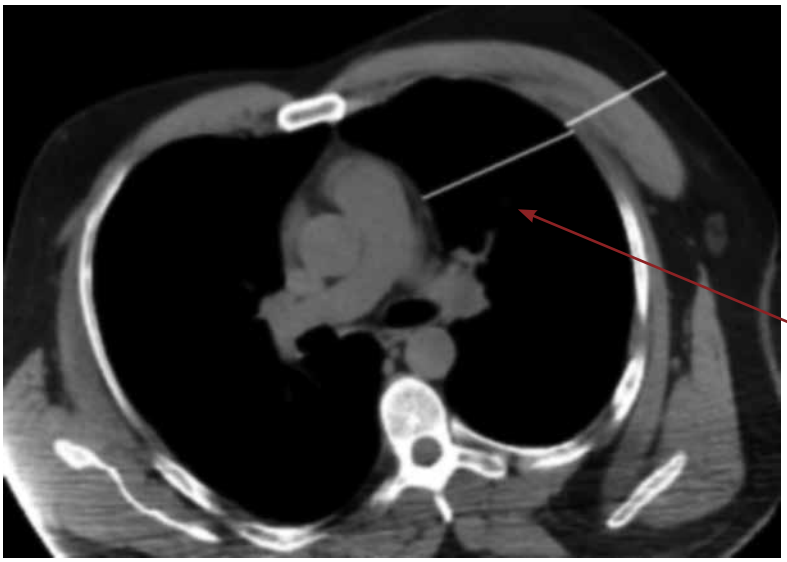

Figure 4: Computed Tomography showing the distance from pleura to mediastinum

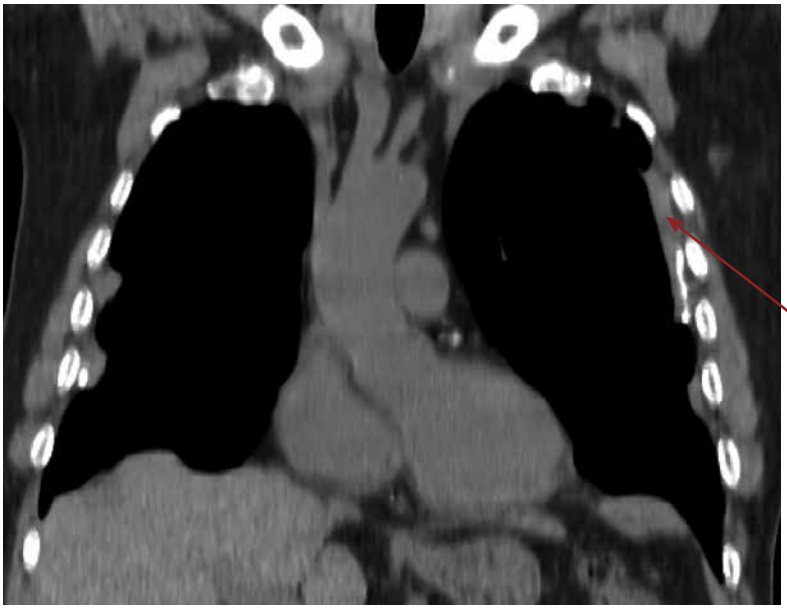

Figure 5: Presence of asbestos plaques are important in identifying a safe location for port placement.

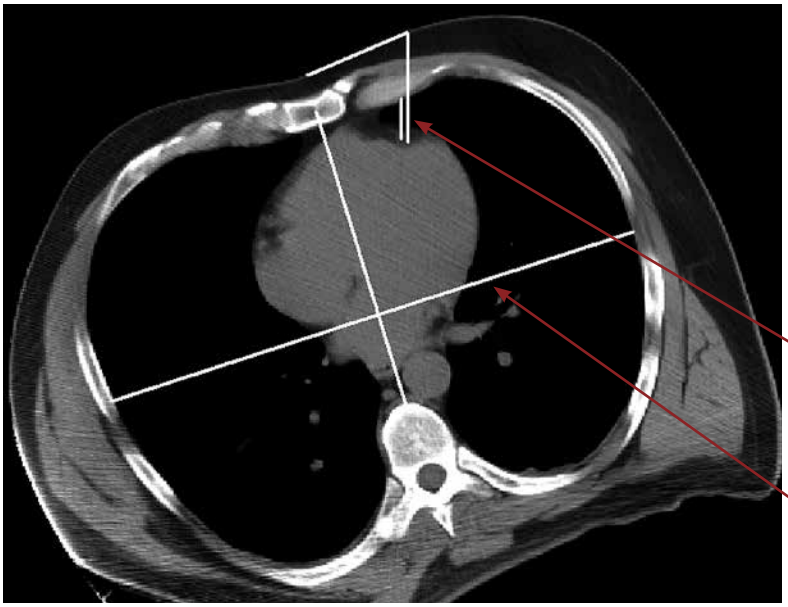

Figure 6: Antero-posterior (AP), Transverse measurement (Trv), and left anterior descending (LAD) to chest wall distance

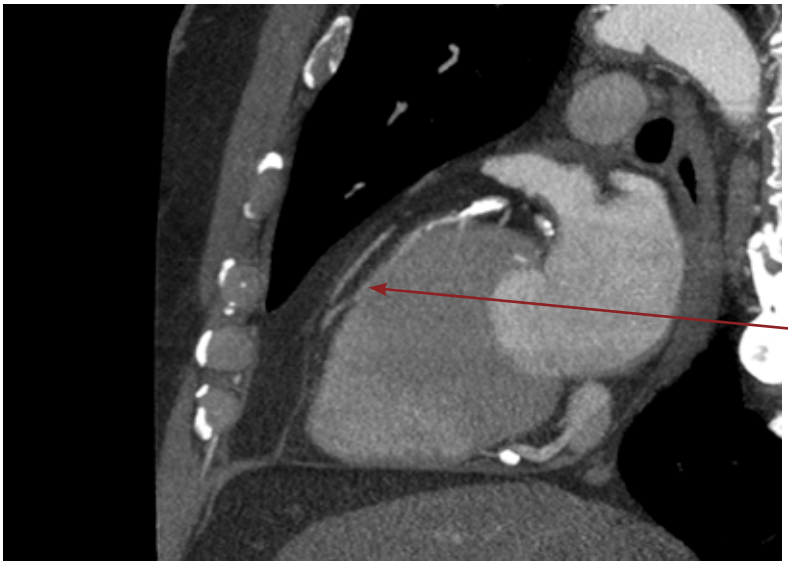

Figure 7: Intramyocardial location of LAD (left anterior descending) coronary artery

Direct Examination of the patient's thorax

- Evaluate the external anatomical characteristics of the patient's thorax and conceptualise the internal anatomical characteristics based on the previously viewed chest radiograph, CT and preoperative coronary angiogram.
- Outline with a felt marker precisely where each port is to enter the thoracic cavity using the standardised guidelines as discussed (Figure 3). Make necessary adjustments for individual patients based on information acquired from diagnostic imaging and patient examination.

3. Endoscopic Port Insertion

- The left lung is deflated and a 12-mm port inserted in the 5th ICS.
- CO_2 insufflation for intrathoracic pressure of 5 to 10-mmHg (watch blood pressure).
- 30° endoscope inserted. Under the guidance of the endoscope, two 7-mm ports are inserted in the 3rd and 7th ICS.
- Endoscopically or robotically, the LIMA is harvested from 1st rib to the 6th rib as a pedicle or skeletonised.
- Prior to ligation of the LIMA, the patient is given intravenous bivalirudin or heparin depending on whether 1-stage or 2-stage procedure.
- If the LIMA is harvested as a pedicle, a clip is attached at the site where the anastomosis is to be performed to the edge of the pericardium in the normal anatomical orientation to avoid torsion after the pedicle is transected.
- The LIMA-LAD anastomosis is performed under direct vision through the mini-thoracotomy.
- Only soft tissue retraction is generally required, minimising trauma.

D. Pericardiotomy

- Pericardial fat is first removed.
- 2-3 cm anterior to the phrenic nerve the pericardium is opened down to the diaphragm and towards the right pleura.

E. Manual anastomosis

- The LAD is identified based on its location on the interventricular septum and traversing to the apex.
- Insert a long needle under direct visualisation of the endoscope to identify the optimal ICS to perform thoracotomy for best exposure of LAD.
- Ventilation can be temporarily stopped to take away the movement of the mediastinum.
- Mark the intercostal space from inside using electrocautery.
- If robot-assisted, then the robot is undocked and instrument ports removed.
- Mini-thoracotomy is performed.

Figure 8: Octopus Nuvo Stabiliser (Medtronic, Minneapolis, MN)

- Identify the pericardiotomy site and the IMA pedicle.
- Detach the IMA and deliver through incision and immediately place two suspension sutures to prevent the pedicle from twisting.
- Assess IMA length and flow and prepare for anastomosis.
- Select port site for the endoscopic Octopus Nuvo stabiliser (Medtronic, Minneapolis, MN) (Figure 8) - 6th ICS if LIMA directly harvested or 5th intercostal port site if LIMA harvested robotically.
- Achieve stabilisation.
- Apply proximal and distal occlusion snares or intravascular shunt depending on the patient's haemodynamics.
- Perform the anastomosis in the usual fashion.
- Check graft flow using an intraoperative flow measuring device.
- Intraoperative angiography checking IMA patency and PCI of other coronary vessels for a single stage procedure in a specialised hybrid operating room (Figure 10).

F. Robotic anastomosis

In TECAB, the anastomosis can be performed on an arrested heart (AHTECAB) or beating heart (BHTECAB). In AHTECAB, the patient is placed on cardiopulmonary bypass (CPB) usually peripherally and cardiac arrest is usually achieved using the endoaortic balloon clamp. The anastomosis is then performed [26,27].

- Once the site of anastomosis on the LAD is identified, occlusion silastic snares are placed proximally and distally.
- The suture to be used for the anastomosis is placed in the thoracic cavity to avoid CO_2 leaks during the procedure.
- The da Vinci Endowrist stabiliser (Figure 9) is inserted through a sub-xiphoid port and stabilisation of the selected area is achieved.

- The anastomosis is started in the usual fashion by inserting the first stitch in the IMA while still attached to the chest wall.
- After this stitch the IMA is detached and the anastomosis completed in the usual fashion.
- If available, the anastomosis can be performed with the help of connectors such as the Cardica C-port distal anastomosis system (Cardica Inc., Redwood City, CA) [8].
- Irrigation or a blower is used during the anastomosis to keep the vessel clear of blood and provide adequate visualisation of the LAD.
- Intraoperative angiography to check IMA patency and PCI at the same time of the other vessels if needed in the hybrid operating room (Figure 10).

Figure 9: Da Vinci Endowrist Stabiliser

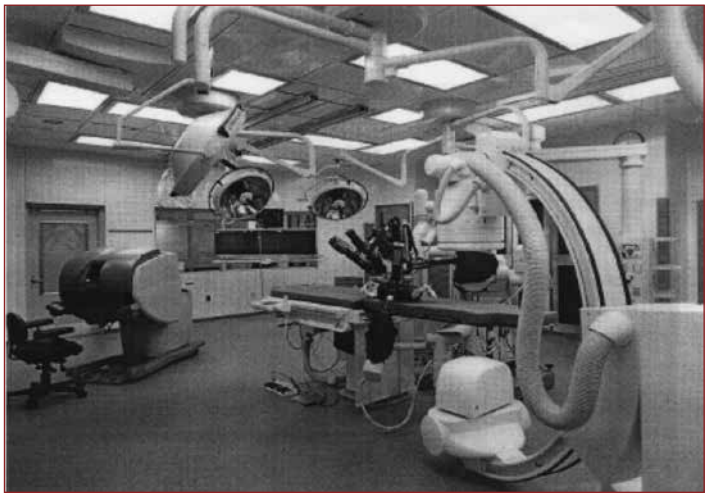

Figure 10: Hybrid cardiac operating room at the London Health Sciences Centre. The room is fully equipped for robotic surgery, angiography, and percutaneous coronary intervention.

Results, Institutional Experience and Current Evidence

Since 2004, at the London Health Sciences Centre, a total of 191 consecutive patients (mean age 61.4±11.1 years; 142 males and 49 females) underwent HCR (robotic-assisted coronary artery bypass graft of the LIMA to the LAD and PCI in a non-LAD vessel) in a single or double stage. Successful HCR occurred in 183 of the 191 patients (8 patients required intraoperative conversion to conventional coronary bypass): 138 patients underwent simultaneous surgical and percutaneous intervention, 24 patients underwent PCI before surgery, 29 patients underwent PCI after surgery. Drug-eluting stents were used in 177 patients, whereas 14 patients were treated with bare metal stents. In the series of patients who underwent successful HCR, no perioperative mortality occurred, there was only one perioperative myocardial infarction (0.5%), two cerebrovascular accidents (1.1%), and one respiratory failure with prolonged ventilation (0.5%). The rate of reoperation for bleeding was 2.1% (n=4). Only 11.0% of patients (n=20) required a blood transfusion. None of the patients developed acute kidney injury (AKI) with need for renal replacement therapy. The average ICU stay was 1±1 days and the average hospital stay was 4±2 days. Six-month coronary angiogram follow-up has been performed in 95 patients. Angiographic evaluation demonstrated a LIMA anastomotic patency of 97.9% and PCI vessel patency of 92.6%. At 83.6±11.1 months, clinical follow-up demonstrated 93.9% survival, 91.2% freedom from angina and 88.5% freedom from any form of coronary revascularisation (PCI to LIMA-to-LAD anastomosis was performed in 5 patients, in one case the anastomosis was surgically revised and PCI was repeated to non-LAD vessels in 11 patients).

We also performed a comparative analysis of HCR against conventional on-pump CABG, adjusting using inverse-probability weighting (IPW) based on the propensity score of receiving either on-pump CABG or HCR [28]. We considered all double on-pump CABG (n=682) and HCR (147 robotic-assisted minimally invasive coronary artery bypass graft of the LIMA to the LAD and PCI to one of non-LAD vessels) between March 2004 and November 2015. We performed IPW-adjusted analysis of the outcomes using the teffects ipw package (Stata) and using the average treatment effect ($p<0.05$ was considered significant). In the two groups, there was no statistically significant difference in the rate of re-exploration for bleeding (CABG 1.7%, HCR 2.8%, p=0.44), perioperative myocardial infarction (CABG 1.1%, HCR 1.4%, p=0.79), stroke (CABG 2.4%, HCR 2.1%, p=0.83), need for haemodialysis (CABG 0.4%, HCR 0%, p=0.16), prolonged mechanical ventilation (CABG 2%, HCR 0.7%, p=0.15), or ICU length of stay (CABG 1.7±2.3 day, HCR 1.0±0.8 day, p=0.23). Hybrid coronary revascularisation was associated with a lower blood transfusion rate (CABG 25%, HCR 14%, p=0.002), lower in-hospital mortality (CABG 1.3%, HCR 0%, p=0.008), and shorter hospital length of stay (CABG 6.7±4.7 day, HCR 4.5±2.1 days, $p<0.001$). After the median follow-up period of 70 (37-106) months (CABG group) and 96 (53-114) months (HCR group), there was no significant difference in survival (CABG 92%, HCR 97%, p=0.13) or freedom from any form of revascularisation (CABG 93%, HCR 91%, p=0.27). Hybrid revascularisation was superior in freedom from angina (CABG 70%, HCR 91%, $p<0.001$).

Using the same methodology, we also performed a comparative analysis to off-pump CABG. Our sample consisted of all double off-pump CABG (n=216) and HCR (147 RACABG graft of the LIMA to the LAD and PCI to one of the non-LAD vessels) performed between March 2004 and November 2015. We found that in the two groups there were no statistically significant differences in the rates of re-exploration for bleeding (CABG 1.5%, HCR 3.5%, p=0.36), postoperative atrial fibrillation (CABG 19%, HCR 12%, p=0.13), perioperative myocardial infarction (CABG 0.5%, HCR 1.4%, p=0.36), stroke (CABG 1.0%, HCR 2.1%,

p=0.88), renal failure with need for haemodialysis (CABG 0.5%, HCR 0%, p=0.31), blood transfusion (CABG 28%, HCR 15%, p=0.60), in-hospital mortality (CABG 1.0%, HCR 0%, p=0.15), or ICU length of stay (CABG 1.8±1.3 day, HCR 1.0±0.8 day, p=0.10). There was a higher rate of in-hospital graft revision in the HCR group since the HCR group all had post-operative LIMA angiography (CABG 0%, HCR 3.4%, p=0.029). The HCR group had a lower incidence of postoperative prolonged mechanical ventilation (CABG 4%, HCR 0.7%, P=0.017). The hospital length of stay was significantly shorter in the patients who underwent HCR (CABG 8.1±5.8 day, HCR 4.5±2.1, p<0.001). After the median follow-up period of 81 (48-113) months (CABG group) and 96 (53-115) months (HCR group), there was no significant difference in survival (CABG 85%, HCR 96%, p=0.054) and freedom from any form of revascularisation (CABG 92%, HCR 91%, p=0.80). Hybrid revascularisation was superior in term of freedom from angina (CABG 73%, HCR 90%, p<0.001).

Our experience and that of others suggests that a hybrid revascularisation strategy is safe and provides excellent short and long-term results with a low rate of post-operative complications, short hospital stay, fast recovery and very high rate of freedom of angina, freedom from any revascularisation and good long-term survival. In recent years, there has been an increasing trend towards hybrid revascularisation procedures due to a continuous improvement of drug eluting stent (DES) performance and due to a broader use of minimally invasive techniques, especially with robotic assistance. The major advantages of HCR when compared with conventional CABG are the avoidance of cardiopulmonary bypass, aortic clamping and sternotomy, while still providing the survival benefit of the LIMA-LAD anastomosis. With the addition of PCI, this ensures complete revascularisation of all significantly diseased arteries. However, if the rationale behind this alternative form of coronary revascularisation is well established, HCR has failed so far to be broadly adopted, and the Society of Thoracic Surgeons adult cardiac surgery database showed that, between July 2011 and March 2013, HCR represented only 0.48% of the total CABG volume (950 of the total 198,622 patients underwent CABG) [29]. The reasons why physicians and surgeons have not embraced this technique in routine clinical practise could be related to the fact that the minimally invasive LIMA-LAD anastomosis is technically demanding and there are still costs and logistic problems associated with performing two procedures with different peri-procedural management protocols. There is also a lack in validation from randomised clinical trials comparing HCR with conventional CABG.

However, a few recent studies have highlighted the good preliminary results of this technique, including its advantages and disadvantages. Harskamp et al. reported the first meta-analysis of more than 1,100 patients who underwent HCR from 6 observational cohort studies [30]. They observed that patients undergoing HCR have a similar risk of the composite of death, MI, stroke, and repeat revascularisation than those treated with CABG during hospitalisation and during follow-up (4.1% of patients after HCR and 9.1% of patients with CABG at 1 year follow up). Death, MI, and stroke rates were numerically but not statistically lower with HCR. The need for repeat revascularisation occurred more frequently with HCR (8.3% after HCR and 3.4% after CABG at 3 years follow-up, p<0.001). These findings were similar when HCR was performed as a single or dual stage procedure. The data generated by this meta-analysis also support that HCR performed without conventional sternotomy results in shorter duration of hospital stay, earlier return to work, and fewer in-hospital complications. It also showed that self-reported quality of life is significantly higher at follow-up.

These data are in line with our findings. In fact, in our analysis, we observed a shorter length of stay in ICU (1±1 days) and an average hospital stay of 5±2 days. None of our

patients developed renal failure with the need for dialysis, and only 11% of the patients required a blood transfusion. We also observed a low rate of repeat revascularisation, with a very good long-term freedom from any revascularisation (in 90.7% of patients at 78±41 months follow-up). The results of new generation DES are playing an important role in coronary revascularisation and could contribute to a wider diffusion of HCR [31-33]. Newer DES, in fact, show favourable outcomes especially when compared with vein grafts, which are more prone to atherosclerotic degeneration, progressive narrowing and high early and long-term failure rates, as shown in the PREVENT IV study [7]. In another meta-analysis, Zhu et al. analysed data from 10 cohort studies involving 6176 patients [10]. They calculated summary odds ratios for primary endpoints (death, stroke, myocardial infarction, target vessel revascularisation, major adverse cardiac or cerebrovascular events) and secondary endpoints (atrial fibrillation, renal failure, length of stay in the intensive care unit, length of stay in hospital, and red blood cell transfusion). They found that HCR was non-inferior to CABG in terms of major adverse cardiac or cerebrovascular events during hospitalisation (OR 0.68, CI 0.34-1.33) and at one-year follow up (OR 0.32, CI 0.05-1.89), and no significant difference was found between HCR and CABG groups in in-hospital and one-year follow up outcomes of death, myocardial infarction, stroke, atrial fibrillation and renal failure, whereas HCR was associated with a lower requirement of blood transfusion (weighted mean difference -1.25 units, 95% CI, -1.62 to -0.88) and shorter length of stay in ICU (weighted mean difference -17.47 hours, -31.01 to 3.93) and hospital than CABG (weighted mean difference -1.77 days, -3.07 to -0.46).

Harskamp et al. compared HCR versus standard CABG using a propensity score matching algorithm [11]. They considered 306 patients underwent HCR and matched them 1:3 to 918 patients who underwent standard CABG. They found that the 30-day composite of death, MI, or stroke after HCR and CABG was 3.3% and 3.1% respectively (OR 1.07; 95% CI, 0.52-2.21; p=0.85). Hybrid revascularisation was associated with lower rates of in-hospital major morbidity (8.5% vs 15.5%; p=0.005), lower blood transfusion use (21.6% vs 46.6%, p<0.001), lower chest tube drainage (690 mL, interquartile range (IQR) 485-1050 mL vs 920 mL, IQR 710-1230mL; p<0.001), and shorter postoperative length of stay (<5-day stay: 52.6% vs 38.1%, p=0.001). During the 3-year follow up period, mortality was similar after HCR and CABG (8.8% vs 10.2%; Hazard Ratio=0.91; 95% CI, 0.55-1.52; p=0.72).

There is only one small randomised controlled trial comparing HCR with CABG that has recently been published in the literature [34]. In this study, a total of 200 patients with multi-vessel coronary artery disease involving the LAD and another critical lesion in at least one major epicardial vessel amenable to both PCI and CABG were randomly assigned to undergo HCR or CABG in a 1:1 ratio. The primary endpoint was the evaluation of the safety of HCR. The feasibility was defined by the percentage of patients with a complete HCR procedure and the percentage of the patient with conversion to standard CABG. They also assessed the occurrence of major adverse cardiac events such as death, MI, stroke, repeated revascularisation, and major bleeding within 12-months follow up. Of the patients in the HCR group, 93.9% had complete HCR and 6.1% patients were converted to standard CABG. At 12-months, the rates of death (2.0% vs 2.9%, p=NS), MI (6.1% vs 3.9%, p=NS), major bleeding (2% vs 2%, p=NS), and repeat revascularisation (2% vs 0%, p=NS) were similar in the two groups and no cerebrovascular accidents were observed. Another crucial key factor in HCR is patient selection, and the role of the heart team in guiding

appropriate patient selection for HCR is crucial. The ideal patient is a patient with multivessel CAD with a complex proximal LAD lesion suitable for LIMA-LAD grafting associated with non-LAD lesions suitable for PCI and no contraindication for dual antiplatelet therapy. The high likelihood of achieving complete revascularisation with this approach is certainly one of the most important guiding factors. Complex distal left main lesions are also ideal for HCR if the circumflex artery territory is amenable to PCI.

In addition, the most recent observational study comparing multivessel PCI to HCR suggested that there is no difference in major adverse cardiac event rates over 12 months in patients treated with PCI or HCR. They recommended a randomised trial with long-term outcome measures to definitively compare the effectiveness of the two revascularisation strategies [35].

The lack of randomised controlled trials precludes the identification of an HCR target group of patients. Another important factor is the choice of timing for the two procedures, in other words, if it is better to utilise a one-stop strategy (single stage HCR) or two separate sittings (two stage HCR). Most of our patients (71.9%) underwent single stage HCR. This decision is guided by patient characteristics and available facilities but we acknowledge that this approach has several advantages including cost-effectiveness, reduced length of stay, increased patient satisfaction, and immediate confirmation of the patency of the LIMA graft. The main disadvantage is the risk of bleeding due to the use of dual antiplatelet therapy and incomplete heparin/bivalirudin reversal. For this approach, having an equipped hybrid operating room is mandatory.

The two-stage procedure is generally favoured accordingly on the basis of clinical presentation and anatomy. Usually, the PCI is followed by CABG for patients who have an acute coronary syndrome with a non-LAD culprit lesion. The main disadvantages are the risk of bleeding due to antiplatelet therapy and the fact that the PCI is performed with the LAD territory still not revascularised. In the two-stage approach, we generally prefer performing the LIMA-LAD bypass grafting before the PCI. The main advantages of this strategy are the immediate angiographic check of the LIMA-LAD anastomosis at the same time as the PCI, the protection of the anterior wall of the left ventricle that lowers the risk of the PCI and the decreased risk of bleeding considering that it is possible to start full antiplatelet therapy one or a few days after the completion of the CABG.

One of the major perioperative concerns of HCR is the management of the antiplatelet therapy, with the related risk of bleeding or stent thrombosis. In our series, we did not observe any acute stent thrombosis and we also had a low rate of re-operation for bleeding (only 4 patients). One of the arguments against HCR has been the fact that the LIMA-LAD anastomosis is technically highly demanding, and this could interfere with patency rates. We previously reported two studies with angiographic follow-up of patients who underwent HCR. In the first study, 58 patients underwent HCR and, at a mean follow-up of 20.2 months, the LIMA-LAD anastomosis was patent in 49 (91%) of the 54 patients who had repeat catheterisation [36]. Later, in 2013, we published a series of 94 patients who underwent HCR and at 6-month angiographic follow up, the LIMA-LAD anastomosis patency was 94% [37]. On the other hand, it is difficult to compare this patency rate to patients who underwent conventional CABG considering that these patients generally do not undergo angiographic follow up.

Conclusion

Current evidence suggests that HCR is a feasible, safe and effective coronary artery revascularisation strategy in selected patients with multivessel coronary artery disease with favourable coronary anatomy. It offers complete coronary revascularisation with a faster recovery, fewer post-operative complications and at least similar long-term outcomes. However, more prospective randomised controlled trials comparing HCR with conventional CABG procedures or multi-vessel PCI will be necessary to further evaluate the effectiveness of this alternative and complementary technique of coronary artery revascularisation.

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SECTION 1 CARDIAC SURGERY

Aortic Valve Surgery

"Audaces fortuna juvat"

Publius Vergilius Maro (70BC-19BC)
From the Aeneid

Chapter 2

The Durability of Tissue Valves in the Aortic Position

Hristo Kirov, Sophio Tkebuchava, Mahmoud Diab, Gloria Färber and Torsten Doenst

"Aut viam inveniam aut faciam"

Introduction

Since the first implantation of a prosthetic valve in the aortic position by Harken in 1961, valve replacement surgery has dramatically altered the prognosis of valvular heart disease, affecting the lives of millions of patients [1-3]. Over the last two decades, aortic valve replacement has drastically evolved, with a decline in the implantation of mechanical prostheses and a significant shift towards the use of aortic bioprostheses [2,4]. With this increased use of bioprostheses and the advent of transcatheter aortic valve implantation (TAVI), the durability of tissue valves has moved centre stage.

The comparison of treatment outcomes, specifically that of valve durability due to structural valve deterioration (SVD), requires uniform reporting of results. The first efforts to standardise the reporting of valve-related outcomes were made in the 1980s [5] and revised 8 years and again 20 years later [6,7]. However, there is still a lack of consistency in outcomes reporting and, especially with the aim of comparing valve durability to TAVI, there is significant uncertainty about the way SVD was reported in the past. Finally, to put outcomes and potential differences in SVD into perspective, the potential failure mechanisms are important.

We summarise here the current knowledge on biological valve durability and illustrate the difficulties in interpreting durability data. We begin with a description of current efforts made to standardise valve outcomes reporting and then describe the available information for SVD for both conventional as well as TAVI bioprostheses. We continue with a comparison of tissue valves to mechanical valves, which by definition are free from SVD. Although they have attained a negative perception for their need for continuous anticoagulation, the clinical performance of mechanical valves may even be superior [8,9]. It is therefore important to know the pros and cons of both tissue and mechanical valves when durability is addressed. We finish with a description of suggested mechanisms of bioprosthetic valve failure, providing valuable information for consenting patients and for individualised decision-making.

Definitions of Valve-Related Outcomes and Prosthetic Valve Dysfunction

Figure 1 shows the current classification of bioprosthetic valve dysfunction [10]. The classification illustrates that valves can fail without the need for their structure to deteriorate. Structural valve deterioration is only one of four categories of failure, although it may be closely related to the mechanism of valve thrombosis. These two mechanisms will be addressed more closely in the text below, while non-structural valve deterioration (such as paravalvular leaks) or endocarditis are not part of this review.

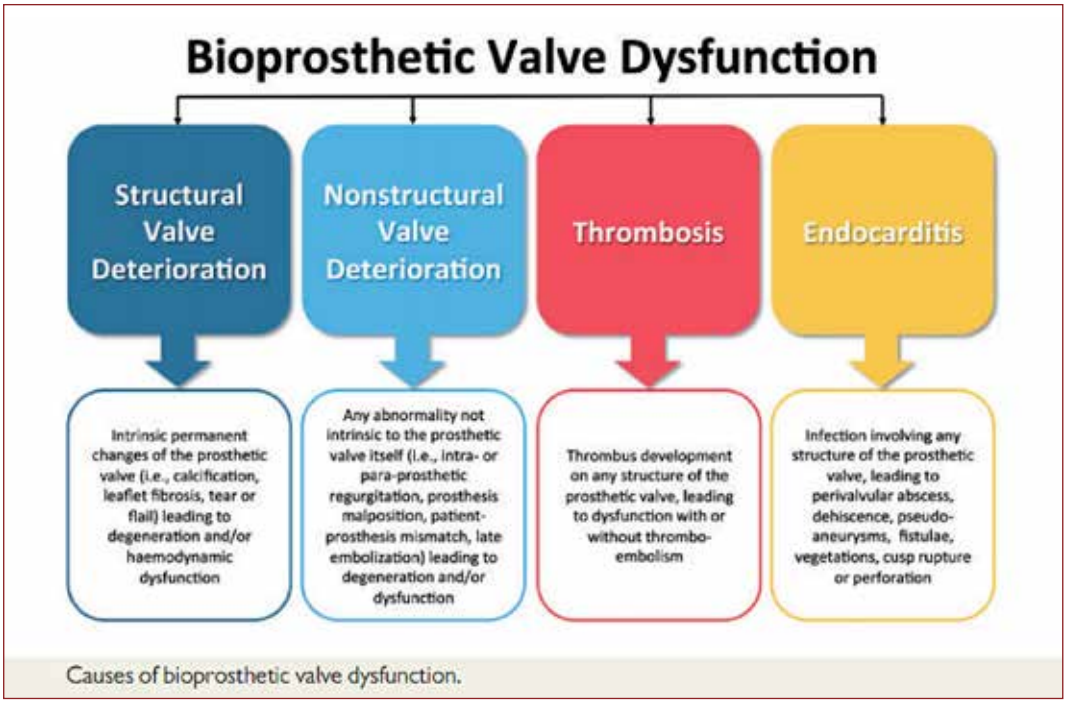

Figure 1: Current European Association of Percutaneous Cardiovascular Interventions (EAPCI) Classification for causes of bioprosthetic valve dysfunction. Reproduced with permission from Capodanno et al. [10]

Classic structural valve deterioration defines processes that affect tissue valve leaflets in their opening and closing movement leading to valve dysfunction [7]. In the majority, these mechanisms are tissue degeneration such as calcification, sclerosis and/or leaflet tears or restriction due to fibrosis [10]. However, valve or cusp thrombosis may cause the same situation and has been listed as a cause of SVD in previous guidelines [5,6]. The lack of its recognition and/or the lack of its successful treatment may lead to consolidation of thrombus and the development of classic signs of SVD. Since the mechanism of bioprosthetic valve thrombosis is specifically relevant for transcatheter valves (it appears with a rate of 14% - up to 4 times more frequent than in surgically implanted tissue valves) and anticoagulation treatment is successful in the majority of cases, it is reasonable to list this failure mechanism as a separate entity in the new classification [10-12].

The first efforts to unify reporting of valve-related outcomes were made 30 years ago in 1988 and updated reports were published thereafter [5-7]. From today's perspective, the definitions were not precise enough to generate full comparisons of outcomes (e.g. what echo gradient indicates SVD) and publications on valve-related outcomes did not consistently follow these recommendations, especially for SVD. Thus, the available publications present a mix of data, where it is not always clear whether SVD was detected during reoperation or whether it was detected echocardiographically based on one of several different ways to detect prosthetic valve dysfunction.

Figure 2 illustrates the magnitude of these differences in SVD reporting based on data from a publication that presented both freedom from SVD using echocardiographic signs for severe aortic stenosis and freedom from reoperation [13]. The authors show that freedom from reoperation is 84% at 9 years, while freedom from echocardiographic signs of SVD (defined as the presence of a mean trans-prosthetic gradient >40mmHg or aortic regurgitation/stenosis more than moderate) at the same time is only 66%. In general, there may be up to 20% difference in outcome depending on the exact endpoint that is chosen. Since the majority of publications in this field do not provide clear information on how SVD was assessed, it is clear that the current evidence is difficult to compare and to interpret. But even for the future, comparability remains a challenge. There are currently two entities that provide recommendations for SVD documentation and reporting. Although they are a step in the right direction, they still differ considerably.

The Valve Academic Research Consortium suggests defining SVD as follows [14,15]:

- increase in the mean gradient >10 mmHg.
- decrease in the EOA >0.3–0.4 cm^2.
- reduction in the DVI >0.1–0.13.
- whenever valve dysfunction is suspected, careful evaluation of valve morphology should confirm a structurally abnormal valve.

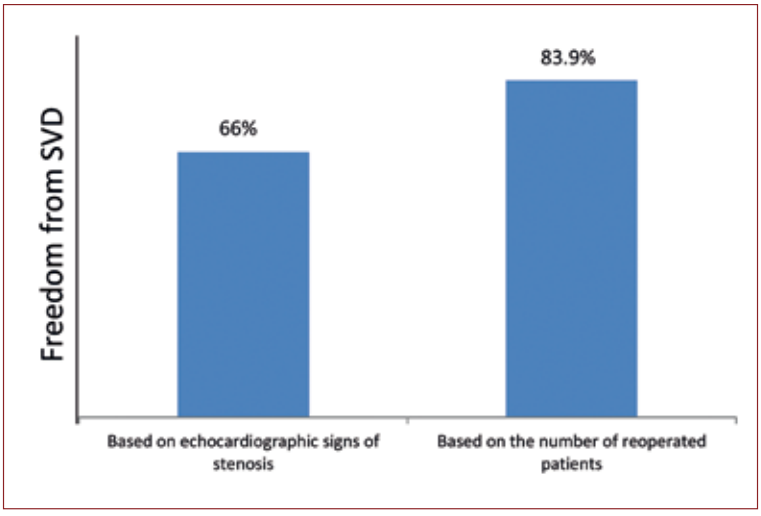

Figure 2: Illustration of the difference between freedom from structural valve deterioration (SVD) using echocardiographic signs for severe aortic stenosis vs freedom from reoperation due to SVD. Data represent values at 9 years for the Mitroflow aortic bioprosthesis and are taken from Ius et al.[13].

A consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI), endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), was published in 2017 [10]. It suggested the following definitions for SVD, separated into moderate and severe SVD, and morphological SVD:

Moderate haemodynamic SVD:

- Mean transprosthetic gradient ≥20 mmHg and <40-mmHg, or
- Mean transprosthetic gradient ≥10 and <20 mmHg change from baseline, or
- Moderate intra-prosthetic aortic regurgitation, new or worsening (>1+/4+) from baseline.

Severe haemodynamic SVD:

- Mean transprosthetic gradient ≥40 mmHg, or
- Mean transprosthetic gradient ≥20-mmHg change from baseline, or
- Severe intra-prosthetic aortic regurgitation, new or worsening (>2+/4+) from baseline.

Morphological SVD:

- Leaflet integrity abnormality,
- Leaflet structure abnormality,
- Leaflet function abnormality,
- Strut/frame abnormality.

Thus, a truly uniform definition is still not available. Assessing these definitions in the context of the differences illustrated in Figure 2 suggests that data will be more (but not fully) uniform in the future. However, it allows the information already available on prosthetic valve durability to be put into perspective.

Durability of Conventional Tissue Valves

A plethora of investigations have reported long-term outcomes of bioprostheses implanted by surgical replacement of the aortic valve. Many prostheses have been used and disappeared over time, presumably due to SVD. Examples include the SJM stentless Toronto SPV and Root [16], the Medtronic Hancock Pericardial Valve [17], the Edwards porcine aortic valve [18], as well as several others. For the prostheses still in current use, experience of up to 20 years exists.

Table 1 summarises the evidence for valve durability following surgical AVR for bioprostheses commonly used in contemporary practice. The table shows freedom from SVD as reported by the investigators of the quoted studies. Since it is not always clear which definition was used for SVD, it may be wise to consider the unclear values as “freedom from reoperation due to SVD”. The table is labeled to indicate the definition used for SVD, if available. The various publications report different observation periods, but it becomes clear that SVD at 5 years is practically non-existent. Differences begin to appear at 10 years, and of the four valves reporting 20-year outcomes, all show freedom from SVD rates of between 50 and 80%.

Figure 3 shows a graphic illustration of SVD development over time from those studies where echocardiographic information was the basis of SVD assessment. This illustration

underscores the findings of Table 1, in that it shows an average freedom from SVD of 60% at 20 years.

Table 1: Summary of available studies reporting freedom from Structural Valve Deterioration (SVD) of surgically-implanted tissue valves.

	Freedom from SVD (%)				
Study	5 years	10 years	15 years	20 years	Valve type
McClure et al. 2010 [36] *	99.8	97.1	82.3	n.a.	CE PP Bovine Pericardial
Johnston et al. 2015 [37] ×	n.a.	98.1	n.a.	85	CE PP Bovine Pericardial
Poirier et al. 1998 [38] *	99	93	80&	n.a.	CE PP Bovine Pericardial
Bourguignon et al. 2015 [39] #	n.a.	94.2	78.6	48.5	CE PP Bovine Pericardial
Pelletier et al. 1995 [40] *	100	87.3	n.a.	n.a.	CE PP Bovine Pericardial
Bernal et at. 1995 [41] *	n.a.	n.a.	62	n.a.	CE-SAV Porcine
Corbineau et al. 2001 [41] ∞	n.a.	98.6	79.4	n.a.	CE-SAV Porcine
Ruggieri et al. 2012 [43] ∞	99.2	95.9	85.9	48.6	CE SAV Porcine
Jamison et al. 2005 [44] ¿	n.a.	n.a.	88.9	86.4¥	CE SAV Porcine
David et al. 2010 [45] ×	99.7	97.6	86.6	63.4	Hancock II
Rizzoli et al. 2006 [46] *	100	98	91.9	n.a.	Hancock II
Mosquera et al. 2016 [47] ÷	99.5	97.4	88.2	n.a.	Mitroflow
Jamieson et al. 2009 [48] ¿	100	99. 6	85.6	n.a.	Mitroflow
Benhameid et al. 2008 [49] ¿	n.a.	82.5	n.a.	n.a.	Mitroflow
Asch et al. 2012 [50] ×	97.8	n.a.	n.a.	n.a.	Mitroflow
Piccardo et al. 2016 # or ∞	99	95	95	n.a.	Mitroflow

Sjögren et al. 2006 [51] ×	98.5	81.9	n.a.	n.a.	Mitroflow
Guenzinger et al. 2015 [52] ¿	97.9	92.1	84.8	67	Biocor
Bottio et al. 2003 [53] ¿	n.a.	90.3	n.a.	n.a.	Biocor
Eichinger et al. 2008 [54] ¿ and #	98.4	93.1	88.4	70.3	Biocor
Amabile et al. 2014 [55] ¿	n.a.	94	n.a.	n.a.	Freestyle
Anselmi et al. 2017 [56] ¿	98	n.a.	n.a.	n.a.	Trifecta
Lehmann et al. 2017 [57] *	97.9	n.a.	n.a.	n.a.	Trifecta
Stanger et al. 2015 [58] ¿	92	60	n.a.	n.a.	Freedom Solo
Anselmi et al. 2014 [59] ∞	99.3	97.9	86.3	n.a.	Mosaic
Matsumoto et al. 2015 [60] *	100	96.7	n.a.	n.a.	Mosaic

Labels used for definitions of SVD:

** freedom from reoperation due to SVD.*

× Echocardiographic follow up present, no information on how SVD was defined.

¿ SVD defined according to guidelines Edmunds et al. 1996 6 or Akins et al.[7].

∞ SVD defined by the presence of valve incompetence or regurgitation on clinical examination, on echocardiography, or at reoperation.

 # SVD defined as mean transvalvular gradient > 40 mm Hg or severe aortic regurgitation.

÷ SVD defined as changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve, ¥ at 18 years, & at 14 years, § at 9 years.

Abbreviations: CE PP - Carpentier-Edwards Pericardial Bioprosthesis, CE-SAV - Carpentier-Edwards Supra-annular Valve, n.a. -no information available

One important aspect in the context of durability of tissue valves is its dependence on age. In general, the younger the patient at the time of implantation, the lower is the freedom from SVD. Figure 4 shows this relationship from a recently published meta-regression for four conventional aortic bioprostheses [19]. While a patient receiving the same valve at an age below 50 years may only have a freedom from SVD at 15 years of 30%, this value may increase to around 90% if age at implant is >70 years. While it may be argued that the difference is influenced by the lower life expectancy of older patients, the magnitude and continuity of this finding argues against it. Suggested mechanisms include differences in calcium metabolism, in patients' exercise level or in immune responses (see below),

but a convincing explanation has not been identified. In addition, there are considerable differences between the valve types, with the Mitroflow valve performing poorer than the Perimount, the Hancock II or Biocor/Epic (see Figures 3 and 4).

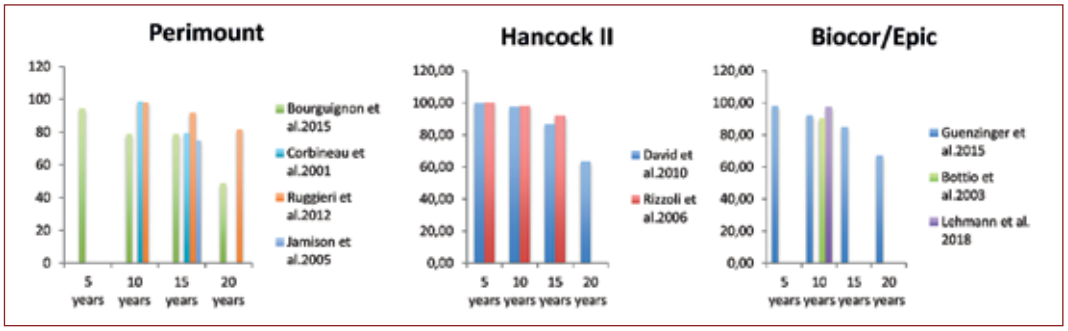

Figure 3: Graphic illustration of freedom from SVD reported for Perimount, Hancock II and Biocor/Epic bioprostheses over time for those studies having used some sort of echocardiographic information for the detection of SVD. Biocor and Epic were combined since they represent the same physical valve except for the additional anti-calcification treatment of the newer Epic valve.

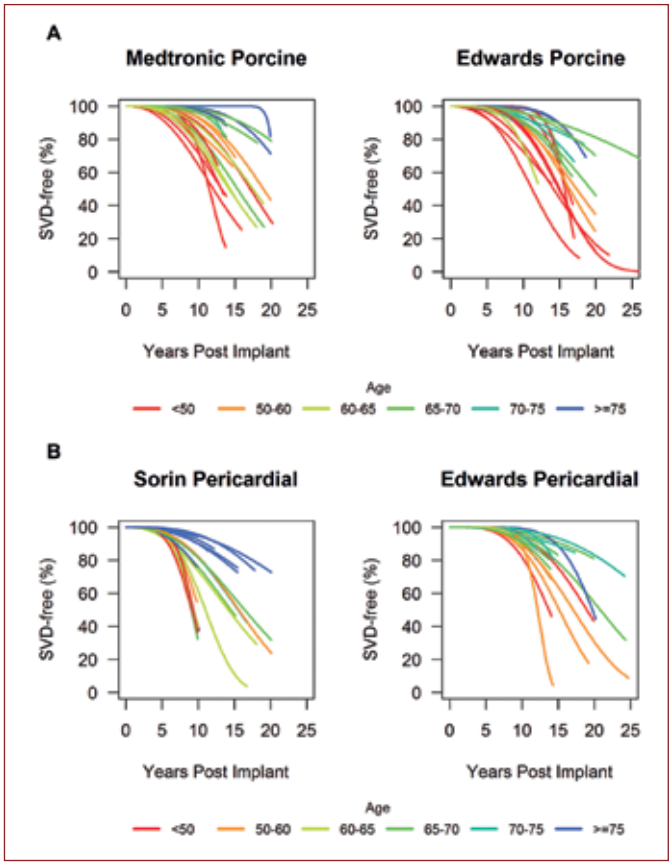

Figure 4: Bioprosthetic aortic valve durability of the Mitroflow, the Perimount, the Hancock II and the Edwards porcine bioprostheses as a function of patient age at implantation. Individual curves are color coded according to mean patient age. Reproduced with permission from Wang et al. [19]

Another aspect potentially affecting tissue valve durability is the haemodynamic performance of a valve. Good haemodynamics may be associated with better results, possibly including survival and durability. The previously quoted study on the Mitroflow aortic pericardial bioprosthesis showed, in over 800 patients, that bigger valves may have less SVD compared to smaller ones. Freedom from SVD in this analysis was 81.9% at 9 years for size 23mm, but only 55% for size 21mm [13]. Others have created a link between freedom from SVD and patient-prosthesis mismatch [20,21], suggesting the same relationship. This finding may be relevant not only for surgical valve replacement but also for its comparison to transcatheter valves. For instance, the CoreValve trials have demonstrated superior haemodynamic performance of the CoreValve compared to surgical prostheses [22,23].

Transcatheter Aortic Valve Implantation (TAVI)

Transcatheter aortic valve implantation (TAVI) has received widespread application only in the last 10 years and has been used mostly in elderly patients. Thus, long-term durability data is not yet available. Table 2 lists the studies reporting freedom from SVD at up to 10 years based on echocardiographic definitions. Comparable to conventional prostheses, results at 5 years are excellent, with an SVD occurrence between 0 and 3.4 %. There may be a tendency towards increased SVD at 7 years (14.9% SVD in Deutsch et al. 2018 [66]) or even more at 6-10 years (Dvir et al. 2016). However, the latter study has only been presented at meetings and never published and there were serious concerns about the way SVD was defined and reported. Nevertheless, the results have to be seen in the context of patient age (remember Figure 4) and also the characteristics of each individual bioprosthesis, thus raising significant concern regarding durability of TAVI prostheses.

Table 2: Summary of currently available studies reporting freedom from SVD in transcatheter valves.

Study	Follow up (yrs)	SVD (%)	Valve Type
Kapadia et al. (PARTNER1) [61] *	5	0	Edwards Sapien
Mack et al. [62] *	5	0	Edwards Sapien
Toggweiler et al. 2013 [63] §	5	3.4	Cribier-Edwards or Edwards Sapien
Dvir et al. 2016 ∞ ×	6-10	50	Cribier-Edwards / Sapien or SapienXT
Barbanti et al. 2015 [64]×	5	1.4	CoreValve
Eltschainoff et al. 2018 [65]	8	3.2	n.a.
Deutsch et al. 2018 [66]	7	14.9	CoreValve; Sapien
Gerckens et al. 2017 [67] (ADVANCE) §	5	2.6	Core Valve
Sondergaard et al. 2018 (NOTION)# §	6	4.8	CoreValve

Labels used for definitions of SVD:

× freedom from reoperation due to SVD.
§ according to VARC [14,15].
? no information on how SVD was defined.
#Presented at EUROPCR 2018.
∞ Presented at EUROPCR 2016.
n.a. -no information available.

In contrast, however, a 6-year report on SVD from the NOTION trial points towards higher freedom from SVD in the TAVI group (Sondergaard et al. 2018 - presentation at EUROPCR), but the type of surgical valves used in this trial have not been reported. In other words, we will have to wait, and we will also have to report outcomes for every single prosthesis separately, be it surgically implanted or placed by catheter [24].

Mechanical Valves – the Gold Standard for SVD

Based on the definition shown in Figure 1, SVD does not exist in mechanical valves (with the possible exceptions of extremely rare material fracture or, possibly more often, pannus formation). It is therefore no surprise that studies repeatedly demonstrate less need for reoperation with mechanical valves, specifically in the younger patient population [8]. There are no randomised trials with the currently implanted valve types, but data from registries does exist. A prominent study of more than 45,000 patients in a Californian registry demonstrated a survival advantage for mechanical valves in the aortic position up to an age of 55 years and in the mitral position of up to an age of 70 years [25]. These findings are supported by two older randomised trials for the aortic position, but there are contemporary registry studies demonstrating no such advantage with biological prostheses in patients between 18 and 50 years of age [26]. The guideline committees currently see no need to lower the age in the current recommendations [2]. The advantages of mechanical valves come at the expense of the requirement for permanent anticoagulation. Individual decision-making for each patient therefore requires understanding of different modes of bioprosthetic valve failure.

Mechanisms of Prosthetic Valve Failure

There are several mechanisms explaining dysfunction of prosthetic valves in the aortic position. Figure 1 shows one current definition. As stated above, endocarditis and non-valvular valve dysfunction such as paravalvular leaks or valve dislocation are not addressed here. With respect to the mechanical function of the valve, e.g. its outlet function, the following main mechanisms are discussed.

Calcification and Mechanical Stress

Bioprostheses undergo glutaraldehyde fixation in order to decrease their antigenicity and reduce immune response reactions. This might predispose them to calcium deposition on the valve cusps and, combined with phospholipids, this might result in leaflet thickening and calcification [27]. From this perspective, durability of TAVI prostheses is interesting because the crimping process has been suggested to lead to microfractures in the connective tissue of the cusps, which may confer a higher susceptibility to this calcification process [28,29]. The constant wear and tear on the cusps (they open and close roughly 37 million times per year) also leads to fatigue of the material. Such mechanical stress has been identified as an independent determinant of early bioprosthetic calcification in humans [29].

Immune Response

Glutaraldehyde fixation of biological valves is standard with the goal to limit the immune response to the biological material. However, despite this fixation, rejection processes are not completely eliminated but their magnitude is small and there is no data showing increased durability through immunosuppression [30-32].

Pannus formation

One well known mechanism for dysfunction of both biological and mechanical valves is pannus formation. Fibrotic tissue growth that may occur along the cusps and or the sewing ring may lead to reductions in the outflow tract or disturb tissue cusp or mechanical leaflet mobility. Thus, pannus formation may be considered a mechanism for classic SVD if tissue cusp mobility is affected but may also cause non-valvular valve dysfunction, by creating outflow tract stenosis or interfere with the moving parts of mechanical valves [33].

Thrombosis

Thrombosis of prosthetic tissue valves has recently gained significant attention after Makar et al. demonstrated the presence of thrombus on up to 40% of transcatheter valves shortly after implantation [12]. This failure mechanism for tissue valves has been known for conventional tissue valves for some time, but its magnitude is much lower [5]. A recent registry analysis demonstrated more than 3-fold higher occurrence of tissue valve thrombosis in TAVI prostheses [11]. Although these numbers are worrying and the presence of thrombosis is not free of risk, permanent anticoagulation treatment is successful in the majority of patients [34]. However, if treatment is not successful or thrombosis occurs without being diagnosed, thrombus may consolidate on the cusps and cause classic SVD [35]. Since a large fraction of thromboses seem to occur without symptoms, regular echocardiographic follow-up for all tissue valve patients appears mandatory [12,35].

Conclusion

Valve durability and the development of SVD continue to be one of the main limitations of biological valves. Mechanical valves still show excellent long-term results, especially in younger patients. The current evidence shows that the durability of currently available bioprostheses begins to decline considerably after 10 years. With the leading conventional valve bioprostheses, approximately 60% freedom from severe aortic stenosis can be expected at 20 years. Higher values can be expected in the older and lower values in the younger patient population. Finally, durability needs to be assessed individually for every single prosthetic valve type available.

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Chapter 3

Debate: The Optimal Treatment for the Failing Aortic Bioprosthesis:

Redo AVR:

Carlo Olevano, Clifford W Barlow and Danai M Karamanou

Transcatheter Aortic Valve Implantation:

Pavel Overtchouk, Ibrahim Alqdeimat and Thomas Modine

"Nemo regere potest nisi qui et regi"

Redo AVR

Carlo Olevano, Clifford W Barlow and Danai M Karamanou

"Et ipsa Scientia potestas est"

Introduction

Improvements in surgical technique and prolonged life expectancy in the current population have increased the frequency of reoperative heart valve surgery in the last two decades. The choice of prosthesis should be tailored to the individual patient depending on age, life expectancy, valve size and co-morbidities, both cardiac as well as extra-cardiac. However, the current and potential future developments in bioprosthetic technology, combined with increasing patient preference to avoid lifelong anticoagulation therapy, has led to a shift in prosthesis selection from mechanical valves to bioprostheses in ever younger patients.

Brown et al. interrogated The Society of Thoracic Surgeons National Database for all isolated aortic valve replacements between 1997 and 2006. In a selected cohort of 108,791 patients, the use of bioprostheses increased from 43.6% to 78.4% with a dramatic shift away from mechanical valves, reduced from 49.9% to 20.5% of the total number of valve implantations performed in the United States [1]. Recently the German heart surgery registry presented data of all aortic prostheses surgically implanted in Germany in 2016 showing that 89% were bioprostheses [2].

The biological tissue used for a bioprosthesis is prone to structural valve degeneration (SVD), a gradual and multifactorial process characterised by progressive calcification, fibrosis, and wear and tear of the valve leaflets, ultimately leading to valve dysfunction secondary to stenosis, regurgitation or both [3]. Structural valve degeneration is becoming an increasingly common scenario in cardiac surgery. This is particularly attributable to younger patients refusing mechanical valves due to the associated burden of anticoagulation management. In addition, the recent availability of valve-in-valve transcatheter aortic valve replacement (ViV-TAVR) technology has swayed the decision-making process for prosthesis choice to a more strategically planned staged approach to allow for future TAVR intervention.

The question we therefore pose is whether transcatheter aortic valve-in-valve replacement or redo surgical aortic valve replacement (SAVR) is the best strategy in a patient with a degenerative bioprosthetic aortic valve.

The current American Heart Association/American College of Cardiology (AHA/ACC) Guidelines for the Management of Patients with Valvular Heart Disease recommend the use of aortic valve bioprostheses in patients more than 70 years old, or in those with a contraindication to lifelong anticoagulation [4]. In patients between 50 and 70 years of age, there is more uncertainty as to the most appropriate choice of prosthesis, and the guidelines recommend an individual approach taking into consideration patient factors and preferences. The latest European Society of Cardiology (ESC) guidelines of 2017 recommend the use of bioprostheses for aortic valve replacement in patients older than

65 years, whilst between 60 and 65 years the choice should be tailored to the individual patient, considering life expectancy and comorbidities [5].

Redo SAVR should be considered the first line option in the following:

- young patients,
- patients with prosthetic valve endocarditis,
- those with paraprosthetic leaks,
- those with planned concomitant cardiac procedures,
- patients at increased risk of patient-prosthesis mismatch,
- patients with peripheral vascular disease prohibiting transfemoral access,
- and those in whom there are other technical contraindications for ViV-TAVR.

Surgical aortic valve replacement remains, at present, the gold standard for treating bioprosthetic valve failure and is associated with an acceptable in-hospital mortality rate of up to 5.1%, including those high-risk patients with prosthetic valve endocarditis [3,6]. The risk of death for redo SAVR is much higher when the indication for treatment is infective endocarditis or paraprosthetic leak than in structural valve deterioration [7]. Jamieson et al. reported a mortality rate of 6.8% in more than 300 patients undergoing redo SAVR treated for aortic bioprosthesis degeneration [8]. Grubitzsch et al. reported in-hospital mortality of 17% in patients undergoing surgery for prosthetic valve endocarditis [9]. A retrospective study of the Italian National Registry, published in 2017, reported that 582 patients having surgery for prosthetic valve endocarditis (PVE) had an early mortality of 19.2% in the years from 1979 to 2015 [10]. Considering that infective endocarditis and paraprosthetic leak are considered exclusion criteria for treatment with ViV-TAVR, the comparator with regard to mortality data should therefore be limited to patients undergoing redo-SAVR for SVD only.

The first reported transcatheter aortic valve-in-valve replacement for a failing aortic bioprosthesis was reported in 2007 [11]. The procedure was performed in an elderly and fragile patient who was high risk for conventional redo SAVR. After this experience, numerous studies have demonstrated the feasibility and the safety of the ViV approach [12-13].

In 2014, the Multinational Valve-in-Valve Registry (VIVID) reported data of 459 patients with degenerated bioprosthetic valves undergoing valve-in-valve implantation between 2007 and May 2013 [13]. The 30-day and one-year mortality were 7.6% and 16.8% respectively. Previous AVR with a small valve (≤21mm) was a risk factor for increased 1-year mortality (74.8% survival), and these patients are therefore not recommended to undergo ViV-TAVR. On the basis of this registry data, the AHA recommendations in 2017 included ViV-TAVR as being a reasonable treatment option for patients who are severely symptomatic with aortic bioprosthesis stenosis and have a prohibitively high re-operative risk [14].

Transcatheter Valve-in-Valve Implantation versus Redo Surgical Aortic Valve Replacement: The State of the Art.

The introduction of transcatheter valve-in-valve implantation in the last decade has transformed the treatment of severe aortic stenosis in high risk patients for conventional surgery. There are few studies published that directly compare ViV-TAVR against redo SAVR and those that exist are observational studies, with no randomised controlled trials performed to date.

ViV-TAVR versus Redo SAVR Outcomes

Silaschi et al. performed an observational case-control study to compare ViV-TAVR with redo SAVR for failing bioprostheses [15]. This included 130 patients, treated from 2002 to 2015 (71 ViV-TAVR and 59 redo SAVR). Despite the ViV patients being older and with a significantly higher predicted EuroSCORE, 30-day and 180-day mortality was not different between the groups. Patients treated with redo SAVR had longer intensive care unit stay (3.4±2.9 vs. 2.0±1.8 days, $p<0.01$) with significantly higher rates of bleeding (33.9% vs. 9.9%, $p < 0.01$) and pacemaker implantation (25.4% vs. 9.9%, $p=0.01$).

Ejiofor et al. studied 91 patients treated for isolated AV bioprosthetic SVD [16]. In this small study, STS risk score matching was performed, creating 22 matched pairs comparing patients treated with redo SAVR and ViV-TAVR. The ICU stay was significant longer in the SAVR group, with a higher rate of new onset atrial fibrillation (63% vs. 18%, $p = 0.005$). Five of the ViV-TAVR patients (22%) had mild paravalvular leak, compared with zero in the SAVR group. None of the paravalvular leaks were graded moderate or severe. Actuarial survival at 3 years was comparable between the 2 groups (76.3% SAVR versus 78.7% ViV-TAVR). These data must be taken in context of the small numbers involved, but the authors concluded that their study supports the feasibility of ViV-TAVR for the failing aortic bioprosthesis.

Spaziano et al. used propensity score matching in a multicentre study to compare ViV-TAVR to redo-SAVR [17]. They identified 78 well-matched pairs of patients with failing bioprostheses treated either with ViV-TAVR or redo-SAVR. All-cause mortality was similar between groups at 30 days (6.4% redo-SAVR vs. 3.9% ViV-TAVR, $p=0.49$) and one year (13.1% redo-SAVR vs. 12.3% ViV-TAVR, $p=0.80$). Both groups also showed similar incidences of stroke (0% redo-SAVR vs. 1.3% TAV-in-SAV, $p=1.0$) and new pacemaker implantation (10.3% redo-SAVR vs. 10.3% TAV-in-SAV, $p=1.0$).

The most up to date review and meta-analysis of the few publications directly comparing ViV-TAVR with redo-SAVR is that of Gozdek et al. [18]. Pooled data from observational studies shows that, despite patients in the ViV-TAVR group having higher risk profiles, the mortality outcomes are comparable between the groups. However, most importantly, the redo-SAVR patients had significantly better post-procedural haemodynamic profiles with reduced risk of PPM. The authors therefore concluded that redo-SAVR should remain the standard of care, particularly in the low risk population.

ViV-TAVR and Patient Prosthesis Mismatch

In 1978, Rahimtoola first described the concept of patient prosthesis mismatch (PPM) as follows: "Mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve" [19]. This concept effectively deals with the situation that arises when the effective orifice area (EOA) of a prosthetic valve is small in relation to the patient's body surface area, leading to an increased transvalvular gradient. The PPM is considered to be moderate if the EOA is ≤ 0.85 cm^2/m^2 and severe if the EOA is ≤ 0.65 cm^2/m^2 [37]. In the case of ViV-TAVR, the inherent concern is that implantation of a new valve within the existing frame of the degenerated bioprosthesis will lead to a smaller EOA.

Studies based on the surgical aortic valve replacement population have previously reported that severe PPM leads to worse short and long-term mortality [20,21]. Pibarot et al. demonstrated that patients treated with aortic valve replacement who ended up with even

moderate post-operative PPM (EOA ≤ 0.85 cm^2/m^2) had significantly less postoperative improvement in the New York Heart Association (NYHA) functional class. This was independent of other predictors, such as age or pre-procedural NYHA class, but did not lead to an increase in mortality [22]. Fuster et al. performed a clinical echocardiographic study in 339 consecutive patients undergoing surgical valve replacement for aortic stenosis, examining left ventricular mass regression at 1 year post-operatively [23]. Patient prosthesis mismatch (defined as EOA ≤ 0.85 cm^2/m^2) was found in 38% of the patients, and in these patients there was less left ventricular mass regression at 1 year follow up. In patients with pre-existing higher left ventricular mass, there was a significant difference in mortality in the presence of severe PPM (EOA ≤0.65cm^2/m^2) compared to patients without PPM (13.0% vs 2.9%, $p<0.05$). Similarly, Kandler et al. reported a significant reduction in left ventricular mass regression between PPM and non-PPM patients as soon as 3 months post-operatively. On echocardiographic follow-up, the LV mass regression in patients with no PPM was 31.4 ± 28.0 g/m^2, moderate PPM was 1.1 ± 34.4 g/m^2, and severe PPM was -5.9 ± 29.7 g/m^2, respectively ($p=0.01$) [24].

A more recent publication examined the STS database for long term results of PPM following aortic valve replacement in patients over 65, identifying nearly 60,000 patients operated within a ten year period (2004-2014) [25]. This study also concluded that both moderate and severe PPM lead to significantly decreased survival ($p<0.001$), and increased rates of heart failure admission, as well as redo AVR.

In the Silaschi cohort, the rate of severe patient prosthesis mismatch (PPM) was higher in the ViV-TAVR group compared to SAVR (14.1% vs. 3.4%, $p=0.06$), with a significant decrease in trans-prosthetic gradients after redo-SAVR ($p=0.01$) [15]. Nearly half of the ViV-TAVR patients had a mean transvalvular gradient >20 mmHg (46% vs. 5%, $p<0.01$). In addition, the proportion of severe PPM increased in the ViV-TAVR patient population from 5.6% pre-procedurally to 14.1% post-procedure. The haemodynamic outcome of 102 patients treated by Erlebach et al. for failing bioprostheses was not dissimilar. The mean gradient of patients treated with ViV-TAVR was significantly higher than the redo SAVR group (18.8 ± 8.7mmHg vs. 13.8 ± 5.4mmHg, $p=0.008$), with 24% of the ViV-TAVI patients showing mean gradients of >25mmHg [26]. Spaziano et al. reported that redo SAVR was associated with a significantly lower mean aortic valve gradient compared to VIV-TAVR at 30 days (14.3 mmHg vs. 18.1 mmHg, $p=0.01$) [17]. Surprisingly, in the Ejiofor study, the 2 groups had similar post-operative mean transaortic valve gradients (12.4 vs. 13.5 mmHg, $p=0.58$) [16]. The rate of severe PPM in the VIVID registry was reported at an impressive 31.8% of surviving patients, with the risk of increased gradients being higher in patients undergoing ViV-TAVR for stenotic SVD rather than regurgitant [13].

One proposed solution for the problem posed by PPM in ViV-TAVR has been the evolution of the technique of bioprosthesis valve fracture (BVF) [27-30]. This technique involves fracturing the frame of the degenerated bioprosthesis using high pressure balloon inflation, similar to valvuloplasty procedures. This allows for a larger ViV-TAVR device to be deployed, significantly reducing the transvalvular gradients, particularly in the smaller size bioprostheses of 19mm and 21mm. One limitation of this technique is that not all commercially available bioprostheses can fracture: neither Trifecta (Abbott, previously St Jude, Minneapolis, MN, USA), nor Hancock II (Medtronic, Minneapolis, MN, USA) valves are suitable for this procedure. On the other hand, Mitroflow (Sorin, Milan, Italy), Magna Ease (Edwards Lifesciences, Irvine, CA, USA), Mosaic (Medtronic), Magna (Edwards Lifesciences), and Biocor Epic (Abbott) valves have all been shown to fracture. Another consideration when

employing this technique is that the position of the bioprosthesis leaflets after fracturing may be unpredictable, which could lead to coronary ostial obstruction. In addition, the high pressures required to fracture the valve may present a risk for aortic root rupture, in particular in patients with very calcified aortic roots. At present the case series reported are too small to derive any conclusions for the future outcomes of this technique, other than proof of feasibility.

ViV-TAVR: Technical Considerations

Two of the major procedural complications in ViV-TAVR are coronary obstruction and malposition of the device. Coronary obstruction is a life-threatening event, with a non-negligible rate of 3.5% reported in 2012 in the Valve-in-Valve International Data Registry [12]. In-hospital mortality in patients with ostial coronary obstruction was 57.1%. Dvir et al. associated low-lying coronary ostia, prior aortic root replacement with coronary reimplantation, supra-annular bioprosthetic valve implantation and stentless bioprosthesis as potential risk factors. In a focused update of the VIVID registry data published in 2018, the rate of coronary obstruction in 1612 procedures had decreased to 2.3% [31]. This rate is likely to have been affected by both the evolving technology, and the greater operator experience with the procedure. This includes the careful consideration of the anatomy of the root to direct the treatment pathway to redo SAVR rather than ViV-TAVR in cases considered to be at higher risk of coronary obstruction.

Ribeiro et al. identified three factors significantly increasing the risk of coronary obstruction in ViV-TAVR. These include stentless bioprostheses, stented bioprostheses with externally mounted leaflets (of which both commercially available valves are supra-annular), and a CT-derived measure identifying distance of the predicted ViV prosthesis ring to the coronary ostia of <4mm as factors.

Stentless Bioprostheses

Stentless xenografts comprise of a subset of aortic bioprostheses used by their proponents for their favourable haemodynamic profile [15-17]. These can be more challenging in the setting of the failing prosthesis, as implantation techniques vary (sub-coronary, inclusion cylinder, root replacement) and radiographically they lack markings to guide ViV-TAVR. Grubitzsch et al. reported data of 52 consecutive patients undergoing re-intervention for failed stentless aortic valve prostheses, comparing patients undergoing redo SAVR with ViV-TAVR [32]. The decision on type of intervention was made by the heart valve team, based on individual patient characteristics, with 25 patients having redo SAVR and 27 ViV-TAVR. Post-procedural 30-day mortality was similar (SAVR 8%, ViV-TAVR 11%) as was one-year overall survival (83.1±7.7% SAVR vs 81.5±7.5%, p=0.76). They reported procedural success in 100% of the redo SAVR cases and 89% of the ViV-TAVR cases, with complications contributing to the failure of the case being coronary obstruction (n=4), device malposition (n=3), intraprocedural resuscitation (n=1) and conversion to open surgery in 11% (n=3). This highlights the complexities of re-intervention in this particular group of patients. In this cohort, the haemodynamic outcome was no worse in the ViV-TAVR group, with two patients having severe PPM compared to one in the redo-SAVR group. In the ViV-TAVR group, there were 2 patients with mild post-procedural aortic regurgitation and 3 with moderate. The likelihood is that the lack of difference in the haemodynamic profile is due to a downsizing of the prosthesis when a stented valve is implanted compared to the prior stentless prosthesis, which was also highlighted by Finch et al. [33].

Bapat et al. also describe the difficulties of ViV-TAVR in the stentless bioprosthesis patient population [34]. They identify the increased risk of coronary obstruction, with bulky calcified leaflets and the proximity of the suture line to the ostia as associated risk factors. The lack of annular calcification or other radiographic markers, in addition to the higher prevalence of regurgitation as the SVD pathology leading to the need for re-intervention, were found to be risk factors associated with device malpositioning. Finally, device migration or embolisation is also more common, due to the difficulty in accurately sizing the device, given the variable nature of the internal diameter of stentless valves post-implantation.

Bioprosthesis Durability

Structural valve degeneration is a gradual and permanent process affecting bioprostheses, ultimately leading to valve dysfunction secondary to stenosis (40%), regurgitation (30%), or a combination of stenosis and regurgitation (30%) [35]. Historically, publications referred to freedom from SVD as freedom from re-intervention, and survival was used as a surrogate marker. Gradually the focus shifted to the dynamic changes reflected in physiological markers affecting the changing haemodynamic profile of the prostheses over time assessed echocardiographically, but many different definitions of SVD still exist. In the era of TAVR, there has been an increased need for a standardised definition of SVD, to allow scientific comparison of SAVR bioprostheses with TAVR bioprostheses. Recent publications on TAVR SVD have relied on the definitions from the Valve Academic Research Consortium 2 (VARC-2) consensus report [36]. This defines an increase in the mean gradient >10 mmHg, a decrease in the EOA >0.3-0.4 cm^2, or a reduction in the doppler velocity index (DVI) >0.1-0.13 on echocardiography as necessitating further investigation and rigorous follow up. The authors caution that both flow and flow-independent measures on echocardiography can lead to false assumptions dependent on morphological characteristics of the heart anatomy (LVOT size) or the patient's size (high BMI, low BSA). Therefore, trends over time are important to consider.

Bourguignon et al. [37] defined SVD of surgical aortic bioprostheses as severe aortic stenosis (mean transvalvular gradient >40 mm Hg) or severe AR (effective regurgitant orifice area >0.30cm^2, vena contracta >0.60cm). In 2016, the European Association for Cardiovascular Imaging (EAPCI) published guidelines defining criteria for SVD. This was defined as morphological SVD at autopsy, including abnormal leaflet structure, morphology, function or strut/frame abnormality. Haemodynamic SVD was also defined and classified as moderate (mean gradient ≥20mmHg or an increase in mean gradient ≥10mmHg from baseline) or severe (mean gradient ≥40mmHg or increase of ≥20mmHg from baseline), and/or new onset or worsening of intra-prosthetic regurgitation (moderate or >1+/4+, severe or >2+/4+) [38].

Surgical AVR

Over the years there have been many studies looking at the durability and incidence of SVD in surgical valves, the results of which vary greatly based on the era and the type of bioprosthesis, as well as the definition used for SVD.

Most studies reveal a <15% incidence of degeneration during the first decade after SAVR with a bioprosthesis. There is also data available for very long term follow up to 20 years. Valfrè et al. reported on 25 years' experience with a second generation porcine bioprosthesis, the Hancock II [39]. Patients underwent SAVR between 1983 and 1993 with this prosthesis

(n=208), 80 of whom also had concomitant procedures. Overall survival was 66.2±2.7%, 39.5±2.9% and 23.3±3.1% at 10, 15 and 20 years. Reported freedom from re-operation was excellent, 94.6±1.5%, 85.5±2.7% and 79.3±4.4% at 10, 15 and 20 years respectively, with 100% follow up. This was confirmed by David et al., publishing on the same bioprosthesis the results of follow up of 1134 patients undergoing SAVR [40]. They reported freedom from SVD of 63.4%±4.2% at 20 years in the entire cohort, 29.2%±5.7% in patients younger than 60 years, 85.2%±3.7% in patients aged 60 to 70 years, and 99.8%±0.2% in patients older than 70 years. There was a significant association of age at index procedure with the likelihood of developing SVD.

A series of publications on very long term results following implantation of the Carpentier-Edwards Perimount pericardial bioprosthesis (Edwards Lifesciences, Irvine, CA) in the aortic position were those of Bourguignon et al. reporting on 2,659 patients operated on in a 24 year period (1984-2008) [37,41-42]. Age-stratified freedom from reoperation due to structural valve deterioration at 15 and 20 years was 70.8% ± 4.1% and 38.1% ± 5.6%, respectively, for the group aged 60 years or less, 82.7% ± 2.9% and 59.6% ± 7.6% for those 60 to 70 years, and 98.1% ± 0.8% at 15 years and above for those over 70 years. In the youngest group of patients, they reported an excellent re-operative mortality rate of 2.3%. They concluded that the overall expected valve durability is 19.6 years for the entire cohort, and 17 years for patients below 60 years of age.

Forcillo et al. also reported on the same bioprosthesis in 2405 patients operated on in a 20-year period (1981-2011). The overall freedom from reoperation for prosthetic valve dysfunction averaged 98%±0.2%, 96%±1%, and 67%±4% at 5, 10, and 20 years. They also identified a significant association with age at the time of index procedure, with freedom from reoperation for SVD averaging 98%±1%, 90%±3%, 60%±6%, and 30%±8% at 5, 10, 15, and 20 years after surgery in patients younger than 60 years of age, compared with 99%±0.3%, 95%±1%, 90%±3% at 5, 10, and 15 years after surgery in patients aged between 60 and 70 years old, and 100%, 99%±0.5% at 5 and 10 years after surgery in patients older than 70 years of age (p=0.001).

Finally, Johnstone et al. reported on an extraordinary 12,569 patients undergoing SAVR with the Carpentier-Edwards Perimount bioprosthesis between 1982 to 2011. Actuarial estimates of explant for SVD at 10 and 20 years were 1.9% and 15% overall, respectively, and in patients younger than 60 years, 5.6% and 46%, respectively [43].

A recent report on the long-term outcomes of the Mosaic (Medtronic) bioprosthesis (third generation stented porcine bioprosthesis) (n=797 patients) has shown freedom from reoperation due to SVD was 47.5% in patients under 60 years old and 89.1% in patients over 60 years old at 17 years follow up [44].

Guenzinger et al. reported data for 455 patients receiving a St. Jude Medical Biocor valve in the aortic position between January 1985 and December 1996 [45]. The freedom from SVD at 10 and 15 years was 92.1% ± 1.7% and 84.8% ± 3.0%, respectively.

Transcatheter AVR

The data on durability of TAVR bioprosthesis is more limited. There are now some publications on 5-year outcomes, with very limited data above that range, and next to none for 10-year results. The limited availability for this data is understandable for a procedure that was first performed in 2001, with more widespread use starting in 2007 in Europe, and 2011 in North America (when TAVR was licensed for use). In addition to the more

limited time frame for follow up, the initial TAVR procedures were performed in the setting of inoperable patients who had limited prognosis due to age and co-morbidities. As such, there were very few patients available for intermediate term outcome analysis, particularly compared to the SAVR populations which number in their thousands.

The 5-year outcomes of the PARTNER 1 trial reported in 2015 showed no difference in mortality between the SAVR and TAVR groups and, importantly, no structural valve deterioration requiring intervention [46]. A more recent publication based on the haemodynamic follow-up in the PARTNER 1 cohort (PARTNER 1A, 1B and continued access observational patients, TAVR n=2,482) shows that 5 TAVR patients required re-intervention for SVD with a median follow up time of 3.1 years and maximum of 5 years [47]. In addition, 3.7% of the TAVR patients had moderate-severe AR, which was associated with significantly increased mortality.

Barbanti et al. reported on 5-year outcomes of the self-expanding CoreValve prosthesis (Medtronic Inc., Minneapolis, Minnesota). Patients with complete follow up (n=353) were assessed after undergoing TAVR between 2007 and 2009 with the third generation CoreValve. At 5 years the incidence of SVD was only 1.4% with a further 2.8% showing mild stenosis on echocardiography, with a 5-year all-cause mortality rate of 55% [48]. Gleason et al. also recently reported on 5-year outcomes using the CoreValve (n=391) in a study comparing with SAVR (n=359). Five-year outcomes showed no difference in mortality (55.3% TAVR vs 55.4% AVR) and very little SVD using the VARC-1 definition with freedom from SVD re-intervention of 99.2% versus 98.3% (p=0.32). Of note, the rate of permanent pacemaker implantation in the TAVR group was 33% versus 19.8% in the SAVR group. Holy et al. recently published a case series of 152 consecutive patients undergoing TAVR with the CoreValve device before 2011 [49]. The mean follow-up was 6.3 years with a mortality rate of 65% at 6 years and 73% at 8 years. Sixty patients had complete echocardiographic follow up, and 4 were excluded after having undergone re-intervention due to paravalvular regurgitation. VARC-2 criteria for the definition of SVD were used, and the estimated rate of SVD at 7 and 8 years was 7.9% actuarial and 4.5% for the actual analysis. The main component of SVD was prosthetic valve regurgitation, which was none/trace in 13 patients (23.2%), mild in 31 (55.4%), moderate in 10 (17.9%), and severe in 2 patients (3.6%).

Another recent publication examined high risk TAVR patients in a registry, with first generation CoreValve and Sapien devices (n=300) implanted between 2007 and 2009. At a median follow-up of 7.14 years there were 73 survivors. Using the European Association of Percutaneous Cardiovascular Interventions (EAPCI) definition, they identified an overall crude cumulative incidence of SVD of 14.9% (CoreValve 11.8% vs. SAPIEN 22.6%, p=0.01) which was higher than other published studies. The authors commented that their results were consistent with data presented by Dvir et al. with 378 patients post-TAVR followed up to 10 years, finding freedom from SVD at 5 years of 82% and 50% at 8 years.

Conclusion

The choice of redo SAVR or ViV-TAVR should be made after rigorous assessment by the heart valve team and tailored to the individual needs of the patient. In some cases, there are patient characteristics that would firmly dictate one strategy over the other. Redo SAVR would be preferable in patients with infective endocarditis, paraprosthetic leaks, those requiring concomitant procedures, pre-existing PPM or small bioprosthesis (19-21mm) with high left ventricular mass. In favour of ViV-TAVR would be patients with a hostile chest environment, porcelain aorta or patent internal mammary grafts crossing the midline,

patients with prohibitive surgical risk in view of severe co-morbidities or frailty. Several ViV-TAVR studies have demonstrated feasibility of the procedure. The pertinent question however is not can it be done, but rather should it be done? It is the position of the authors, that in the current era of evidence-based medicine, the default position of clinicians on the management of patients with degraded aortic valve bioprostheses should be to offer a redo SAVR unless contraindicated. Long term durability of TAVR or ViV-TAVR are not available, in contrast to the large body of evidence for surgical bioprostheses, in addition to the superior haemodynamics and reduced incidence of PPM which should continue to favour better long-term outcomes of redo-SAVR. This may well change in the future as technology evolves and new data becomes available, however the decisions we make for patients should be based on what is current best evidence.

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Transcatheter Aortic Valve Implantation

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"Nitidae vestes ornatiorem reddunt"

Introduction

When surgical aortic valve replacement is required, bioprostheses (BP) are increasingly favoured over mechanical prostheses because they do not require lifelong anticoagulation, which is otherwise mandatory after the implantation of a mechanical prosthesis. However, the Achilles' Heel of bioprostheses is their limited durability leading to a stenotic, regurgitant or mixed dysfunction. It has been reported that between 15% and 35% of surgically implanted BPs will require re-replacement after fifteen years [1,2]. The younger the patient, the higher the risk of structural valvular deterioration, especially beyond 10 years after implantation [3]. Other reported risk factors include the usual cardiovascular risk factors (such as diabetes mellitus or dyslipidaemia), chronic renal insufficiency and persistent left ventricle hypertrophy [1,4]. Also, baseline prosthetic dysfunction such as patient-prosthesis mismatch and improper expansion with uneven leaflet motion increases the likelihood of need for a repeat intervention [3,5,6]. While there is now plenty of data on the durability of surgical BPs, there is a lack of published reports on structural deterioration of transcatheter heart valves (THV). This is mostly due to the fact that TAVI (transcatheter aortic valve implantation) is still a relatively recent development [7]. Nevertheless, given that THV are biological prostheses similar to those implanted surgically, we would expect similar risk factors for degeneration. Valve-in-valve TAVI procedures and small prostheses (≤23 mm) are associated with a higher risk of structural valve deterioration [8]. Certain factors however are specific to TAVI, related to leaflet damage during the crimping process or asymmetric expansion with suboptimal leaflet coaptation.

Once structural valvular deterioration has become severe and symptomatic, the patient will require reintervention by either redo surgical replacement (re-SAVR) or transcatheter valve-in-valve implantation (VIV). Studies comparing these two strategies are scarce, and no randomised trial has yet addressed this. The elderly population suffering from aortic stenosis often has multiple comorbidities. Valve-in-valve TAVI may be the only option in inoperable patients, but it may also be a suitable choice for operable patients. In this comprehensive review, we summarise the existing literature on VIV, its practical considerations, and comparative results as opposed to redo-surgery.

Pre-operative Considerations of Valve-in-Valve TAVI

Most BPs are xenografts, although homografts have also been proposed [9]. Furthermore, xenografts are of various types, including stented intra-annular BPs (e.g. Edwards Perimount, Medtronic Hancock II), stented supra-annular BPs (e.g. Edwards Magna, Medtronic Mosaic), stented BPs with externally mounted leaflets (e.g. Sorin Mitroflow, St

Jude Medical Trifecta), and stentless BPs (St Jude Medical Toronto, Medtronic Freestyle). More recently, sutureless BPs (e.g. Sorin Perceval S), intra-annular (e.g. Edwards Sapien) and supra-annular (Medtronic CoreValve) transcatheter heart valves were added to the list of commercially available BPs. These xenografts have very different characteristics which are important to be aware of for VIV TAVI (Table 1). The choice of transcatheter heart valve and its positioning will differ from one BP to another, such as the different positions of radio-opaque markers seen on fluoroscopy during the VIV procedure[10]. Some of this information can be obtained from patient records and manufacturer instructions but sometimes the BP characteristics are unavailable, and operators will rely on imaging.

Table 1: Characteristics of the failing bioprosthesis

Characteristic	Variations
Type	Stented, stentless, sutureless surgical, TAVI
Label	e.g. Edwards, Medtronic, St Jude
External diameter (mm)	To estimate the size of the THV
Manufacturer inner diameter (mm)	To estimate the size of the THV
True inner diameter (mm)	Often different from manufacturer inner diameter
Leaflet mounting	Internally, externally
Mechanism of degeneration	Stenosis, regurgitation, mixed mechanism
Degree of calcification	High, intermediate, low

Operators should be aware of the different dimensions of bioprostheses including external diameter, manufacturer reported inner diameter and true inner diameter. Despite the true inner diameter being one of the most important characteristics to consider because it affects the size of the new THV, it is often unreported or incorrectly reported [11,12]. Bapat et al. used in vitro experiments to demonstrate that surgical valves with porcine leaflets have a mean true inner diameter approximately 2 mm less than the reported stent inner diameter. Also, pericardial valves with leaflets sutured inside the stent had a mean inner diameter at least 1 mm less than the reported stent inner diameter, while valves with leaflets mounted outside the stent had a measured inner diameter equal to the stent inner diameter[11]. Some authors have proposed smartphone applications to overcome this [13]. Alternatively, estimation of the true inner diameter can be obtained from multi-slice computed tomography (MSCT). However, operators should be aware that MSCT tends to overestimate the true inner diameter by 2.1±2mm [14]. Standardisation of MSCT evaluation of bioprosthetic heart valves has been improved by recent guidelines [15].

Transoesophageal echocardiography (TOE) was once frequently used during TAVI procedures due to reports that TOE provides accurate estimation of the true inner diameter in vitro [16,17]. Another option is to use valvuloplasty balloons but as the use of peri-operative TOE and pre-dilatation have tended to decrease, non-invasive imaging by MSCT and cardiovascular magnetic resonance (CMR) are likely to be used more in the future. The latter also provides important functional and anatomical information including ruling out thrombus as the dominant cause of bioprosthesis dysfunction which could be resolved by anticoagulation, hence avoiding an unnecessary reintervention [15]. Cross-sectional imaging also provides valuable information for pre-procedural planning such as the proximity of

the coronary ostia to the landing zone during implantation (to estimate the risk of coronary obstruction), quantification of leaflet calcification and most appropriate route of vascular access.

Technical Considerations of Valve-in-Valve TAVI

Given that TAVI was initially developed for inoperable patients suffering from aortic stenosis, valve-in-valve procedures were described in a pre-clinical model soon after its introduction [18,19]. The first-in-man successful VIV procedures followed shortly afterwards [20,21]. It is increasingly considered as a suitable alternative to redo-SAVR, as reflected by the increasing number of VIV procedures in patients with a history of SAVR in contemporary registry data[22].

Approach

The first-in-man VIV procedure was performed transapically, which for some time remained the dominant approach for VIV procedures[16,23]. However, as technical improvements were implemented, VIV procedures were increasingly performed through the transfemoral approach and non-transapical alternative approaches. According to the data of the VIVID (Valve-in-Valve International Data) registry published in 2014 (patients included between 2007 and 2013) the transfemoral approach was undertaken in 59% of patients, while trans-subclavian and transaortic pathways were used in 2.8 and 1.1% of cases respectively. The transapical approach was associated with an increased risk of 1-year mortality (HR 2.25, 95% CI: 1.26-4.02, p=0.006). More recently, the transcarotid pathway has been added to the armamentarium of VIV approaches [24].

Device

The choice of THV will be based on anticipated risk of complications of VIV, such as coronary obstruction, embolisation, para-prosthetic regurgitation, and high post-VIV transprosthetic gradients. Most of the published registries included Edwards Sapien and Medtronic CoreValve family devices. However, recent reports have included several other devices such as Symetis Acurate, Portico, Medtronic Engager and JenaValve (Table 2) [25,26]. The CoreValve Evolut R self-expandable THV presents some advantages when compared to the Edwards Sapien 3 THV. The recapturability-repositionability of the THV allows the operator to adjust the position of the device. In addition, the supra-annular position along with the ability to implant in a high position might yield lower mean gradients. Simonato et al. analysed the VIVID registry to assess independent predictors of high mean gradients and found device position (high: odds ratio [OR] 0.22; 95% confidence interval [95% CI] 0.1–0.52; p=0.001) and the type of device used (Evolut R as opposed to the Sapien model: OR=0.5; 95% CI 0.28–0.88; p=0.02) predicted high post-operative mean gradient [27]. Data from in vitro models further confirmed that the depth of implantation was associated with the mean gradient after VIV in small bioprostheses for Sapien XT, Evolut R and Portico THVs [6,28].

When treating degenerated stentless bioprostheses, some authors advocate the use of CoreValve instead of Sapien, because they believe it allows the operator to oversize the transcatheter valve without risking annular rupture, whilst simultaneously reducing the risk of embolisation due to the lack of bulky calcification (stentless failing bioprostheses often lack this and usually have a regurgitant mechanism of failure). They also argue that

self-expanding valves have a lower risk of coronary obstruction and high residual gradients while implanted at a similar depth as balloon-expandable valves, because of the supra-annular position of the leaflets [29]. However, a recent cohort including patients with failing stentless BP that treated half of them with balloon-expandable and half with self-expandable devices, did not report any notable differences in outcomes [30].

In a recent propensity matched comparison of St Jude Portico and Medtronic CoreValve in a cohort with predominantly stented failing BP, the CoreValve was found to have better haemodynamic profile. The mean gradient was 17±7.5 mmHg with Portico and 14±7.5 mmHg with CoreValve (p= 0.02), while the rates of severe prosthesis-patient mismatch were 40% and 19.5% respectively (p=0.03). While no difference in clinical outcomes was noted at 1 month, and despite a tendency towards more THV malposition (requiring a 2nd THV in most cases) with the CoreValve (3.7 versus 10%, p=0.22), the 1-year mortality was higher in the Portico group: 22.6% versus 9.1%, p=0.03 [31].

Camboni et al. reported that the use of newer THVs allowing commissural alignment and leaflet capturing, such as Acurate TA and Medtronic Engager, can prevent coronary obstruction during VIV procedures [32]. However, further research is needed to confirm this hypothesis due to the small size of their cohort.

Overcoming the Main Limitations of Valve-in-Valve TAVI

The most widely recognised adverse events of VIV are coronary obstruction, malpositioning, and elevated postprocedural gradients [25,27].

Coronary occlusion

Coronary obstruction is more frequent for VIV procedures than TAVI in native valves, with an incidence estimated at 2.3% and is associated with an increased risk of mortality. Based on the VIVID registry, patients with coronary obstruction had a 30-day mortality of 53% as compared to 3.9% in the controls (p< 0.001). The study also identified stented BPs with external mounted leaflets and stentless bioprostheses to be associated with a higher risk of coronary obstruction (OR 7.67, 95% CI 3.14-18.7, p<0.001), while previous coronary artery bypass graft surgery to the left coronary artery tended to be protective (OR 0.38, 95%CI 0.13-1.09, p=0.07). Authors also proposed some CT-based measures to evaluate the risk of coronary obstruction, including the virtual distance between the simulated THV ring and the coronary ostia [33]. Other possible risk factors include low coronary ostia, high implantation of the THV, coronary ostial severe calcification, and bulky bioprosthetic valve leaflets.

Identifying patients at risk of coronary occlusion would allow operators to plan accordingly, such as positioning a guidewire in the coronary artery, or possibly redirect referrals to more experienced centres [32]. In case of coronary obstruction during a VIV procedure, emergent percutaneous coronary intervention (PCI), haemodynamic support and conversion to open heart surgery should be initiated immediately.

Device malpositioning

Even in recent cohorts with the Evolut R, embolisation or migration of the THV is not infrequent (Table 2 overleaf). The risk has been reported to be higher for VIV in stentless

Table 2: Published studies of VIV registries

	No of patients	Euro Score I	STS score	Procedure success (%)	30-day mortality (%)	Mechanism of BP failure	Failing BP type	VIV approach	VIV THV
Gotzmann et al., 2010	5	52.3 ± 10.3	NR	100	0	80% AS, 20% MD	ST	TF	SE
Khawaja et al., 2010	4	NR	NR	75	0	25% AS, 25% AR, 50% MD	75% ST, 25% SL	75% TF, 25% TS	SE
Kempfert et al., 2010 [40]	11	31.7 ± 14.5	7.2 ± 2.6	100	0	72% AS, 28% MD	ST	TA	BE
Pasic et al., 2011 [41]	14	45.3 ± 22.2	21.9 ± 10.9	100	0	65% AS, 15% AR, 20% MD	72% ST, 7% SL, 21% HG	TA	BE
Bedogni et al., 2011 [42]	25	31.5 ± 14.8	8.2 ± 4.2	100	12	36% AS, 64% AR	72% ST, 28% SL 88% TF,	12% TS	SE
Eggebrecht et al., 2011 [43]	47	35 ± 18.5	11.6 ± 8.5	96 (2 second THV)	17	47% AS, 32% AR, 21% MD	96% ST, 4% SL	53% TF, 47% TA	75% BE, 25% SE
Piazza et al., 2011 [44]	20	27 ± 13	7 ± 4	90	15	50% AS, 45% AR, 5% MD	70% ST, 15% SL 15% HG	40% TF, 60% TA	80% BE, 20% SE
Seiffert et al., 2012 [45]	11	31.8 ± 24.1	12.5	100	20	36% AS, 36% AR, 28% MD	91% ST, 9% SL	TA	BE
Linke et al., 2012 [46]	27	31 ± 17	NR	92% (2 second THV, incl. 1 embolised)	7.4	22% AS, 8% AR, 70% MD	81% ST, 15% SL, 4% SrL	TF	SE
Latib et al., 2012 [47]	17	37.4 ±20.8	8.2 ±5.2	94%	0	30% AS, 53% AR, 17% MD	82% ST, 18% SL	88% TF, 6% TS, 6% TA	BE

Bapat et al., 2012 [48]	23	31.8 ± 20.3	7.6 ± 5.4	96% (1 second THV)	0	61% AS, 39% AR	65% ST, 18% SL, 17% HG	91% TA	BE
Ihlber et al., 2013 [49]	45	35.4 ± 16.1	15.0 ± 10.8	95.6 (1 second THV, 1 open)	4.4	51% AS, 29% AR, 20% MD	75% ST, 11% SL, 7% HG	38% TF, 53% TA, 4% Tao, 1% TS	73% BE, 27% SE
Dvir et al., 2014 [16]	459	29 (19–42)	10 (6.2–16.1)	93.1	7.6	39% AS, 30% AR, 30% MD	80% ST, 20% SL	59% TF, 37% TA, 3% TS, 1% TAo	54% BE, 46% SE
Subban et al., 2014 [50]	12	NR	6.7 ± 3.7.	92 (1 MP with 2nd THV)	0	50% AS, 50% AR	75% ST, 25 SL	58% TF, 25% TA, 8% TS, 8% TAo	50% BE, 50% SE
Camboni et al., 2015 [32]	31	NR	20.9 ± 8.8	88 (2 MP with 2nd THV, 1 conv)	22.5	22% AS, 39% AR, 39% MD	97% ST, 3% SL	46% TF, 54% TA	48% BE,
Conradi et al., 2015 [26]	54	28.4 ± 18.3	8.7 ± 7.7	96 (2 embolised. with 2nd THV)	5.6	44% AS, 35% AR, 20% MD	83% ST, 15% SL	54% TF, 43% TA, 3% TAo	40% BE, 60% SE (3 Portico, 2SE Engager, 2SE JenaValve)
Duncan et al.,2015	22	38 ± 18	14% ± 8%	82 (4 MP)	0	AR	19% SL, 77% HG, 5% AG	86% TF, 9% TS, 5% TAo	SE
Gonska et al., 2016 [51]	9	NR	8.6 ± 4.1	100	11.1	78% AS, 22% AR	78% ST, 22% SL	TF	BE (Sapien 3)
Webb et al., 2017 [35]	365	12.3 ± 9.8	9.1 ± 4.7	97.5 (2nd THV in 7 cases, 2 conv.)	2.7	55% AS, 24% AR, 21% MD	92% ST, 6% SL or HG	75% TF, 24% TA, 1% TAo	BE

AG : auto-graft; AS: aortic stenosis; AR: aortic regurgitation; BE: balloon-expandable (Edwards Sapien valves); conv.: conversion to open surgery; HG: homograft; MD: mixed disease; MP : device malpositioning including migration and embolization; NR: not reported; SE: self-expandable (Medtronic CoreValve unless otherwise specified); ST: stented; SL: stentless; SrL: sutureless; TF: transfemoral; TS: trans-subclavian

bioprostheses[29]. Migration could result in an excessively low position of the THV resulting in severe paravalvular regurgitation - retracting the THV with a snare could be an option in such cases. Embolisation can result in the THV migrating to the ascending or descending thoracic aorta or even the abdominal aorta. Assessing the impact of the presence of the THV on branches of the aorta is essential. In case of organ malperfusion, emergency open surgical extraction of the THV should be considered. In case of device malposition, the implantation of a second THV is often required [34].

High post-procedural gradients

Valve-in-valve TAVI can result in a significantly worse haemodynamic profile than redo-surgery, with higher mean gradients. This predisposes to higher long-term mortality (for mean gradient ≥20 mmHg, HR: 2.27, 95% CI: 1.16, 4.46, p=0.014 in the PARTNER 2 VIV registry [35]) and impacts on symptom resolution. On average, the mean gradient after VIV is higher than after TAVI in a native valve, with a mean value estimated at 16-17 mmHg post-operatively, which remains stable at 1 year[16,27,34,35].

Identifying risk factors for high post-operative gradients is important to develop preventative strategies. Besides a high position and possibly the type of THV (discussed above), the mechanism of failure of the BP seems to influence the risk [27,31]. While VIV is technically feasible to treat all types of BP failure, stenosis or mixed failure are at higher risk of high mean gradients than pure regurgitation (OR 3.12, 95% 1.51–6.45, p=0.002)[27,35,36]. Based on data from the PARTNER II trial (Sapien THV), smaller failing BP are associated with a higher risk of post-VIV mean gradients ≥20mmHg compared to intermediate or large BP (48.5% versus 21.9% respectively, p=0.02). In intermediate and large surgical BPs, small internal annular area as determined by MSCT yields higher post-VIV mean gradients, with a cut-off value of 329mm^2 [23].

Overall, implanting the THV in a high position might reduce the risk of high post-operative mean gradients. However, small failing BPs are currently a limitation for VIV and new approaches are needed to improve the haemodynamic profile of the VIV technique if this approach is to be applied in low and intermediate risk patients who have longer life expectancy. Some authors have proposed stent fracture techniques to improve the haemodynamic result of VIV with promising outcomes, although this approach needs further validation [37,38].

Mortality after Valve-in-Valve TAVI

VIV has been reported to be safe in a wide range of failing bioprostheses, both stented and stentless, and using balloon-expandable as well as self-expandable THVs. The observed 30-day mortality rate is very variable in the reported cohorts and ranges between 0 and 22.5%. The observed mortality increases with the STS and Euroscore risk scores [1,16,29,39].

The VIVID and the PARTNER 2 Valve-in-Valve are the largest reported registries of VIV procedures[16,35]. In the PARTNER 2 VIV registry (Sapien XT device, 75% transfemoral access) that included 365 patients at high surgical risk (STS score 9.1 ± 4.7%), the 30-day mortality was 2.7% while one-year mortality was 12.4% [35]. In the VIVID registry (STS score 10 [6.2–16.1]), the 30-day mortality was 7.6% while one-year mortality was 16.8% [16]. Several factors have been reported to increase long-term mortality after VIV. Small surgical bioprostheses are associated with an increased 30-day as well as one-year mortality risk

(≤21 mm versus >21mm; HR 2.25, 95% CI 1.03-4.93, p=0.04 and HR 2.04; 95%CI 1.14-3.67, p=0.02 respectively) [16]. Baseline stenosis was also reported to be associated with a higher mortality risk than regurgitation (HR 3.07, 95%CI 1.33-7.08, p=0.008). These factors all lead to higher post-operative mean gradients. Similar to TAVI in native aortic valve stenosis, the use of transapical access was associated with increased mortality risk (HR 2.25, 95% CI 1.26-4.02, p=0.006)[16].

Strategies aimed at reducing perioperative and long-term mortality of VIV require improvements in procedural safety (prevention of coronary obstruction and device malpositioning), prevention of high post-operative mean gradients, and access routes favouring transfemoral or non-thoracic approaches.

Comparison of VIV and Redo-SAVR

Some patients are unsuitable for VIV, such as those with paravalvular regurgitation and infective endocarditis, and redo-SAVR is the only option. On the other hand, some patients are unsuitable for this such as those with prohibitively high risk, and VIV TAVI is the only option other than medical therapy. But for most patients, in whom both VIV and redo-SAVR are acceptable options, the optimal choice is a matter of debate (Tables 3A and 3B). Recent international guidelines recommend both redo-SAVR and VIV as suitable options, although VIV has been granted a cautious class of recommendation IIa (level of evidence C). The guidelines leave the Heart Team to decide if VIV is the best option for a given patient depending on the risk of reoperation, bioprosthesis type and size (Figure 1) [52]. To date, there are no randomised trials comparing redo-SAVR with VIV although observational studies can guide us.

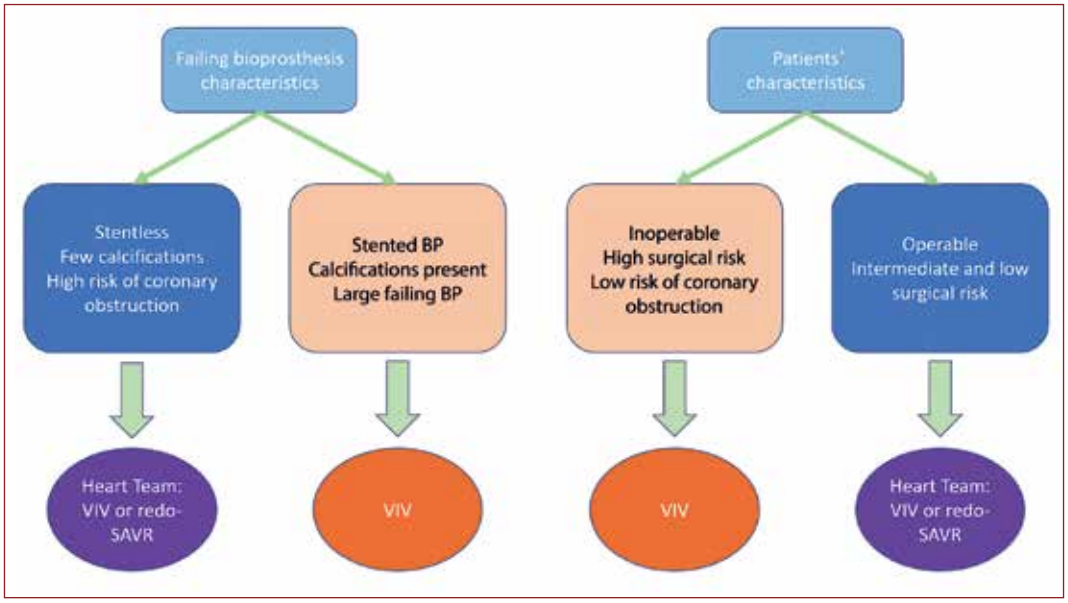

Figure 1: Proposed algorithm for the interventional treatment of failing bioprosthesis

Table 3A: Comparative observational retrospective studies of VIV and redo-SAVR [53,54]

Study	N (ViV vs redo SAVR)	Euro SCORE	STS score or ES II	Failing BP type (ST/SL)	VIV pathway	VIV THV	Confounding treatment
Ejiofor et al., 2016 [56]	22 vs 22	NR	STS 7.5 ± 3.0 vs 7.7 ± 3.4	ST in both groups	77% TF, 13% Tao, 5% TA, 5% TS	77% BE, 23% SE	STS matching
Erlebach et al., 2015 [57]	50 vs 52	27.4 ± 18.7 vs 14.4 ± 10.0	NR	14% non-ST vs 31% non- ST	36% TF, 54% TA, 8% Tao, 2% TS	34% BE, 64% SE, 2% Jena Valve	None: major differences, VIV patients older, higher risk
Grubitzsch et al., 2017 [54]	27 vs 25	NR	ES II 13.0 ± 10.4 vs 8.9 ± 6.5	SL	93% TF, 7% TA	56% BE, 4% SE	None: VIV patients older, higher risk
Silaschi et al., 2017 [58]	71 vs 59	25.1 ± 18.9 vs 16.8 ± 9.3	NR	87/13 vs 80/20	49% TF, 47% TA, 4% TAo	51% BE, 49% SE including 3 Portico, 2 Engager, 2 JenaValve	Case-control (per age, prior surgery). VIV older, higher risk
Spaziano et al., 2017 [55]	78 vs 78	22.1 ± 16.0 vs 22.1 ± 18.3	7.2 ± 4.9 vs 5.8 ± 4.6	83/17 vs 78/22	54% TF, 31% TA,	41% BE, 59% SE	PSM

Both strategies have strengths and weaknesses. Valve-in-valve TAVI yields higher post-procedural gradients and has a higher risk of coronary obstruction and malpositioning. These complications are associated with higher peri-operative and long-term mortality risk [53]. However, redo-SAVR has risks such as conduction disturbance requiring permanent pacemaker implantation, major bleeding, atrial fibrillation, and need for dialysis. No noticeable difference in stroke rates or perioperative mortality have been observed between the two techniques [1,53,54]. One meta-analysis suggested that mortality might be significantly lower after redo-SAVR than VIV TAVI with a pooled HR 1.91 (1.03-3.57) but the small observational studies included in the meta-analysis addressed confounding variables poorly, yielding a comparison between older patients with more comorbidities in the VIV group against a younger and healthier surgical group [53]. A more recent study with propensity matching found no significant difference in one-year mortality (with VIV as the reference: OR 0.74 [0.24-2.31]) [55].

Table 3B: Comparative observational retrospective studies of VIV and redo-SAVR 53,54

Study	Median length of stay (days) (IQR). (total or ICU)	Post-operative mean gradient (mmHg)	Risk for pacemaker (RR with 95% CI)	Mortality risk (HR or OR with 95% CI)
Ejiofor et al., 2016 [56]	5 (2–7) vs 10.5 (8–18)	12.4 ± 6.2 vs 13.5 ± 13.2	1.0 (0.07-15)	HR 2.16 (0.96-4.87)
Erlebach et al., 2015 [57]	13.7± 9.7 vs 14.9 ± 13.8	18.8 ± 8.7 vs 13.8 ± 5.4	0.28 (0.08-0.96)	HR 5.68 (1.24-25.96)
Grubitzsch et al., 2017 [54]	3.0 (7.5-21.5) vs 11.0 (9.0-17.0)	12 ± 6 vs 14.2 ± 6.8	0.46 (0.04-4.80)	HR 1.17 (0.31-4.37)
Silaschi et al., 2017 [58]	2.0 ± 1.8 vs 3.4 ± 2.9	19.7 ± 9 vs 12.2 ± 4	0.36 (0.16-0.82)	HR 1.03 (0.28-3.85)
Spaziano et al., 2017 [55]	9 (7-13) vs 12 (8-24)	18.1 ± 2 vs 14.3 ± 2.5	1.00 (0.36-2.81)	1-year OR 0.74 (0.24-2.31)

Continuous variables are median (IQR) or mean ± standard deviation. Risk estimates are reported with VIV being the reference group. 95% CI: 95% confidence interval; BE: balloon-expandable (Edwards Sapien valves); ICU : intensive care unit; ES II : EuroSCORE II; HG: homograft; HR: hazard ratio; NR: not reported; non-ST : non-stented bioprostheses including stentless, sutureless and homografts; PSM: propensity score matching; OR: odds ratio; SE: self-expandable (Medtronic CoreValve unless otherwise specified); ST: stented; SL: stentless; SrL: sutureless; TF: transfemoral; TS: trans-subclavian

Of note, redo-SAVR has been reported to provide better results than VIV for failing stentless bioprostheses (one-year mortality 32.7% for VIV vs 0% for redo-SAVR, p=0.01)[55]. However, another cohort that only included patients with failing stentless bioprostheses found no difference in mortality between VIV and redo-SAVR.

As opposed to TAVI in native valves, which frequently results in high degree atrioventricular block, the need for pacemaker implantation after VIV is one of the advantages of VIV when compared to open surgery. One meta-analysis estimated that the risk of permanent pacemaker insertion after VIV was reduced by 43% when compared to redo-SAVR: 8.3% after VIV versus 14.6% after redo-SAVR, RR 0.57 (95% CI 0.32-1) [54]. Recent data suggest that the risk of pacemaker implantation could be as low as 1.9% at 30-days [35].

Post-operative paravalvular regurgitation (PVR) is more frequent after VIV TAVI than redo-SAVR: 21.1% vs 5.5% respectively, with RR 3.83 (95% CI 1.2-12.22)[54]. Also, high residual mean gradients after VIV are an important limitation of this technique, and it is more frequent in smaller bioprostheses. Existing data however does not suggest that redo-SAVR yields better haemodynamic outcomes than VIV. In a meta-analysis, Gozdek et al. showed no significant difference in mean gradient or risk of post-operative aortic gradient >20 mmHg between VIV and redo-SAVR (risk ratio 3.66 [0.44-30.58]) [53]. Valve-in-valve and redo-SAVR in small BP with a true inner diameter <19 mm were found to have similar post-operative mean gradients in a recent propensity matched cohort[55].

Overall, VIV has some major limitations, such as poor haemodynamic function, coronary obstruction and malpositioning. Those limitations can be overcome by further technical

improvements of the devices and patient selection with the help of imaging. However, redo-SAVR is not without its own limitations. Major patient comorbidities, including chronic pulmonary insufficiency and multiple previous cardiac surgeries, can render the surgical risk prohibitive for open surgery. Reoperative surgery yields longer hospital stay, probably due to more frequent surgical complications including renal failure, bleeding, post-operative atrial fibrillation and wound infection. The need for a permanent pacemaker implantation is reduced with VIV compared to redo-SAVR.

Conclusion

Valve-in-valve transcatheter aortic valve replacement provides a suitable option for inoperable patients suffering from a failing aortic bioprosthesis. Given the current state-of-the-art of VIV, for patients eligible to both VIV and redo open surgery, the decision must be made by a Heart Team, after considering patient and bioprosthesis characteristics. Indeed, both techniques have their strengths and weaknesses. However, arguably, the weaknesses of VIV may be overcome in the future by technical improvements whilst the weaknesses of redo-SAVR will remain. Thus, VIV is probably the future of the treatment of failing aortic bioprosthesis, rather than open surgery.

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Chapter 4

Arguing the Choice of Prosthesis for a Young Person: Bioprosthesis versus Mechanical Prosthesis

Niki Nicou and Olaf Wendler

"Nil satis nisi optimum"

Introduction

The prevalence of valvular heart disease is constantly increasing due to demographic changes in the western world. In most patients, heart valve surgery is the gold standard of care. Despite a desire to preserve native heart valves during the operation, numerous pathologies such as aortic stenosis still require valve replacement. No optimal prosthetic heart valve has been developed yet, which explains why there is an ongoing discussion about the strengths and weaknesses of biological and mechanical valves.

The aortic valve is currently the commonest valve to require surgical intervention in the United Kingdom (UK) [1]. It is estimated that 10% of the adult population over 18 years suffer from aortic valve stenosis and 8.5% from aortic regurgitation [2]. While a significant number of regurgitant aortic valves can be successfully repaired, most patients undergo aortic valve replacement (AVR) using prosthetic heart valves.

Out of the group of adult patients with mitral valve disease, the majority in the UK suffers from degenerative and functional pathology, which are usually amendable to mitral valve repair. Nevertheless, out of the 3781 patients who underwent first time mitral valve surgery in 2017, around 35% were operated using a mitral valve replacement (MVR) [3].

Worldwide, the number of mechanical valve replacements is constantly reducing, while there is also a trend observed to shift towards bioprosthetic valves, not only in elderly but also younger patients. While this can be explained to a degree by recent changes in guideline recommendations, part of the increased usage of biological prostheses (BP) is also explained by increasing patient concerns about anticoagulation and quality of life interests, particularly in younger patients. In this article, we try to provide some evidence on how an appropriate decision about the use of prosthetic heart valves, mechanical or biological, can be achieved for young patients with aortic and mitral valve disease.

Current Trends in Aortic and Mitral Valve Surgery

The annual number of AVRs in the UK increased from 7396 in 2004/05 to 9333 in 2008/09 [4]. At the same time, the number of younger patients - less than 55 years of age - who received a BP increased from 18% in 2004/2005 to 25% in 2008/2009 [4]. In the United States of America (USA), the number of patients who underwent isolated AVR increased by 74% from 16,957 in 2006 to 29,462 in 2014 [5]. In 2016, a total of 45,233 patients underwent AVR with or without coronary artery bypass grafting [6].

The number of aortic valve-sparing surgical procedures has remained low, as has the percentage of patients with aortic valve disease who undergo a Ross Procedure. This is mainly due to the complexity of these procedures, which makes it challenging for surgeons to implement these techniques in their routine. In addition, after a Ross Procedure, patients can potentially develop complications with two heart valves, the aortic autograft and the pulmonary homo/xenograft, which some surgeons and patients perceive as a disadvantage.

In contrast, mitral valve repair techniques have been much more accepted by surgeons and as a result the number of repairs in the UK in patients with degenerative mitral valve disease has increased to 63% in 2015 [7]. Excellent long-term outcomes have been reported [8,9] and, as a result, current guidelines are in favour of mitral valve repair whenever technically feasible [10,11].

However, some mitral valves need to be replaced and there is evidence that MVR using BPs is also becoming increasingly popular. In a recent review of 38,431 patients who underwent MVR, the number of those in whom the mitral valve was replaced using a BP increased from 16.8% in 1996 to 53.7% in 2013 [12].

Part of the trend to use BPs in younger patients is explained by new evidence on long-term durability of BPs as highlighted below. Nevertheless, there are also a number of scientifically unproven reasons as to why younger patients and surgeons may prefer BPs. This is also reflected in the recent published European [10] and American guidelines [11] on the treatment of valvular heart disease.

Nowadays patients have a strong focus on quality of life and are well informed through social media on the complications of anticoagulation, structural valve degeneration (SVD) and new technologies for treatment of biological valve failure. As a result, even younger patients frequently ask for biological valve replacements to avoid chronic anticoagulation, with its specific long-term complications. The fact that some see transcatheter valve-in-valve (ViV) implantation as an opportunity to avoid repeat open-heart surgery in the future has certainly supported this trend [13].

Surgeons on the other hand, may also see the reduction of perioperative complications and improved early discharge as a motivation to implant BPs. Thus, they can avoid the negative effects of anticoagulation and may also be less affected by the provision of future complex repeat procedures, due to the availability of ViV treatment. In addition, cardiologists have supported the development of transcatheter therapies and are therefore also not opposed to this strategy.

Determining the mode of surgery and the choice of a prosthetic valve, especially for younger patients is therefore multifactorial and should be the outcome of a thorough discussion between the surgeon and the patient, based on scientific evidence and preferences of the individual.

What is the Evidence for Preservation of the Aortic Valve in Patients with Aortic Regurgitation?

The best way to prevent prosthesis-specific heart valve complications is to preserve native valves. While valve repair has been successfully introduced for the mitral valve, it is still not performed very frequently in patients with aortic regurgitation. Despite the fact that valve-sparing aortic root surgery using techniques of re-implantation and re-suspension was introduced more than 30 years ago, a recent review of the Society of Thoracic Surgeons found that, of those patients who underwent aortic root replacement between 2004 and 2009 for aortic regurgitation, only 15% were operated using valve-sparing procedures [14]. Apart from the opportunity to reduce complications such as thromboembolism, bleeding, endocarditis and SVD, repaired valves can grow which is of particular value for the treatment of adolescents [15].

In his 20-year experience, Tirone David observed a long-term survival of 89%, 76% and 69% at 10, 15 and 20 years respectively [16]. El-Khoury et al. published a series of 475 patient who underwent aortic valve-sparing root replacement surgery. The 30-day mortality observed was 0.8% for both tricuspid and bicuspid aortic valves. At 10 years, survival was 73%, while 86% of patients were free from re-operation [17]. Results were similar to those of Schaefers et al., who also reported 88% freedom from all related complications at 10 years, with thromboembolism observed in 0.2% and endocarditis in 0.16% per year [18].

Despite the fact that aortic valve and aortic root repair techniques are reproducible and result in excellent outcomes, they currently remain uncommon procedures. However, given the excellent long-term outcomes, they should be considered for all patients with aortic regurgitation of less than 70 years, who potentially face a risk of SVD in the future if treated using BPs.

What Role does the Ross Procedure Play Today?

The Ross Procedure was introduced by Donald Ross at a time when no long-term proven BPs were available. Using a pulmonary autograft potentially improves durability of the biological valve in the aortic position but patients are left with two replaced heart valves and undergo a more complex surgical procedure [19]. As a result, the Ross Procedure has not been widely accepted and currently in the USA it represents less than 1% of all AVRs performed [20].

Nevertheless, the Ross Procedure has remained an important treatment option for adolescent patients, as the autograft has a potential to grow over time and chronic anticoagulation in this patient group can also be challenging. In the UK, 38% of AVRs performed for congenital aortic valve disease in patients younger than 40 years of age were replaced using an autograft [21].

In a recent propensity-matched study, Mazine et al. compared long-term survival (mean follow-up 14.2 ± 6.5 years) and adverse valve-related events of younger patients who underwent Ross Procedures with those who received mechanical prostheses (MP). There was no difference in the overall survival between the two groups although valve- and cardiac-related mortality as well as stroke and bleeding complications were significantly lower in Ross patients [19].

Mechanical versus Biological Prostheses

The ideal valve prosthesis would last life-long, provide optimal haemodynamics and would not need any form of anticoagulation. Unfortunately, this kind of valve has not been developed yet and therefore we have to weigh mechanical and biological prostheses against each other for their implantation in individual patients.

Given the relatively low penetration of complex techniques such as the Ross Procedure, AVR and MVR are usually performed using MP or conventional BP. While younger patients face SVD of BPs earlier after surgery, they also have a longer life expectancy compared to older patients and thus a higher cumulative lifetime risk of bleeding, thromboembolism and prosthesis-related complications after valve replacement.

Having these potential complications in mind, the decision about the kind of prosthetic heart valve used should take into consideration the patient's lifestyle and preferences as well as outcomes of currently available prostheses. Results of valve replacement are not only affected by the patients' age and comorbidities, but also by the valve prosthesis itself selected in individual patients.

Structural valve degeneration is a multifactorial process and different mechanisms of passive and active degeneration have been proposed [22]. Published studies present great variability in their results, because until recently, there was not even consensus around the definition of SVD. Factors associated with SVD are patient-related, related to cardiovascular risk factors, or explained by the valve position and the risks of specific BPs as shown in Table 1 [22].

Table 1: Factors associated with structural valve degeneration. Modified from Rodriguez-Gapella [22]

1.Patient Age
2. Cardiovascular Risk Factors and Comorbidities
a. Smoking
b. BMI
c. Diabetes Mellitus
d. Dyslipidaemia
e. Renal Insufficiency
f. Hyperparathyroidism
3. Valve related factors
a. Prosthesis size
b. Patient-prosthesis mismatch
e. Higher post-operative gradients
d. Persistent left ventricular hypertrophy
e. Make of the prosthesis

The most important patient-related factor is age at the time of implantation. While the incidence of SVD at 10 years is <10% for elderly patients, the incidence increases to 30% for patients under 40 years of age [22,23]. Cardiovascular risk factors such as hypertension, diabetes mellitus, smoking and dyslipidaemia are also having a negative impact on SVD [22].

Chronic renal insufficiency and secondary hyperparathyroidism are likely to increase the risk of SVD due to the alteration of calcium metabolism [24]. However, particularly in patients with renal failure, it is important to keep in mind that their life expectancy after valve replacement is severely impaired and therefore a BP could still be the appropriate conduit in these patients.

The biological material used to manufacture bioprostheses may also directly affect the incidence of SVD. Bovine pericardial valves seem to have superior haemodynamics compared to porcine valves [25,26], but certain porcine valve models also show excellent long-term outcomes. Hancock porcine valves (Medtronic, Minneapolis, MN/USA) showed up to 65.4% freedom from reoperation at 20 years in randomised trials [27,28]. Similarly, a native porcine aortic root prosthesis, the Freestyle™ (Medtronic Inc, Minneapolis, MN/USA), shows even in patients below 60 years of age, a 70% freedom from reoperation for SVD at 15 years after aortic root replacement while it also offers superior haemodynamics compared to conventional stented BPs [29].

A number of studies, particularly those in which patient-prosthesis mismatch was analysed, demonstrate that small size BPs show higher rates of SVD, most likely explained by higher gradients and increased mechanical stress on the valve leaflets [23,25,30,31].

The risk of bleeding as a result of anticoagulation is generally low for younger patients, however, in those over 60 years of age it is 7 times higher [32]. When assessing the individual risk of bleeding, it is also important to gain information about patient compliance and their access to regular follow-up of anticoagulation levels.

Aortic Valve Replacement

Data from randomised controlled trials and registries provide conflicting results on long-term survival of patients after AVR using MPs or BPs [27,28,33,34]. In the Veteran Affairs Randomised Trial, 394 patients from all age groups were enrolled and underwent isolated AVR between 1977-1982 [28]. Patients were randomised to receive either a Bjork-Shiley spherical tilting disc MP (no longer commercially available) or a Hancock (Medtronic, Minneapolis, MN/USA) porcine bioprosthesis. Over a 15-year follow-up they reported lower mortality for patients who received a MP (66% versus 79%, p=0.02). However, valve-related deaths were similar (MP 37% versus BP 41%) but the higher perioperative mortality risk at that time resulted in a higher risk for those patients who needed repeat AVR surgery for SVD [28].

Oxenham et al. reported on 211 patients who were randomised to isolated AVR with either a Bjork-Shiley MP or a porcine BP (mean age 53.9 years; follow-up 20 years). They did not find any difference in the long-term survival between the two groups (MP 28.4% versus BP 31.3%, p=0.57) [27].

The results align with the latest randomised controlled trial results by Stassano et al. During their 13-year follow-up of 310 patients, who underwent isolated AVR with either MP or BP with low perioperative mortality (MP 2.6% versus BP 3.9%, p=0.4), they found no difference in long-term survival (MP 27.5% versus BP 30.6%, p=0.6) [34].

In contrast, an analysis on 4545 patients between 50-69 years old from the Swedish Web-system for Enhancement and Development of Evidence-Based Care in Heart Disease, who underwent AVR showed improved long-term survival in the MP group compared to BP at 5,10 and 15 years respectively (92%, 79%, 59% versus 89%, 75%, 50%, p=0.006) [33].

Apart from mortality, it is important to keep in mind that younger patients usually live longer with their prosthetic valves. For that reason, they are also more likely to face higher morbidities, even from complications with low incidence. Van Geldorp et al. investigated in detail the risk of valve-related events after AVR. The great majority of their 3934 patients (73%) received a BP (mean age 70 years; mean follow-up 6.1 years) and 27% a MP (mean age 58 years, mean follow-up 8.5 years). Despite the age difference, they found that event-free life expectancy was improved in BP group [35].

Numerous trials consistently show that the risk for reoperation is higher after bioprosthetic AVR, especially in those younger than 65 years of age [27,28,34-36]. The lifelong risk for re-operation for patients with a BP is 25% compared to 3% for those with MP [35,36]. However, it is important to notice that certain stented [37] and stentless BPs [29] show excellent long-term outcomes even in younger patients below 60 years of age, with freedom from SVD after AVR of 50% at 17 years after surgery and freedom from reoperation in those young patients of 70% at 10 years after aortic root replacement [39].

There is also consistency on the risk of bleeding, which is higher in patients who received a MP [27,28,34,35,38]. The risk per year for bleeding after AVR using a MP is estimated at 1-2% [38] with a lifetime bleeding risk in those patients of 41%, compared to 12% in patients with BPs [35]. The thromboembolic risk is interestingly similar between the two groups [27,28].

Quality of life is of increasing importance, especially when discussing AVR with younger patients. However, available studies show little objective difference in the quality of life in relation to the type of implanted prosthesis [39,40].

Mitral Valve Replacement

The excellent long-term outcomes achieved following mitral valve repair and its improved penetration into routine surgery has limited the role of MVR [8,9]. However, when patients require a prosthetic mitral valve, the decision-making can be even more complex as many patients with mitral valve disease are already on anticoagulation for other reasons. Again, the discussion with the patient should balance individual preferences, contraindications to long-term anticoagulation and the risk of SVD [10,11]. A summary of the factors in favour of the 2 types of prostheses is shown in Table 2.

Two historical randomised trials have shown no difference in long-term survival between patients who underwent MVR using BPs or MPs [27,28], and Chikwe et al. recently published similar findings [41]. These findings conflict with non-randomised data from an analysis of 15,503 patients who received isolated MVR between 1996 and 2013 in California [12]. Long-term mortality in younger patients who received BPs appeared significantly higher [12,42], as well as their 30-day mortality (BP 5.6% versus MP 2.2%) [12]. However, it appears that this was most likely a result of the higher operative risk of the BP patients.

Table 2: Factors in Favour of Mechanical and Biological Prostheses. Modified from Nishimura et al 11.

Favour Mechanical Prosthesis	Favour Bioprosthesis
Age <50y	Age>70y
Patient preference -avoid re-intervention	Patient preference - avoid risk of anticoagulation - avoid lifestyle modification - avoid valve sound
Low risk for long term anticoagulation	High risk for long term anticoagulation
Patient compliant with anticoagulation treatment and INR monitoring services available	Patient not compliant with anticoagulation treatment or does not have easy access to INR monitoring services
Other indications for anticoagulation	
Patient with potential high risk for re-intervention (e.g. porcelain aorta)	Access to surgical centres with low reoperation mortality risk
Patient potentially not a TAVI candidate (e.g. AVR with small root)	

The risk of SVD is well known to be higher in the mitral position, most likely as a result of greater haemodynamic stress. Fifteen-year durability has been reported as 66% for a group of 310 patients (mean age 65 years) who were treated using BP's [43]. The incidence of SVD is higher in patients with a BP in the mitral position when younger than 65 years of age[27,41,42]. It appears that there is no difference for those older than 65 years[28]. In terms of morbidity, the risk of bleeding is higher for patients with a MP, but the risk of thromboembolism is the same among the two groups[12,28,41,42].

Current Guideline Recommendations and Factors Determining the Choice of Prosthesis

Over recent years, guideline recommendations have recognised that patients are well informed and that therefore the choice of prosthesis should not be made by the physician on their own, only considering the patient's age and scientific evidence, but also needs to include the patient and their personal lifestyle and preferences [10,11]. Therefore, an appropriate consent process should include the patient and ideally a relative, and it is key to establish the desire of the individual. It needs adequate documentation, including the risk of potential future complications such as SVD, bleeding, thromboembolism and endocarditis.

Obviously, the main concern for BPs is SVD and the need for re-intervention. Therefore, MPs are recommended for AVR in patients under 60 years of age and MVRs in patients under 65 years of age, or those patients at risk of accelerated SVD, such as hyperparathyroidism [10]. They should also be considered whenever repeat surgery carries a high risk, while the patient has a reasonable life expectancy (>10 years) [10]. In this context, the opportunity of

ViV procedures, available for BPs in the aortic (and also mitral) valve position, is playing an important role. While short-term effectiveness has been demonstrated previously, long-term evidence of its effectiveness and durability are outstanding [44].

On the other hand, the main concern for the use of MPs is bleeding. Therefore, the choice of prosthesis should only be determined after estimating the risk of anticoagulation-related bleeding and thromboembolism [10]. Mechanical prostheses should be considered in patients already on anticoagulation and those with mechanical prostheses in other positions.

In patients who undergo repeat valve surgery due to mechanical valve thrombosis despite adequate anticoagulation, BPs are an alternative. Bioprostheses should also be considered in young women who want to start a family due to the negative side effects of anticoagulation for the foetus and mother during pregnancy. They may also be a very useful alternative if good quality anticoagulation is unlikely to be achieved. In this respect, patients with endocarditis who more frequently have a poor compliance, such as intravenous drug abusers, are often better served with BPs, despite their younger age [10].

In terms of age, BPs are currently seen most adequate for an AVR in patients over 65 years of age, for an MVR above 70 years of age, or for those patients with a life expectancy lower than that of the prosthesis durability. In addition, patients who will require future non-cardiac surgical procedures or those younger patients who present a high risk for bleeding, should be considered for BPs [10].

New Prosthetic Heart Valve Technology

Mechanical Prostheses

Recent investigations have demonstrated good outcomes of reduced anticoagulation when using the On-X MP (Cryolife, Kennesaw, NW/USA) in the aortic position [45]. In the Prospective Randomised On-X Anticoagulation Clinical Trial (PROACT), the level of anticoagulation needed for the On-X valve in patients with high and low risk of thromboembolism events, was investigated (mean age 55.2 ±12.5 years, follow-up 8.8 years). During the first three months after AVR, all patients received Warfarin with a target INR of 2.0-3.0, in addition to low dose Aspirin. Later, patients were randomised according to high and low thromboembolism risk.

High risk patients after AVR were treated using a combination of low dose Warfarin (target INR 1.5 to 2) and low dose Aspirin. In the control group, patients received Warfarin with an INR target of 2.0-3.0 and low dose Aspirin. Major bleeding (3.9% versus 1.6% per patient/year, $p=0.002$) and minor bleeding events (3.5% versus 1.3% per patient/year, $p=0.002$) occurred more frequently in the control group. Thromboembolic events were similar between the two groups [45,46].

The low risk arm of the trial, in which patients were commenced on dual antiplatelet therapy, was terminated early because of an increased incidence of thromboembolic events (3.1% per patient/year versus 0.3% per patient/year, $p=0.02$) in the study group. Compared to the control group, there was no difference in bleeding and all-cause mortality [46].

Biological Prostheses

A new tissue treatment (Resilia™, Edwards Lifesciences, Irvine, CA, USA) has recently been used in a bovine pericardial BP. It is seen as an alternative for younger patients, who want to

avoid long-term anticoagulation. This new tissue treatment, which through glycerolisation blocks free aldehyde bridges in the pericardium, demonstrated improved resistance to calcification in a sheep model and may consequently result in a reduction of structural SVD in humans [47].

Clinically the new tissue has been investigated in the COMMENCE trial [48], in which a total of 689 patients with AVR were enrolled (mean age 67.0 ±11.6 years). First results after a mean follow-up of 1.2 ±0.7 years, showed an overall mortality of 2.7%, thromboembolism 3.1% and rate of major bleeding of 0.9%. While it is not surprising at this early time after surgery that no case of SVD was seen, it is important to notice that no case of valve thrombosis was observed [48].

This newly treated bovine pericardium has now also been incorporated into a new BP for use in the aortic position, the Inspiris Resilia™ valve (Edwards Lifesciences, Irvine, CA, USA), which was first implanted by the senior author of this article in April 2017. Its design is based on the Perimount Magna BP™ (Edwards Lifesciences), for which excellent long-term outcomes data already exists [37].

In addition, it comprises an expandable frame which is designed to facilitate future transcatheter ViV procedures. Through this newly designed technology, placement of a transcatheter heart valve should not only be more easily facilitated, but it should also be easier to achieve appropriate effective orifice areas after ViV treatment in the future.

The senior author has also used this BP for aortic root replacements in combination with vascular prostheses in those younger patients in whom it was not feasible to preserve the native aortic valve. Investigations in multi-national registries and trials are on their way for the aortic model and a future model for implantation in the mitral position is under development.

How Should an Initial Valve Replacement be Performed in Younger Patients?

The key for improved long-term outcomes after AVR and MVR is obviously a successful initial operation. However, when it comes to valve replacements in younger patients, there are additional aspects which need to be addressed during the primary procedure. The likelihood of repeat surgery in those patients is higher and therefore, not only should they be offered limited access surgery, but also the pericardium should be closed during surgery, so that reopening of the chest can be facilitated in the future.

The size of BPs considered for implantation needs to be selected not only according to anatomical space in the aortic root or mitral annulus, but by keeping the patient's body mass index in mind. Prosthetic orifice areas need to be large enough to prevent patient-prosthesis mismatch after surgery. This will not only improve haemodynamic and symptomatic outcomes, but also improves bioprosthetic durability and reduces reoperation rates in patients with MPs. Obviously, this can mean that in patients undergoing AVR, the aortic root may need to be enlarged or even replaced. Bioprostheses used in younger patients may even be oversized, so that future ViV therapy carries less of a risk of patient-prosthesis mismatch. As mentioned above, modern pericardial valves have additional structural advantages in this respect.

In addition, for younger patients, one should focus on BPs which have proven excellent long-term durability in patients less than 60 years of age [38,39]. Bioprostheses which are

known to present increased technical challenges during ViV procedures should be avoided in this age group, particularly those pericardial valves in which the pericardium is wrapped around the stent frame as these carry a high risk of coronary obstruction during transcatheter therapy for SVD [49,50].

In the mitral position it is also crucial that biological valve stents are positioned outside the left ventricular outflow tract during the initial surgery, as they can cause left ventricular outflow tract obstruction perioperatively, but also after future ViV procedures.

Conclusion

It is a fact that if heart valve repair can be facilitated, prosthetic complications can be avoided, and, in this respect, it is surprising that more patients with repairable aortic and mitral valves are not offered valve-sparing operations. However, it is also a reality that worldwide an increasing number of younger patients who undergo AVR and MVR, are choosing BPs. As highlighted above, this is due to patients' interests, increasing evidence of good long-term outcomes after valve replacement and also to a degree supported by recent guideline recommendations.

The choice of prosthesis should be the result of a detailed discussion between the individual patient and surgeon. The consent for surgery should take subjective and objective advantages and disadvantages into consideration and needs to be appropriately documented. If younger patients are operated using BPs, appropriate surgical strategies and prostheses should be used. It remains to be seen how the most recent prosthetic heart valve technology will further improve outcomes in younger patients.

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SECTION 1 CARDIAC SURGERY

Mitral and Tricuspid Valve and Atrial Fibrillation Surgery

"Omnium rerum principia parva sunt"

Marcus Tullius Cicero (106BC-43BC)

Chapter 5

Lesion Sets for Atrial Fibrillation during Mitral Valve Surgery

Stefan RB Schneider and Manuel Castellà

"Pulverulenta novis bene verritur area scopis"

Introduction

The prevalence of atrial fibrillation (AF) in Europe in 2014 was estimated at 1.9% in Italy, Iceland and England; 2.3% in Germany and up to 2.9% in Sweden. For Iceland, a yearly increase of 0.04% for the prevalence of AF has been reported. With the growing elderly population, by 2030 up to 17 million people in Europe might suffer AF with newly diagnosed cases of 215,000 patients per year [1]. Even in highly developed countries with adequate medical management, atrial fibrillation remains a major risk factor for stroke, heart failure and sudden death. The latest ESC guidelines differentiate five types of atrial fibrillation [2]:

Table 1: Different types of atrial fibrillation

AF Pattern	Definition
First diagnosed AF	AF not diagnosed before, irrespective of its duration or severity of symptoms
Paroxysmal AF	Self-terminating within 48h to a maximum of 7 days
Persistent AF	AF for more than 7 days
Long standing persistent AF	Continuous AF lasting for more than 1 year with rhythm control
Permanent AF	AF accepted by patient and physician without rhythm control interventions.

Atrial fibrillation typically originates from micro-reentries in the left atrium (LA) (80%), localised around the ostia of the pulmonary veins and the left atrial appendage (LAA), with frequencies around 400/min. Nevertheless, atrial fibrillation can have its origin in other areas of the left atrium or in areas of the right atrium (RA) (20%). Atrial flutter on the other hand is usually a disease of the right atrium. It originates from macro-reentries with frequencies around 250-300/min [3-5].

In 1987, James L Cox performed the first surgical "maze" procedure (CMP) for the treatment of this heart rhythm disorder [6]. He created lesions in both atria with a "cut and sew" technique resulting in blocking of all macro-reentrant circuits while permitting the sinus impulse to extend through the atria to the atrioventricular node [7]. Due to high rates of chronotropic incompetence and resulting pacemaker implantations, Cox modified the procedure with two evolutionary steps, the last one called the "Maze III" procedure [8]. Its success rate, with over 90% of the patients free from AF after a median follow up of more than three years, still constitutes the benchmark that other techniques are judged by.

Nevertheless, one of its main disadvantages is its invasiveness and the fact that it is time consuming, especially as an add-on procedure in patients undergoing surgery for other pathologies. The question is: What can be done to overcome these disadvantages? The ideal lesion should be easy to apply, transmural and linear. In 2002, Damiano's group (St. Louis, MO, USA) addressed these issues introducing the latest modification of the procedure named the Cox Maze IV procedure (CMP IV) [9]. Instead of the classical cut and sew technique, they used radiofrequency and cryoablation achieving results that almost matched those of the classic technique (Table 2).

Table 2: Long term results after CMP with mean follow up of 3.6 ± 3.1 years, reprinted by permission from Springer Nature: Springer, Journal of Interventional Cardiac Electrophysiology 2011 [39]

Variable	CMP III (n=112)	CMP IV (n=100)	CMP III+IV (N=212)
Follow-up, median (IQR), y	5.9 (2.5–7.8)	1.0 (0.74–1.9)	2.2 (0.9–6.2)
Freedom from AF*	96 (86–98)	90 (81–95)	93 (87–96)
Freedom from AF off antiarrhythmics*	83 (68–88)	82 (71–89)	82 (75–87)
Freedom from warfarin*	86 (75–92)	74 (62–83)	80 (72–86)
Late stroke (>30 d), no. (%)	1 (0.8)	0	1 (0.4)

*Data are given as mean (95% CI).

The main benefits of the CMP in patients with mitral valve disease are lower incidence of stroke and improved long-term survival. In 2001, Lim et al. published their results of a series of 400 patients undergoing mitral valve surgery between 1987 and 1999 [10]. By means of univariate analysis, they identified AF as a risk factor for reduced survival, but they failed to prove this in the multivariate analysis. However, in their study the median follow-up was only 2.8 years. In 2003, Bando et al. published a case series of 812 patients with mechanical mitral valve replacement (1977-2001) [11]. In this long-term observational study, they found "...that late atrial fibrillation and omission of the maze procedure were significant risk factors for late stroke". In 2009, a group from Korea and a group from Belgium published retrospective cohort studies with a mean follow up between 3 and 4 years, which found a survival benefit for patients undergoing concomitant CMP [12,13]. Recently Badhwar et al. published an analysis of the Society of Thoracic Surgeons (STS) database including 86,941 patients with atrial fibrillation undergoing cardiac surgery [14]. After propensity matching of

the two groups with and without CMP, they confirmed a reduction of the relative risk for 30-day mortality and stroke in the group that underwent the CMP.

Preoperative AF is associated with higher long-term mortality in patients with mitral valve disease. Randomised trials have shown benefits regarding maintenance of sinus rhythm, but only observational and cohort studies have been able to show a long-term survival benefit and freedom from stroke.

There are a multitude of publications reporting the results of the surgical treatment for atrial fibrillation. Often, they include the use of different energy sources and different lesion sets, which might lead to a certain degree of confusion regarding the optimal treatment strategy. In this chapter we present the most effective lesion set and energy source for the CMP in patients with mitral valve disease to date.

Left Atrial Lesion Set

In 2006, the group from the Cleveland Clinic published two important studies about the surgical treatment of atrial fibrillation. The first one described the use of different lesion patterns for the treatment of paroxysmal AF in patients undergoing mitral valve surgery [15]. They showed that single pulmonary vein isolation (PVI, Figure 1) achieved comparable

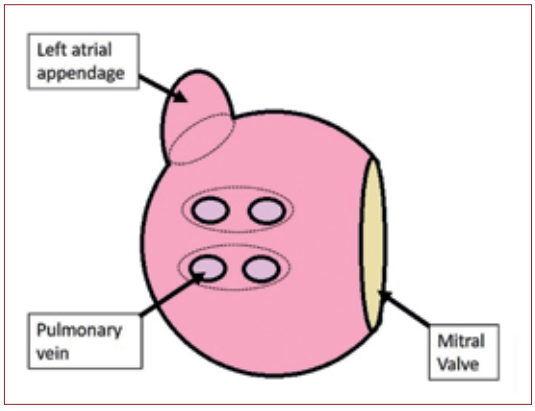

Figure 1: Pulmonary vein isolation. Dotted lines: ablation lesions

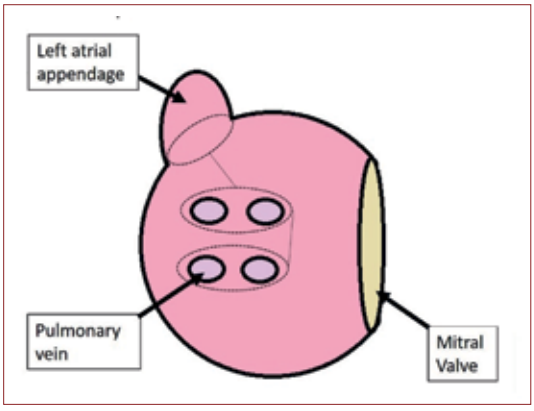

Figure 2A: Lesion set 2

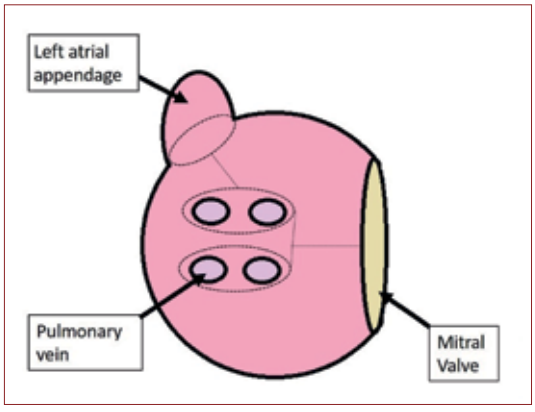

Figure 2B: Lesion set 3

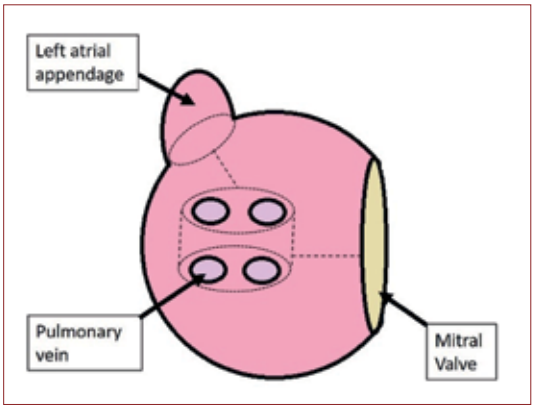

Figure 3: Lesion set 4

results to the full Cox maze procedure (CMP) in this patient subset. Furthermore, they found that patients suffering from rheumatic or degenerative mitral valve disease had higher rates of AF recurrence after ablation procedures. The overall prevalence of AF was 9% after one year. Other risk factors for AF recurrence were a large left atrium and older age.

The second study compared different lesion sets (Figures 1, 2 and 3) for the treatment of persistent/long-standing persistent atrial fibrillation, 74% of the patients included undergoing mitral valve surgery [16]. After one year, the overall prevalence of atrial fibrillation was 24%. The best results were achieved with the complete lesion set (Figure 3), while lesion set 2 (Figure 2) and PVI alone (Figure 1) led to 40-50% recurrence of AF. A large left atrium, patient age and long duration of preoperative AF were identified as risk factors for AF recurrence. The authors concluded "…that in cardiac surgical patients with persistent/long-standing persistent atrial fibrillation, the left atrial lesion set should include wide pulmonary vein isolation, at least one connection between right and left pulmonary veins, and a connection to the mitral annulus". In their study the lesion set in the right atrium did not influence their results.

Right Atrial Lesion Set

Although atrial fibrillation may have its origin in the right atrium in up to 20% of the cases [4], it remains a matter of discussion whether to perform the biatrial CMP or limit the intervention to the LA lesion set only. Figure 4 illustrates the right atrial lesion set.

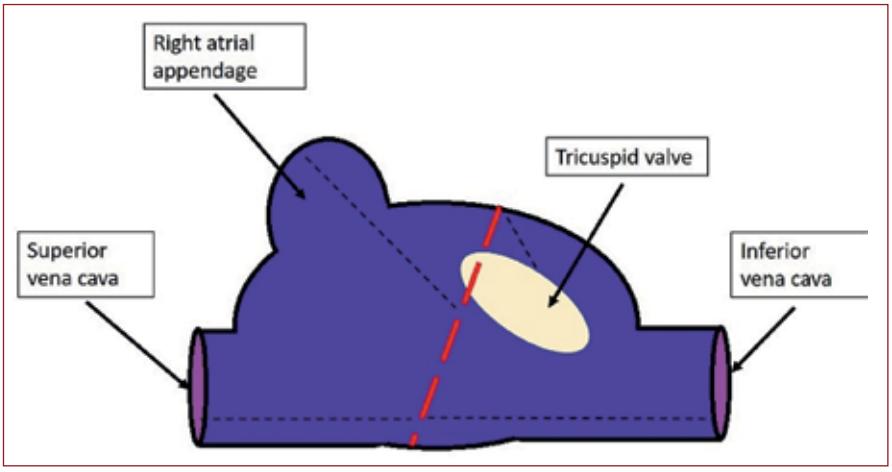

Figure 4: Right atrial lesion set. Red interrupted line: RA incision; dotted lines: ablation lesions

In a meta-analysis including 5885 patients published in 2006, Barnett et. al. found superior rates of freedom from AF for patients who underwent biatrial ablation (92%-87.1%), compared to left atrial ablation procedure alone (86%-73%) [17]. They found no differences regarding survival rates between patients undergoing biatrial and left atrial ablation procedures. Regarding higher rates of post-procedural pacemaker implantation in the biatrial group, the authors speculated that "…this might be due to the fact that there is a higher success rate in ablating AF and that more cases of sick sinus syndrome that are strongly associated with AF are discovered…". Yet the authors of this study did not provide any data supporting their hypothesis.

A study published by Kim et al. in 2011 reported the results of 284 patients who underwent either left atrial ablation (n=85) or biatrial CMP (n=199) [18]. After 2 years of follow up, they

found a significant difference in the incidence of atrial fibrillation with 25.9% in the left atrial group vs. 14.3% in the biatrial CMP group having developed recurrent AF. Regarding adverse events, they did not report significant differences between groups except pacemaker implantation which was not necessary in the left atrial group but occurred in 1.8% of the biatrial group.

A meta-analysis published in 2016 including fourteen studies with more than 2000 patients found that there was no difference between the biatrial and the left atrial Maze procedure regarding the rates of restored sinus rhythm, risk of death, reoperation for bleeding and cerebrovascular events [19]. Patients with biatrial CMP had longer cross clamp and cardiopulmonary bypass times and higher rates of permanent pacemaker implantation (2-11% vs 0-6%), while suffering atrial flutter less frequently (0% vs 3-7%).

In conclusion, for patients with paroxysmal AF, pulmonary vein isolation alone may suffice. In patients with persistent or long standing persistent AF, the lesion set should include pulmonary vein isolation, a connection between right and left pulmonary veins and a connection to the mitral annulus. If the right atrial lesion set is applied, one must weigh the higher rates of pacemaker implantation against the possible benefit of higher rates of freedom from AF and atrial flutter.

Energy Sources

The development of devices using different energy sources was crucial for simplifying the CMP. Those devices made the CMP safer and faster and permitted the development of minimally invasive surgical ablation procedures via port access or mini-thoracotomy even as a stand-alone procedure [20]. The effectiveness of the CMP highly depends on the correct use of these devices for each patient and for each ablation line. Only bipolar radiofrequency and cryothermy can consistently create transmural linear lesions.

Radiofrequency

Radiofrequency (RF) energy uses a current between 100 and 1000 kHz resulting in localized heating to create a tissue lesion [20]. Devices are available from different manufacturers. Bipolar radiofrequency creates the lesion between two electrodes, usually mounted on a clamp longitudinally, thereby maintaining the lesion linear and strictly localised (Figure 5).

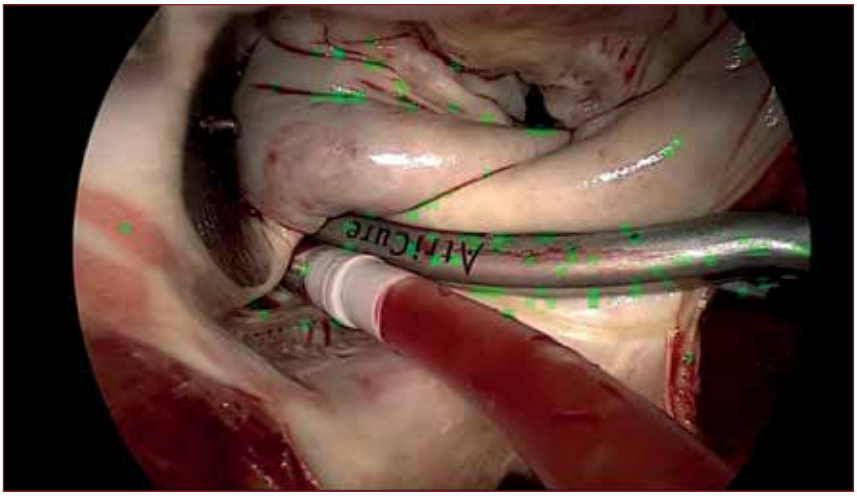

Figure 5: Endoscopic view of bipolar ablation clamp.

To guarantee complete electric isolation, the lesion needs to be transmural. This is usually controlled through measurement of the tissue conduction. The amount of energy needed, the duration of the energy application and the necessity of repeating the application several times differ between different devices.

There remain some concerns, such as if it is possible to achieve the same rates of freedom from atrial fibrillation with radiofrequency on long-term follow up as compared to the classic 'cut and sew' technique. The Mayo Clinic group published their results after introduction of the new energy sources in 2007 and in 2014 [21,22]. The authors stated that the classic 'cut and sew' CMP still provides better results especially on long-term follow up after over 5 years (75% vs 52% freedom from AF without anti-arrhythmic medication). In their publication from 2007, they described that "*in terms of the number of burns with the Atricure® device, typically the surgeons at the Mayo Clinic apply two burns with each lesion set*". Nevertheless, the authors have embraced the new energy sources as reflected in the increasing number of patients treated with them (n>160 patients in 2010) and the decreasing number of patients treated with the classic cut and sew technique (n=10 in 2010).

There does not exist a fixed number of energy applications that guarantees transmurality of the lesions. Achieving complete transmurality on the one hand depends on patient-related factors such as tissue thickness and composition and, on the other hand, on the technical specifications of the ablation device. Manufacturers provide instructions for the correct use of their device that should be followed.

We had the opportunity to histologically prove complete transmurality of RF ablation lesions in a patient that had to undergo re-do surgery four years after a Cox Maze IV procedure. The lesions were macroscopically visible on the epicardial surface. Several biopsies were taken from the RA and LA confirming transmural fibrosis [23].

Another important aspect is that the effectiveness of the RF ablation lesion depends not only on the technical equipment and the design of the ablation clamp, but also on its interaction with the specific anatomy of the heart. In 2008, we published an anatomic study performed on human hearts of recently deceased donors [24]. Usually coronary arteries in the atrioventricular (AV) groove lay on the atrial side, between 3 and 18mm away from mitral and tricuspid annuli. We demonstrated that when the bipolar clamp is closed, the coronary sinus will usually be included in its jaws and when applied in patients with left dominant coronary anatomy, it will also include the circumflex artery which may cause thermal lesions to the coronary artery (Figure 6). The inclusion of the coronary sinus is a necessity, as it is covered with striated muscle extending from the right atrium and presents muscular connections to the left atrium that might serve as a pathway for AF [25]. Negative effects on the drainage of the coronary sinus have not been reported. One of the reasons for this might be that the venous system disposes of multiple connections to the ventricular cavities. On the other hand, in most cases the clamp does not reach the mitral annulus due to the growing tissue thickness of the AV groove (Figure 6). Similar concerns exist for right-sided RF ablation. The right coronary artery (RCA) and its accompanying vein are located on the atrial part of the AV groove. It is impossible to place the ablation clamp down to the tricuspid annulus without including the RCA.

In conclusion, RF bipolar ablation clamps are an ideal instrument to create the PVI and coronary sinus ablation lesions, while in many cases they leave ablation lines to the mitral and tricuspid annulus incomplete, with the additional risk of causing coronary artery injury. Leaving incomplete ablation lesions might even be detrimental and a risk

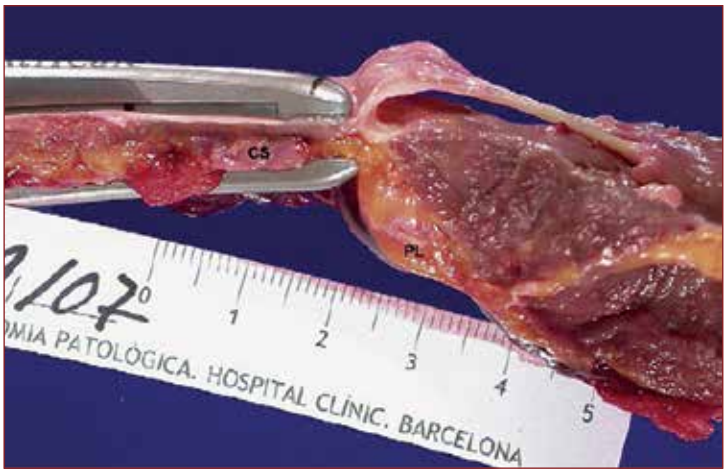

Figure 6: RF Clamp positioned for ablation towards the mitral annulus at the level of P2. The coronary sinus (CS) caught between the jaws. Posterolateral artery (PL) of the right coronary located in its epicardial path. Reprinted by permission from ELSEVIER, Journal of Thoracic and Cardiovascular Surgery [24].

factor for development of atrial flutter, that is in general more poorly tolerated than atrial fibrillation [26]. Consequently, the lines to the tricuspid and mitral annulus should be created by a device with a unipolar energy source such as cryothermy.

Cryothermy

There are two types of cryothermy device from different manufacturers: one is powered by nitrous oxide and the other uses argon gas. With nitrous oxide, tissue can be cooled to -89.5°C, and argon cools even lower down to -185.7°C. While on the arrested heart transmural lesions can be created reproducibly within two to three minutes, on the beating heart the heat sink from the circulating blood is able to impede a full transmural lesion [20]. In the case that a transmural lesion is achieved, it would carry the risk of causing freezing and thrombus formation on the endocardial side. Therefore, the main use of cryothermy is on the endocardial surface of the arrested heart.

Several case reports have suggested that cryoablation can injure the coronary arteries by causing vasospasm, dissection or even total obstruction [27-29]. However, those case reports fail to prove that the lesion in question was caused by the cryoablation procedure and not by concomitant procedures or other factors. In 2013, Cheema et al. published a case series of 20 patients who had undergone a cryomaze procedure [30]. After a mean follow up of 32.6 ± 19.5 months, the patients underwent a computed tomography scan of the coronary arteries. No injuries related to the cryothermy ablation were detected.

Figure 7 shows the tip of a cryoablation tool during surgery before cooling and figure 8 after initiating the cooling procedure. One of the main advantages of cryothermy is that it does not cause structural damage to the fibrous structures of the heart. The design of the probe which can be bent to adapt to the cardiac structures allows it to reach the tricuspid and the mitral annulus without problems. To ensure transmurality of the ablation line to the coronary sinus, cryoablation should be applied both endocardially and epicardially.

Furthermore, cryoablation is the ideal tool for minimally invasive mitral valve surgery. While the bipolar radiofrequency devices are usually rigid and bulky, the flexibility of the cryoablation devices makes them the ideal tool for these cases and they can be used to create the complete lesion set.

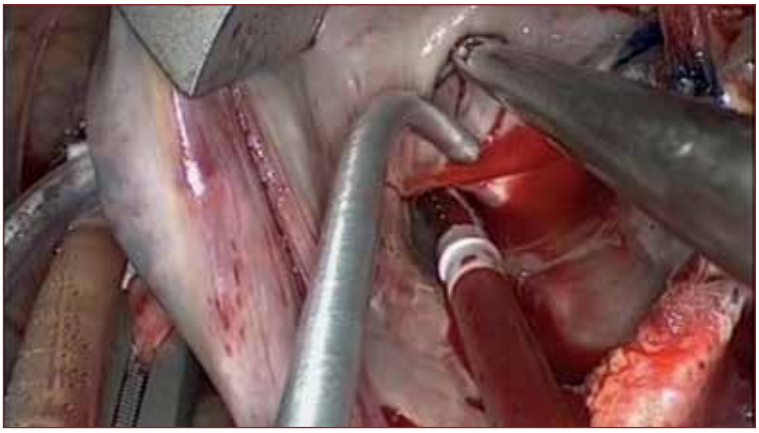

Figure 7: Cryoablation tool, intraoperative use for creation of LA lesion set.

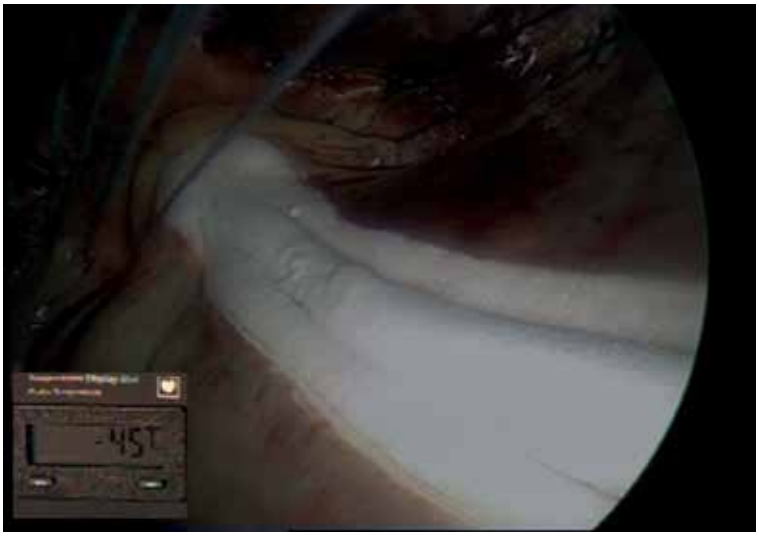

Figure 8: Intraoperative endoscopic view of cryoablation of the mitral annulus.

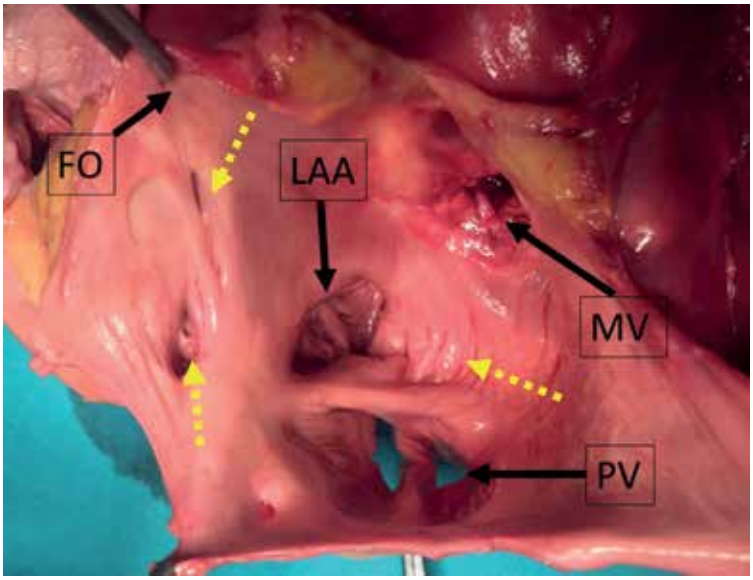

Figure 9: Left atrial appendage anatomy, FO: Foramen ovale grabbed with forceps PV: pulmonary veins, MV: mitral valve, LAA: left atrial appendage. Yellow dotted arrows mark trabeculae in the broad base of the LAA and pouches/ trabeculae of the LA endocardium

Exclusion of the Left Atrial Appendage (LAA)

The left atrial appendage has a variable anatomy. In some cases, it presents a broad base, and variable dimensions of its neck and lobes (Figure 9) [31,32]. It is estimated that between 50% and 90% of atrial thrombi originate from the left atrial appendage [33]. Therefore, its significance for stroke risk is undeniable and its closure leads to a reduced risk of cardiovascular events [33,34]. There are different techniques for closing the left atrial appendage: external ligature, internal closure with direct suture, closure with stapler, amputation, surgical closure with special devices and interventional closure with special devices. The easiest way to close the LAA during mitral valve surgery is to close it with direct suture. However various case studies have proven by magnetic resonance imaging or transesophageal echocardiography that direct suture or external ligation do not always achieve or maintain complete closure [35,36]. This might be the case in a LAA with a wide neck or additional lobes. Healey et al. reported success rates of 45% for closure by suture and 72% using a stapler [36]. Incomplete closure with residual blood flow might even elevate the risk of thromboembolic events [37]. The 2013 "Guidelines for the surgical treatment of atrial fibrillation" states that if LAA exclusion is planned, the use of a special device is preferable over ligature, suture or stapling [38].

Anticoagulation

All patients after surgical CMP should receive effective anticoagulation for at least three months. In our institution we start anticoagulation within the first 48 hours postoperatively if there are no contraindications and the bleeding risk is not considered too high. That has several reasons: firstly, the ablation leaves an uneven, rough and potentially thrombogenic endocardial surface. After an interval of three months, scarring and healing of the endocardial lesions is complete. Therefore, we recommend anticoagulation with a vitamin K antagonist during this period.

The second reason is that the success rates of the CMP do not reach 100%. At least 10-20% of the patients will experience recurrent AF at some point. A successful CMP should be confirmed by a 24-hour Holter study at the end of three months. At our institution we perform yearly Holter monitoring and anamnestic screening to confirm long-term freedom from AF.

Even after LAA occlusion, thrombi can originate from other potentially thrombogenic surfaces within the LA. Figure 9 shows an example of LA anatomy with these features. Between 10% and 50% of thrombi have been reported to originate from these areas [33].

Besides these considerations regarding the procedural aspects of the CMP, the common indications and guidelines for oral anticoagulation apply. If the patient has a mechanical heart valve, the choice of the anticoagulant is clear: anticoagulation with a Vitamin K antagonist must be continued. If this is not the case, the CHA2DS2-VASc score should be calculated to clarify the indication and anticoagulation with novel oral anticoagulants is a viable option [2].

Conclusion

Is it important to treat AF in mitral patients?

Preoperative AF is associated with higher long-term mortality in patients with mitral valve disease. Randomised trials have shown benefits regarding maintenance of sinus rhythm,

but only personal series and cohort studies have been able to show a long-term survival benefit and freedom from stroke.

Which ablation lines should be applied?

In paroxysmal AF, pulmonary vein isolation alone can lead to acceptable rates of freedom from AF. In patients with persistent or long standing persistent AF, the lesion set should include pulmonary vein isolation, a connection between right and left pulmonary veins and a connection to the mitral annulus. If the right atrial lesion set is applied, one must weigh the higher rates of pacemaker implantation against the possible benefit of higher rates of freedom from AF and atrial flutter.

Which energy sources should be used?

For open heart surgery through a standard sternotomy, RF bipolar ablation clamps are the ideal instrument to create most of the lesions, while in many cases they will leave ablation lines to the mitral and tricuspid annuli incomplete. The best tool for the ablation lines to the mitral and tricuspid annuli is a cryoablation device. Cryoablation is also the preferred technique for minimally invasive ablation procedures because the device can pass through small incisions for thoracoscopic access and can be bent to adapt to the cardiac structures. In this setting, it is the ideal tool to create the complete lesion set.

What to do with the LAA?

The LAA should be closed with a specially designed device. Closure reduces the risk for cardiovascular events.

Can anticoagulation be discontinued after surgical ablation?

Effective anticoagulation is mandatory for three months after a surgical ablation procedure. After three months, the individual thromboembolic risk of the patient needs to be assessed. The decision for long-term anticoagulation must be based on the specific risk profile of the patient. A prerequisite for cessation of effective anticoagulation is a successful ablation procedure with no recurrent episodes of AF and closure of the LAA. In case of recurrent episodes of AF, effective anticoagulation must be continued.

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Chapter 6

Should We Ablate All Patients in Atrial Fibrillation Undergoing Mitral Valve Surgery?

Niv Ad

"Nihil sub sole novum"

Introduction

Surgical treatment for atrial fibrillation (AF) has been performed for over 30 years, following the pioneering work of Dr. James L. Cox. The first cut-and-sew maze procedure was performed in September 1987 [1]. Since then, the procedure has evolved and the cut-and-sew procedure was replaced with surgical ablation devices utilising cold and hot energy sources. The introduction of different ablation tools and data related to the role of the pulmonary veins in AF led to multiple modifications of the original maze procedure to treat AF, either as a standalone disease or concomitantly with other open-heart procedures [2,3]. In the past, the lack of consistent guidelines regarding indications, lesion set, and recommended ablation technology led to a state of confusion surrounding a few critical questions:

1. Who should be treated for AF at the time of a concomitant surgical procedure?

2. How should AF be treated at the time of concomitant surgery in general and more specifically in patients with mitral valve disease?

Surgical Guidelines

Newly published guidelines from the major societies and associations should serve as a good source for improving decision-making in surgical ablation for AF [4-7]. In general, these practice guidelines share a very strong recommendation for surgical ablation at the time of mitral valve surgery, including which lesion set is recommended and the type of energy sources that should be used to increase the chances of transmural lesions [4,5].

Generally, surgeons facing patients with mitral valve disease and AF have to make a decision about whether to treat AF at the time of surgery or not. Surgeons frequently express concern that surgical ablation will be associated with increased perioperative risk and that efficacy will be unclear if surgical ablation is added to the mitral valve surgery. The multitude of prospective randomised trials and recent publications of surgical AF guidelines provide us with substantial evidence of the safety and efficacy of such concomitant procedures.

The American Association for Thoracic Surgery (AATS) guidelines recommend surgical ablation and associated it with improved 30-day outcome and reduced operative mortality (Class I, Level A evidence). These guidelines also found that the procedure could be performed with no increased risk of perioperative morbidity and stroke. Surgical ablation also demonstrated a positive impact on long-term survival, reduced risk for long-term stroke, and improved quality of life [4].

The newly published Society of Thoracic Surgeons (STS) guidelines granted a Class I, Level A evidence to surgical ablation at the time of mitral valve surgery to improve the rate of sinus rhythm without increased operative risk in patients with AF at the time of mitral valve surgery [5]. These guidelines noted that surgical ablation at the time of mitral valve surgery was associated with lower risk-adjusted operative mortality. The STS guidelines also recommend a bi-atrial Cox maze procedure in patients with advanced stages of AF and increased size of the left atrium.

Clinical Experience

Reports on the experience of surgical treatment for AF combined with mitral valve surgery date back to the early 1990s [8]. The majority of reports are case series, observational studies, and meta-analyses. However, there are several randomised controlled trials reported as well [9,10]. In general, the studies reported very good safety and variable efficacy. Our own experience reveals a very positive impact on patient outcomes when the Cox maze procedure was added to mitral valve surgery with or without tricuspid valve surgery [11]. Our findings suggest that patients who had AF addressed at the time of surgery enjoyed better survival and very low stroke rate with 95% freedom from stroke at 8 years of follow-up. The study was also encouraging as it documented a success rate of 79% freedom from atrial arrhythmia (without the use of antiarrhythmic drugs) of a single procedure at 5 years following surgery. The reported success rate used the Heart Rhythm Society (HRS) definition of failure, which is any event lasting longer than 30 seconds.

The largest randomised trial in the field demonstrated that surgical ablation was associated with significantly higher rates of sinus rhythm at one year following surgery compared to patients who did not have AF addressed at the time of surgery [9]. The original publication left open the issue of bi-atrial versus left atrial only surgical ablation. A closer look at the success rate in a follow-up publication revealed that the bi-atrial lesion set was associated with a higher success rate compared to a left atrial only lesion set. These results are not surprising in light of the relatively advanced stages of atrial remodeling and the type of AF at the time of surgery that the majority of these patients demonstrated [12-14].

Practice Guidelines

Several guidelines and expert consensus statements support surgical ablation in the concomitant setting [4-7]. Surgical ablation for AF at the time of mitral valve surgery was granted a Class I indication supported by Level A evidence from the STS [5]. Other aspects of surgical ablation that involve risk and long-term outcome have also been discussed, especially in the AATS publication. The AATS consensus statement specifically points to improved 30-day survival (Class I, Level A), no increased risk of perioperative stroke or morbidity, and improved long-term survival and freedom from stroke associated with surgical ablation [4].

Interestingly, the AATS guidelines conclude that the only energy sources associated with consistent transmural lesions for the procedure are cryothermal energy and

bipolar radiofrequency [4]. As for anticoagulation following the procedure, it is generally recommended to adhere to anticoagulation following the procedure and attempts to discontinue it should be on a case-by-case basis. The HRS guidelines specifically highlighted the fact that there is no good evidence for anticoagulation in the surgical ablation population and that the recommendations to continue blood thinners for life in patients with higher CHA2DS2-VASc scores only applies to patients following catheter-based procedures [6].

Is All Preoperative AF the Same?

When assessing patients prior to surgery, the current terminology of AF should be used. The term "chronic AF" is no longer in use and not all intermittent AF is paroxysmal AF [6]. While the terminology is very important for documentation, the perioperative decision-making is usually based on the clinical setting, duration of AF, and size of the left atrium.

An interesting question is: what to do for patients with very short duration of AF prior to the procedure? Several previous publications documented very good return to sinus rhythm with very short duration of preoperative AF, but only if the mitral valve pathology was addressed [15]. However, it is clear that using preoperative duration of AF as the only variable to determine if surgical ablation should be added is probably an oversimplification of the decision-making process. More recent publications suggested that size of the left atrium, age of the patients, and tricuspid valve pathology may be important in directing surgical ablation even in patients with no apparent history of AF at the time of surgery [16,17]. The implications of long-term AF may be significant in terms of survival, thromboembolic complications, and quality of life combined with the more recent data suggesting that it is probably recommended to perform surgical ablation even in patients with very short duration of preoperative AF. However, more studies are required to better identify the most appropriate candidates for prophylactic surgical ablation in patients with no history of AF.

Preoperative duration of AF and left atrial size are important variables to be considered. Often, surgeons do not perform surgical ablation if the left atrial diameter is >6cm and if the duration of AF is greater than 5 years. Indeed, these variables are important to consider, but there are other considerations that should be applied when approaching these patients. The STS guidelines specifically recommended that in such patients, only the biatrial lesion set should be applied because ablation limited to the left atrium only would be extremely ineffective [5]. It is also important for surgeons to use appropriate ablation tools and only use devices proven to deliver consistent transmural lesions [4]. If the Cox maze procedure is applied appropriately in such cases, acceptable results should be anticipated with very low morbidity, pacemaker rates, and high return to sinus rhythm over time (Figures 1-3)[18-20]. The issue of the appropriate energy source to apply during surgical ablation should be examined especially carefully in the future. In particular, for mitral valve surgery, the use of combined bipolar radiofrequency with cryothermal energy or cryothermy as the sole energy source should be carefully compared to ensure acceptable and comparable long-term efficacy [21].

In several long-term studies we identified that surgeon experience with surgical ablation at the time of the procedure is a significant predictor for long-term success [11,22]. Experience of surgeons, like in any other surgical field, would theoretically impact on decision-making (which lesion set and ablation tools) as well as on the technical aspect of the procedure. The challenge of training was addressed in the AATS guidelines and recommendations [4]. The publication of results from the CURE-AF trial is a unique example of the lack of

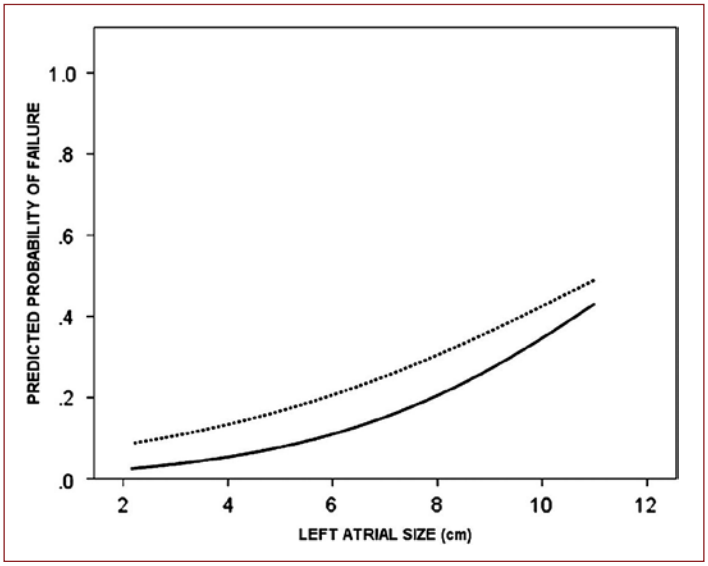

Figure 1: Predicted probability of failure (AF) at 12 months (solid line) and failure (AF or normal SR on antiarrhythmic medications) at 12 months (dashed line) across left atrial size as a continuous variable. Originally published in: Ad N, Henry L, Hunt S, Holmes SD. Should surgical ablation for atrial fibrillation be performed in patients with a significantly enlarged left atrium?. J Thorac Cardiovasc Surg 2014;147:236-41.

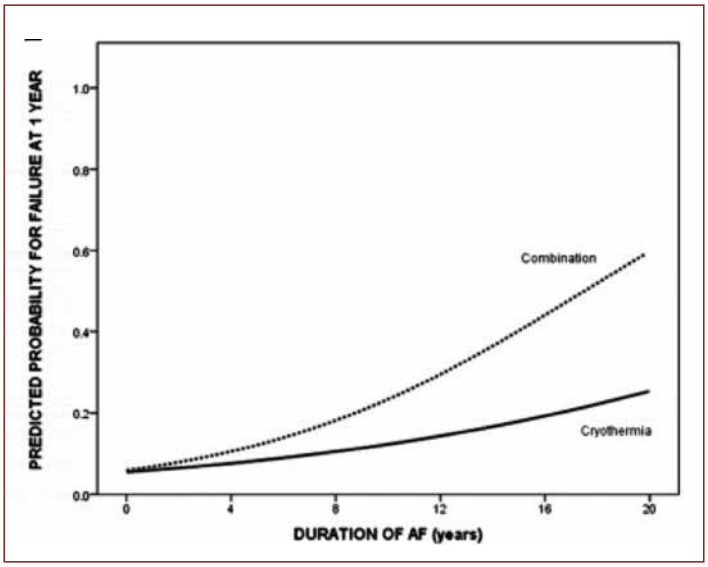

Figure 2: Spline curves demonstrating the association of predicted probability of failure and duration of atrial fibrillation (AF) by energy source at 1 year after surgery. Originally published in: Ad N, Holmes SD, Shuman DJ, Pritchard G. Impact of atrial fibrillation duration on the success of first-time concomitant Cox maze procedures. Ann Thorac Surg 2015;100:1613-9.

standardisation in surgical ablation [23]. The study was designed to grant an FDA indication to the radiofrequency platform from Medtronic (Minneapolis, MN) and failed to demonstrate the primary endpoint. A closer look into the study revealed significant differences in success rates among surgeons despite all centres using the same study protocol, including the proposed lesion set. Significant differences were also revealed in the way the devices were utilised and the duration of each lesion application. This phenomenon is probably related to lack of standard training and experience among the participating centers and it is a good reflection on the current state of surgical ablation, at least in the United States. Therefore, the AATS recommendations on training and proctoring are an important first step to improve and standardise surgeon experience.

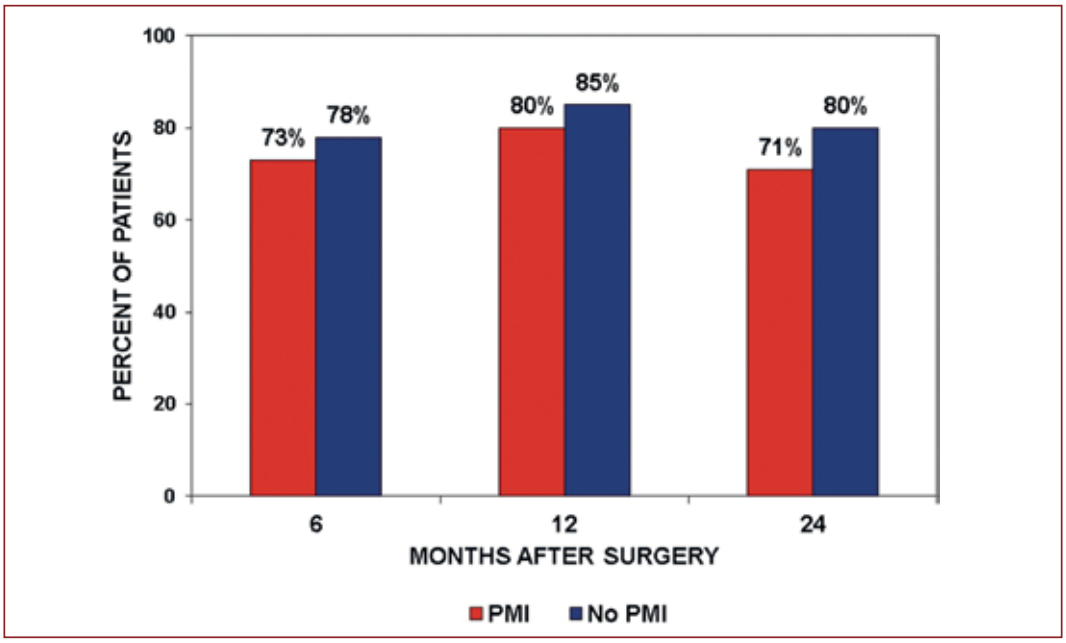

Figure 3: Percent of Cox maze patients with and without in-hospital pacemaker implantation (PMI) who returned to sinus rhythm off antiarrhythmic drugs during follow-up. Originally published in: Ad N, Holmes SD, Ali R, Pritchard G, Lamont D. A single center's experience with pacemaker implantation after the Cox maze procedure for atrial fibrillation. J Thorac Cardiovasc Surg 2017;154:139-146.

Conclusion

In summary, for the vast majority of cases, patients with a history of AF at the time of mitral valve surgery should be surgically ablated if their clinical condition allows. Surgeons should be familiar with the pathophysiology of AF, the technical aspects of the procedure, and the appropriate energy sources to use. Even in cases with longer duration of AF and large left atrial size, the procedure can be very effective. In cases when the decision is made to not ablate a patient with a history of AF, it is appropriate to consider resection or exclusion of the left atrial appendage [5].

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Chapter 7

Mild to Moderate Tricuspid Regurgitation: Should We Perform Concomitant Tricuspid Valve Repair?

Manuel J Antunes

"Quidquid agis, prudenter agas, et respice finem"

Introduction

In 8-10% of cases, tricuspid regurgitation (TR) is of **primary** organic origin. It may be isolated (e.g. congenital, radiation, drugs, pacemaker or defibrillator leads, trauma, infective endocarditis, rheumatic or myxomatous disease) or associated with (but not caused by) left-sided mitral or aortic valve disease, usually of rheumatic origin [1]. In these cases, there is pathological involvement of the tricuspid valve (TV) leaflets and, in some cases, of the chordae tendineae. In chronic cases, the annulus may also be enlarged.

More commonly, in approximately 90% of the cases, TR is **secondary** (functional) to left-side valve disease and/or pulmonary hypertension. The incidence of TR associated with left-sided valve disease has been reported to be from 8% to 35% [4, 5]. In 80-90% of such cases, the TR is truly secondary but in 10-15% of the cases, the lesion is primarily organic (usually rheumatic).

In functional TR, the valve leaflets are morphologically normal, with the regurgitation resulting from dilatation of the annulus and loss of leaflet coaptation. This itself is a consequence of enlargement of the right ventricle (RV), with or without some degree of ventricular dysfunction [2]. Where left sided disease is present, the function of the RV typically parallels that of the left ventricle with the development of pulmonary hypertension, but RV dysfunction may also occur in an isolated manner. In such circumstances, chronic TR may precipitate a vicious cycle of dysfunction and dilatation that can only be resolved by surgical intervention on the tricuspid valve. Prolonged RV volume overload due to chronic TR may result in irreversible RV myocardial damage [3]. Tricuspid regurgitation resulting from significant RV dysfunction has a mortality of up to 50% at 5 years. In these cases, cardiac transplantation may be necessary.

This chapter will be exclusively dedicated to the subject of secondary TR.

Management of Tricuspid Regurgitation

Medical therapy may be used in TR secondary to left-sided valve disease that does not require surgery. In most of these cases, tricuspid valve intervention for mild or moderate TR is not indicated, but other considerations apply when mitral or aortic valve surgery is required.

In the early days, a conservative (non-touch) approach to the tricuspid valve was adopted based on the philosophy, enunciated by Nina Braunwald et al. [6], that in the "majority" of patients with secondary TR, surgical treatment of the mitral (or aortic) valve disease would correct the problems of the right side. Consequently, until about a decade and a half ago, the tricuspid valve was largely ignored during surgery of the left-sided valves, giving rise to the term "the forgotten valve".

However, it started to become apparent that the results of surgery of the mitral valve were less favourable in patients with associated right heart disease. Right ventricular disease with significant involvement of the tricuspid valve represents advanced disease that has a profound effect on the natural history after surgery. Even when intervention on the mitral valve has long-term success, in many cases there is a progressive increase of the TR because functional TR with severe annular dilatation can cause irreversible deterioration of the RV function [3]. Furthermore, a long clinical course can cause further clinical and haemodynamic deterioration, therefore increasing risk at the time of surgery.

Today, nobody questions the need for intervention on the tricuspid valve in patients with severe TR during surgery for left-sided valve disease. The discussion arises with lesser degrees of TR. A little over a decade ago, Gilles Dreyfus and colleagues published a seminal observational paper under the title of *Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair?* [7] In this work, the authors measured the tricuspid annulus intra-operatively of all sequential patients submitted to left-sided heart valve surgery (Figure 1) and came to the conclusion that "secondary tricuspid dilatation is present in a significant number of patients with severe mitral regurgitation without tricuspid regurgitation and it is a progressive disease which does not resolve with correction of the primary lesion alone". Their conclusion was that "tricuspid annuloplasty at the time of mitral valve surgery in these patients results in improved functional capacity without any increase in perioperative morbidity or mortality".

The authors came short of recommending prophylactic tricuspid annuloplasty in all patients subjected to left-side valve surgery. This hypothesis had been suggested much earlier by Professor John Barlow in 1987 who stated that "it is probable that this lesion (tricuspid regurgitation) is often partly or mainly organic" [8]. At that time, he was my Chief of Cardiology and often insisted on us as surgeons to be more aggressive with the treatment of TR.

Dreyfus's findings were later confirmed by Van de Veire in 2011, from Robert Dion's Group in Leiden, who found that "concomitant tricuspid annuloplasty during mitral valve repair should be considered in patients with tricuspid annular dilatation despite the absence of important tricuspid regurgitation at baseline, because this improves echocardiographic outcome" [9]. In another work published in the same year by Calafiore et al., it was concluded that "an aggressive strategy for functional TR correction, using the systolic tricuspid annular diameter, was able to reduce the TR grade at one year after surgery, but mitral surgery alone could not" [10].

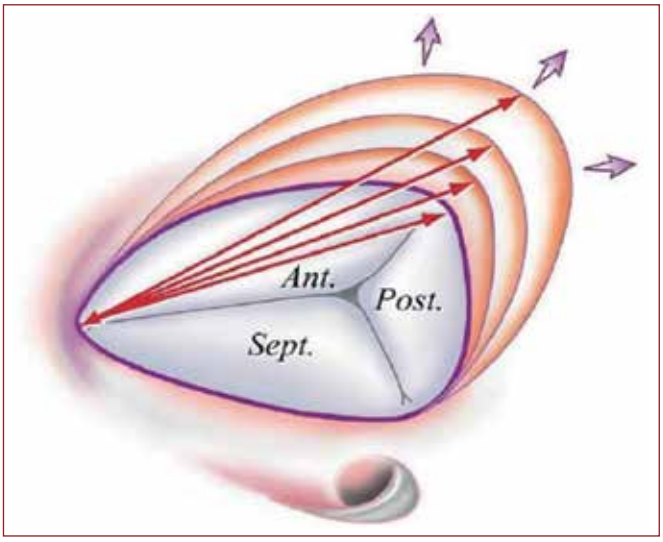

Figure 1: Pathological process of tricuspid annular dilatation. Arrows designate the intercommissural distance that increases with dilatation and that was measured intraoperatively. (Ant. = anterior; Post. = posterior; Sept. = septal.). (Reproduced, with permission, from Dreyfus G et al. [7])

These and other similar studies were the basis for modifications in the guidelines on both sides of the Atlantic. The 2012 ESC/EACTS Guidelines for Management of Valvular Heart Disease clearly stated that "Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus (≥40 mm or >21 mm/m^2) undergoing left-side valve surgery" as a Class IIa indication (Level of Evidence C) [11]. The task force, of which I was a member, then felt that there was no evidence that favoured tricuspid intervention in cases of less than mild TR, irrespective of the annular dimension, and this remains a grey area.

That recommendation was kept unmodified in the 2017 Guidelines, but the following was also added: "Surgery may be considered in patients undergoing left-sided valve surgery with mild or moderate secondary tricuspid regurgitation even in the absence of annular dilatation when previous recent right heart failure has been documented" as a Class IIb recommendation (Level of Evidence C) [12].

The 2014 AHA/ACC guidelines, on the other hand, classify the following as Class IIa indications (should be considered):

1. Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional TR at the time of left-side valve surgery with either tricuspid annular dilation or prior evidence of right heart failure (Level of Evidence: B);
2. Tricuspid valve surgery can be beneficial for patients with symptoms due to severe primary TR that are unresponsive to medical therapy (Level of Evidence: C) [13].

In contrast to the European guidelines, the AHA/ACC also indicated as Class IIb that "tricuspid valve repair may be considered for patients with moderate functional TR and pulmonary artery hypertension at the time of left-side valve surgery" (Level of Evidence: C). The role of pulmonary hypertension in this recommendation remains a focus of discussion.

These guidelines were developed on the basis that, in the majority of experienced centres, the addition of tricuspid valve intervention does not appear to increase procedural morbidity and mortality to any degree.

Another subject of controversy is the degree of annular dilatation. There are no studies that categorically define the difference between normal and dilated. In contrast, there is great variability in the diameter of the tricuspid annulus in healthy patients, with

absolute values that exceed the 40mm indicated in the guidelines [14]. To compound this, echocardiographic evaluation of the tricuspid valve is difficult and subject to considerable interobserver variability. The individual size of the annulus and the degree of TR are highly variable and very dependent on the haemodynamic conditions. For these reasons, the decision regarding tricuspid valve intervention must be made pre-operatively and based on sequential echocardiographic evaluations.

Despite all the apparent evidence pointing towards a more aggressive approach to the treatment of secondary tricuspid regurgitation, the controversy persists. For example, it is still not entirely clear if this approach is similarly applicable to all types of left-sided valve pathology, especially with regards to rheumatic versus degenerative mitral valve disease. After a very heated discussion in a recent Mitral Valve Conclave involving David Adams and Tirone David, the Toronto group recently suggested that "a tricuspid annulus diameter ≥40 mm is not predictive of the development of postoperative TR after mitral valve repair for degenerative diseases" [15].

Similarly, Yilmaz et al. from the Mayo Clinic found that "clinically silent non-severe tricuspid valve regurgitation in patients with degenerative mitral valve disease is unlikely to progress after mitral valve repair and that tricuspid valve surgery is rarely necessary for most patients undergoing repair of isolated mitral valve prolapse" [16]. Hence, these authors call for "a selective approach" to the tricuspid valve in this pathology.

These differences in evidence, and maybe opinion, are the reason why the incidence of repair for tricuspid regurgitation during surgery for left-sided heart valve disease are so variable from institution to institution and even among surgeons within the same surgical

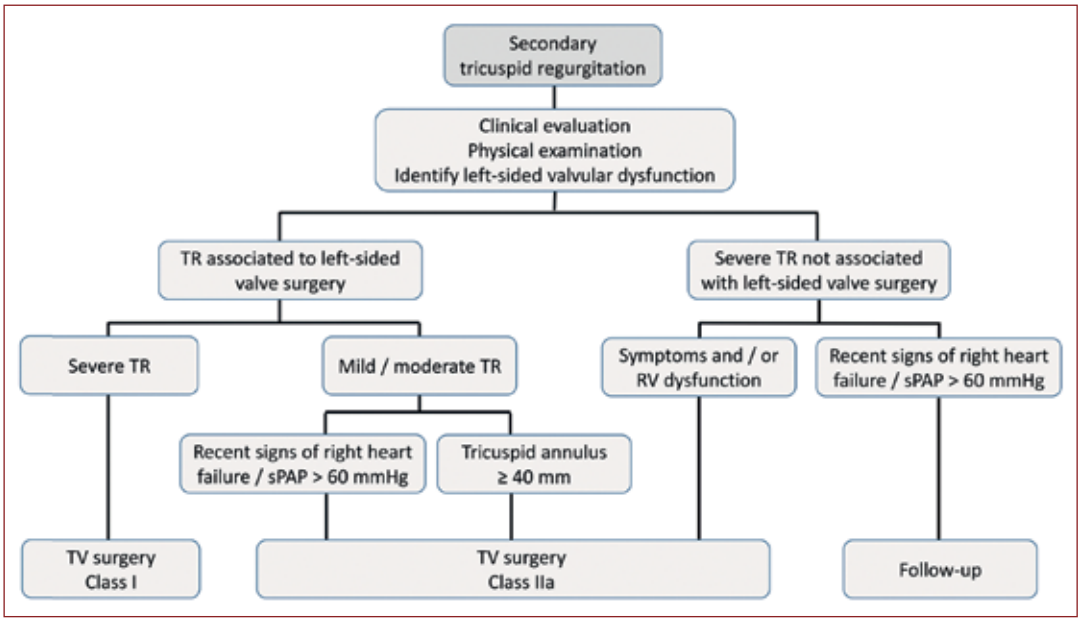

Figure 2: Indications for intervention on secondary TR (Reproduced, with permission, from Antunes MJ et al.) [17].

group. Rates of repair from 20-75% have been reported and may even be lower in some groups. Clearly, the level of adherence to the guidelines is short of expected and far from ideal.

But the guidelines dedicate little space to the tricuspid valve, usually amounting to no more than one table and a couple of paragraphs. In order to assist in clarifying some aspects related to TR and its management, the Working Groups of Valvular Heart Disease and of Cardiovascular Surgery in the ESC recently issued a position statement on the management of tricuspid valve regurgitation [17]. In this document, aspects related to the clinical and pathological presentation as well as the diagnosis and treatment of TR are extensively reviewed. Figure 2 summarises the indications for intervention on the tricuspid valve in patients presenting for surgery of the left-sided valves. Naturally, these comply with the European guidelines.

How to Intervene on the Tricuspid Valve

Aside from the indications for surgery, there are several other debates in tricuspid valve surgery:

1. The choice between annuloplasty and replacement,
2. The efficacy of different methods of annuloplasty,
3. The choice of prosthesis (rings and valves).

In my view, only exceptionally will the TV need to be replaced as a first procedure, especially in secondary TR, because the valve tolerates well a less-than-perfect repair. Hence, annuloplasty is the procedure of choice. Effectively, dilatation of the annulus is the predominant lesion of the valve in secondary TR. Thus, repair by annuloplasty alone is relatively easy, reproducible and effective, and is now the procedure of choice, used in more than 90% of the cases included in the Society of Thoracic Surgeons Database [18]

Tricuspid annuloplasty

The main annuloplasty procedures are the bicuspidisation or Kay procedure (1965), the De Vega suture (1972) and the use of rings/bands (rigid or flexible), of which the Carpentier ring (1971) is the most commonly used.

Ghanta et al. from Cohn's group in Boston reported in 2007 on 237 patients who underwent tricuspid annuloplasty for functional tricuspid regurgitation as part of their cardiac surgical procedure from 1999 to 2003 [19]. Bicuspidisation was performed in 157 patients and ring annuloplasty in 80 patients. They found that "bicuspidisation annuloplasty and ring annuloplasty were effective at eliminating tricuspid regurgitation at 3 years postoperatively", hence concluding that bicuspidisation annuloplasty is a "simple, inexpensive option for addressing functional tricuspid regurgitation". In this series, there was no statistically significant difference in mortality between the two groups, however, the ring annuloplasty patients demonstrated a trend towards poorer survival ($p=0.07$). This group also had a lower preoperative ejection fraction and greater preoperative TR than the bicuspidisation group, which might account for that finding. Similar findings were observed concerning freedom from moderate to severe recurrent TR.

The De Vega annuloplasty, which preserves the tricuspid morphology of the valve and covers the whole length of the annular segments involved by the dilatation process, was the most widely used method for some two to three decades. Sarralde et al., from Santander, Spain,

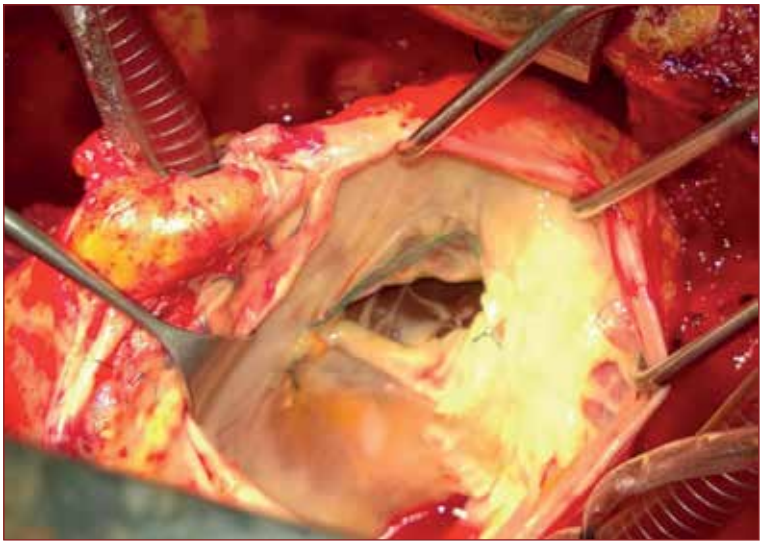

Figure 3: Guitar-string syndrome caused by dehiscence of the annuloplasty suture (De Vega).

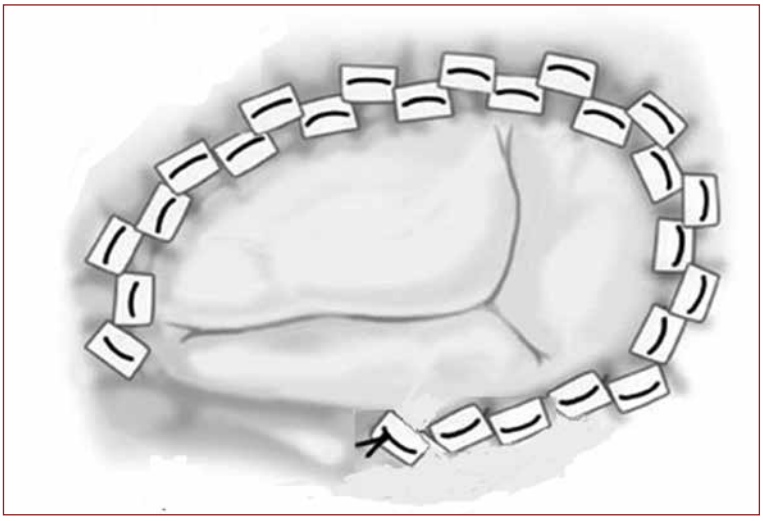

Figure 4: Modification of the De Vega, consisting of interposition of Teflon pledgets to prevent dehiscence

reported better results with the conventional De Vega suture annuloplasty compared to the ring annuloplasty [20]. Suture annuloplasties, it should be noted, are easily performed and inexpensive.

In contrast, Tang et al., from Tirone David's group in Toronto, found that placement of an annuloplasty ring in patients undergoing tricuspid valve repair was associated with improved event-free survival [21].

These differing findings were finally consolidated in a meta-analysis performed by Khorsandi et al., who identified seven studies and concluded that ring annuloplasty had the lowest rate of recurrence compared with the De Vega suture [22]. They reviewed one recent study and four older studies which showed no significant difference between the two techniques, and two studies that reported De Vega's suture repair as a superior technique to ring annuloplasty. Overall, it appears that ring annuloplasty is associated with lower rates of recurrence of TR but this did not translate into differences in patient survival.

Suture and ring annuloplasties each have specific complications associated with them. Pfannmüller et al., from Leipzig, reported an increased risk of dehiscence after tricuspid valve repair with rigid annuloplasty rings [23]. Suture annuloplasties are also prone to dehiscence which is typified by the 'guitar-string syndrome' leading to recurrence of tricuspid insufficiency after the De Vega procedure (Figures 3 & 4). To avoid this complication, Antunes et al. described a modification of the De Vega annuloplasty that consists of interposition of a Teflon pledget between every annular bite [24].

The end result is a very flexible 'band' that partially encircles the tricuspid annulus to a similar extent as that covered by most rings currently in use. It is a fast, technically simple, reproducible and inexpensive procedure. In our experience of over two thousand procedures, extending for more than 30 years, I have never seen a case of dehiscence. Furthermore, the incidence of clinically significant recurrent TR was very low, with only a few cases requiring re-intervention on the tricuspid valve. Of importance, this modification extends the suture well into the septal segment of the annulus, as happens with most ring techniques, which may have a significant impact on the results.

I believe that the implantation of a ring is specifically indicated when there is organic involvement of the TV, usually with stenosis, where commissurotomy is also necessary, as frequently occurs in rheumatic cases [25,26].

Tricuspid valve replacement

Irrespective of the repair technique used, recurrence of TR is much more frequent and severe in patients in whom enlargement of the annulus is associated with significant dilatation of the RV, especially in the presence of severe ventricular dysfunction. In these cases, severe tenting of the tricuspid valve precludes a good result with any method of annuloplasty. Many experienced groups, therefore, would opt for TV replacement in such cases. As an alternative, anterior leaflet augmentation has been suggested to compensate for leaflet tethering and to push the coaptation line deeper into the RV [27].

In the case of replacement, the choice of prostheses is influenced by multiple prosthesis and patient-related factors, similar to replacement of left-sided heart valves. However, bioprostheses may degrade faster and mechanical valves may be prone to more thromboembolic complications in this position. Garatti et al. analysed the twenty-five-year outcomes of TV replacement comparing mechanical and biologic prostheses and found that the type of implanted prosthesis in the tricuspid position did not affect early or long-term outcomes or rates of reoperation [28]. They further concluded that referral before the development of end-stage cardiac impairment could further improve outcomes.

As is already observed with replacement of the left-sided heart valves, the emergence of percutaneous valve-in-valve implantation may shift the balance towards bioprostheses for TV replacement. Although primary percutaneous tricuspid valve replacement or repair have now been experimentally utilised in cases of primary isolated TR or for the treatment of recurrent TR after valve surgery, for the time being there appears to be no indication for use in patients being subjected to left-sided heart valve surgery.

Conclusion

Secondary tricuspid annular dilatation is present in a significant number of patients with severe mitral regurgitation without tricuspid regurgitation. It is a progressive disease which does not resolve with correction of the primary lesion alone. In patients with mild

to moderate TR, tricuspid annuloplasty at the time of left-sided heart valve surgery results in improved functional capacity without increase in perioperative morbidity or mortality. The quality of the repair of the left-sided valvulopathy appears fundamental to avoiding late tricuspid regurgitation.

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SECTION 1 CARDIAC SURGERY

Aortic Surgery

"Non est ad astra mollis e terries via"

Lucius Annaeus Seneca (5BC-65AD)

Chapter 8

Recent Major Trials and Guidelines Update in Type B Acute Aortic Dissection

Salome Weiss, Thomas Wyss and Thierry Carrel

"Sua cuique sponsa, mihi mea; suum cuique pulhrum"

Introduction

Acute aortic dissection is a life-threatening pathology with an incidence ranging from 2.9 to 3.5 per 100,000 patient years [1,2]. Based on the anatomic involvement of the aorta, aortic dissection was first classified by DeBakey in 1965 [3]. Daily et al. later emphasized the prognostic differences between aortic dissection with and without involvement of the ascending aorta, introducing the Stanford classification [4]. This has thereafter dictated the management of acute aortic dissection. While Stanford type A aortic dissection (with involvement of the ascending aorta) is treated by emergency graft replacement of the ascending aorta, patients with Stanford type B aortic dissection (not involving the ascending aorta) have traditionally been managed medically, with open surgery reserved for those with complications such as organ malperfusion or rupture.

The advent of endovascular therapeutic modalities has dramatically changed the management of acute type B aortic dissection in the past few decades. Since the first reports of thoracic endovascular aortic repair (TEVAR) for the treatment of aortic dissection in 1999 [5,6], TEVAR has rapidly evolved to be the therapy of choice in complicated type B aortic dissection and is increasingly being considered an option in uncomplicated type B aortic dissections to prevent late aortic complications [7-9]. Comparable data for medical management, TEVAR and open surgery in type B acute aortic dissection are, however, relatively scarce and most data come from observational studies or registries. Thus, controversies remain. This chapter provides an overview of recent evidence and current guidelines concerning the management of acute type B aortic dissection. Acute dissection is defined as within 14 days of symptom onset.

Medical Therapy

Optimal medical therapy is one of the most important steps in the management of every patient with aortic dissection. The primary aim is to reduce aortic wall stress to prevent false lumen propagation and acute dilatation and thereby avoid branch vessel compromise

and aortic rupture. Aortic wall stress is affected by blood pressure as well as by the velocity and rate of left ventricular ejection. By modifying these factors, beta-blockers are the first line medication to reduce aortic wall stress. All current guidelines recommend beta-blockers as primary medical therapy in aortic dissection to reach the targets of a systolic blood pressure between 100-120 mmHg and a heart rate below 60 beats/minute [7,8,10].

In both the acute as well as in the chronic phase, however, additional drugs are often necessary to adequately control blood pressure. Patients with chronic aortic dissection have been reported to need a median of four antihypertensive drugs [11]. The most recent European guidelines recommend calcium channel antagonists and renin-angiotensin inhibitors complementary to betablockers [8]. Data from the International Registry of Acute Aortic Dissection (IRAD) show that the use of betablockers is associated with overall improved survival in patients with type A and type B aortic dissection. The use of calcium channel antagonists is associated with improved survival in patients with type B dissection while the use of angiotensin-converting enzyme inhibitors is not associated with this [12]. Besides the IRAD data, there is currently little evidence for targeted approaches in the medical management of type B aortic dissection.

Before medical therapy was introduced for the management of type B aortic dissection in 1965, the only alternative treatment was open surgery, usually including graft replacement of the descending thoracic aorta with inherently high mortality and complication rates [4,13]. Early data from the IRAD registry showed a relatively low in-hospital mortality of 10% for patients with medically managed type B dissection.

In patients with uncomplicated type B dissection alone, a retrospective single-centre study showed in-hospital mortality for medical management of 1.2% [14]. Due to the inherently low risks and favorable short-term outcome, medical therapy soon emerged as the standard of care for uncomplicated type B dissection and is the recommended treatment strategy in all current guidelines [7,8,10].

A relatively recent expert consensus paper summarised outcomes for 1480 patients with medically managed type B dissection from the published literature. Due to the heterogeneity of the available studies, the majority – but not all – included patients with uncomplicated dissection. The pooled early mortality rate was 6.4% and the pooled rates of early stroke and spinal cord ischaemia with medical treatment were 4.2% and 5.3 %, respectively [15].

Despite acceptable early outcomes for medically-treated uncomplicated type B aortic dissections, longer-term results have made it evident that the natural history of these patients is not as benign. Data from the IRAD showed that out of the patients discharged alive after medical treatment of acute type B dissection, only 77.6% survived up to three years [16]. In a single-centre series, 58.4% of patients had failed medical treatment of uncomplicated type B dissection after a mean follow-up of 4.3 years, failure being defined as death or aorta-related intervention. Most interventions (66%) were performed for aneurysmal degeneration. Estimated intervention-free survival was 55% at 3 years and 41% at 6 years [17]. Another centre reported an intervention-free survival of 84.8% and 62.7% at 1 and 5 years, respectively [18]. The most recent series included 318 patients with uncomplicated type B dissection initially treated with medical therapy. Among these, estimated intervention-free survival was 49.4% at 5 years and 30.9% at 10 years [19].

TEVAR in Aortic Dissection

The concept of TEVAR in aortic dissection is based on the idea of stent-graft induced aortic remodelling. In theory, a relatively short stent-graft can be used to cover the proximal entry tear in the descending aorta. This allows immediate depressurisation of the false lumen and re-expansion of the true lumen, as well as restoring blood flow to the branch vessels in the majority of cases. Moreover, coverage of the entry tear is thought to induce false lumen thrombosis. This leads to further expansion of the true lumen and reduction of the false lumen by retraction of the thrombus and thus, aortic wall stabilisation or remodeling [6]. Therefore, in addition to treating malperfusion and avoiding rupture in the acute setting, TEVAR is thought to have the potential to stabilise the aorta in the long-term, preventing late complications.

The most important complications of TEVAR in type B aortic dissection are retrograde type A dissection, stroke caused by guidewire manipulation in the aortic arch, and paraplegia. To reduce the risk of retrograde dissection, proximal bare metal stent fixation and balloon moulding to ensure complete stent-graft expansion are avoided and graft oversizing is minimised. Appropriate proximal sealing often requires coverage of the left subclavian artery. Proper true lumen access has to be ascertained before stent-graft delivery. The length of the aorta to be covered by the stent-graft for optimal true lumen stabilisation is still a matter of debate. Although coverage of the proximal entry tear may theoretically induce false lumen thrombosis over the entire length of the dissected aorta, thrombosis often does not occur distal to the stent-graft [20]. To increase the extent of aortic coverage without increasing the risk of paraplegia, the use of bare metal stents for distal extension after TEVAR has been proposed [21].

Nienaber et al. later introduced this technique as the Provisional Extension to Induce Complete Attachment (PETTICOAT) technique and reported its use in 12 patients with distal true lumen collapse and perfused abdominal false lumen despite previous successful sealing of the proximal entry tears with a stent-graft [22].

TEVAR in Complicated Type B Acute Aortic Dissection

After the two sentinel reports of the use of TEVAR in aortic dissection in 1999 [5,6], this technology quickly gained popularity as an alternative to open surgery in those with complicated type B dissection. Dake et al. had shown that TEVAR resulted in revascularisation of ischaemic branch vessels with subsequent relief of corresponding symptoms in 76% [5]. An early meta-analysis of 609 published cases of TEVAR in aortic dissection showed a technical success rate of 98.2% with a 30-day mortality of 5.3% and major complications in 11.2%. Periprocedural stroke occurred in 1.9% and paraplegia in 0.8%. Complication rates and in-hospital mortality depended on the acuity of the pathology: TEVAR in acute dissection had a significantly higher 30-day mortality than in chronic dissection (9.8 vs. 3.1%, $p=0.015$) [23]. Another meta-analysis including 942 patients with complicated type B dissection undergoing TEVAR showed a 30-day mortality of 9% and a stroke and paraplegia rate of 3.1% and 1.9%, respectively [24]. These numbers compare favourably to historical data for open surgical repair in acute type B dissection. Thus, despite the lack of randomised trials, TEVAR is now considered the first-line treatment of acute complicated type B dissection. While a recommendation for TEVAR in complicated type B dissection was lacking in the 2010 ACCF/AHA guidelines (due to the lack of randomised data), it is a Class I recommendation in both the 2014 European Society of Cardiology (ESC) and the most recent 2017 European Society for Vascular Surgery (ESVS) guidelines [7,8,10].

The aforementioned expert consensus document summarised outcomes from 2359 patients undergoing TEVAR for acute aortic dissection from several published studies (mostly including complicated dissections, but with variable criteria). The pooled early mortality rate was 10.2% with pooled rates of stroke and spinal cord ischaemia of 4.9% and 4.2%, respectively [15]. However, there is a paucity of reported long-term results after TEVAR. High rates of reintervention have been brought up as a potential disadvantage of TEVAR in aortic dissection. A recent meta-analysis reported a pooled incidence of reintervention of 15% after 33.7 months of follow-up among 2403 patients from 27 studies reporting reintervention after TEVAR in aortic dissection. The most common reasons for reintervention were endoleak in 33.2%, false lumen perfusion and associated aortic dilatation in 19.8%, and new dissection in 6.9% [25].

Further controversy exists regarding the efficacy of TEVAR in subacute and chronic complicated aortic dissection. The VIRTUE registry, a prospective multicenter European registry, aimed at assessing outcomes for TEVAR in complicated type B dissection with regard to the acuity of presentation. The registry enrolled 100 patients with complicated type B aortic dissection. Outcomes were analysed after 3 years of follow-up by urgency of aortic dissection at the time of TEVAR. The 30-day mortality was 8%, 0%, and 0% for acute, subacute, and chronic dissections, respectively, while 3-year dissection-related mortality was relatively low at 12%, 4%, and 9%. The most important finding, however, was that TEVAR in subacute dissection demonstrated similar aortic remodeling to TEVAR in acute dissection, suggesting that aortic plasticity and susceptibility to stent-graft induced remodeling extends over more than the first two weeks after index dissection [26,27].

The Study of Thoracic Aortic Type B Dissection Using Endoluminal Repair (STABLE) trial was a prospective, non-randomised, multicenter clinical trial conducted in the United States, Europe, and Australia, evaluating the PETTICOAT technique in patients with complicated type B dissection, using a dedicated endovascular system including a proximal stent-graft and distal bare metal dissection stents. The trial enrolled 40 patients, the majority with an acute presentation. The reported 30-day mortality was 5% and stroke and paraplegia rates were 7.5% and 2.5%, respectively. One-year survival rate was 90% and 10% underwent reintervention within a year [28].

TEVAR in Uncomplicated Acute Type B Aortic Dissection

Due to the high rates of patients failing medical management of uncomplicated type B dissection in the long-term, the pre-emptive use of TEVAR has increasingly been advocated. It has been shown to induce early false lumen thrombosis [6], while a patent false lumen has been identified as an independent risk factor for dissection-related death in the long-term [29]. In recent years, two prospective multicenter randomised trials aimed to clarify the role of TEVAR in the treatment of uncomplicated type B dissection: the ADSORB (Acute Dissection Stentgraft OR Best Medical Treatment) trial and the INSTEAD (Investigation of Stent grafts in Aortic Dissection) [20,30]. Both randomised patients with uncomplicated type B aortic dissection to optimal medical therapy (OMT) alone or to TEVAR in addition to OMT. The ADSORB trial randomised patients with acute aortic dissection, i.e. within 14 days of symptom onset, while the INSTEAD trial specifically excluded patients within 14 days of the index event to allow a period to identify early complications, thus excluding patients qualifying as complicated, who were already known to benefit from TEVAR.

ADSORB was an industry-funded trial which randomised 61 patients with acute uncomplicated type B aortic dissection in 17 European centers; 31 were randomised to

OMT and 30 were randomised to OMT + TEVAR, with TEVAR performed a median of 5.5 days following onset of symptoms. There were notably three crossovers from the OMT to the OMT + TEVAR group due to disease progression within one week and two withdrawals from TEVAR. The primary endpoint was a combination of incomplete or no false lumen thrombosis, aortic dilatation and aortic rupture at 1 year. The endpoint was reached by all 31 OMT patients but only by 50% of OMT + TEVAR patients ($p<0.001$), although 14 patients did not have follow-up imaging and were therefore considered to have reached the endpoint. Incomplete or no false lumen thrombosis was found in 97% of those with OMT and in 43% of those with OMT + TEVAR ($p<0.001$). Although the occurrence of aortic dilatation was equally common in OMT and OMT + TEVAR (45% vs. 37%; $p=0.5$), the maximum false lumen diameter was reported to be significantly smaller after OMT + TEVAR. There were no 30-day deaths and only one death in the OMT + TEVAR group during follow-up, but the trial was not powered for mortality [20].

The INSTEAD trial, also industry-supported, included patients with uncomplicated type B dissection "in a stable clinical condition", i.e. between 2 and 52 weeks following onset of symptoms. A total of 68 patients were randomised to OMT alone and 72 patients were randomised to OMT + TEVAR. At 2 years, the trial failed to show improved survival or decreased adverse events for TEVAR compared to OMT alone. However, thoracic false lumen thrombosis as an indicator for aortic remodelling was found in 91.3% of patients with TEVAR but only 19.4% of patients with OMT alone. Under rigourous medical therapy according to the study protocol, mortality was lower than expected in both arms of the trial and the authors concluded that the study was therefore underpowered.

In the INSTEAD-XL trial, the same 140 patients were retrospectively analysed for late outcomes using landmark analysis of years 2 to 5 after the initial aortic dissection. The authors were now able to show lower all-cause mortality (11.1% vs. 19.3%, $p=0.13$), aortic-specific mortality (6.9% vs 19.3%, $p=0.04$), and progression (27.0% vs. 46.1%, $p=0.04$) for TEVAR when compared to medical management after 5 years.

These trials have impacted recent guidelines. Endovascular aortic repair in uncomplicated type B dissection is now defined as a IIa recommendation in the 2014 ESC Guidelines, and a IIb recommendation in the 2017 ESVS guidelines [7,8]. However, the recommendation to consider TEVAR in uncomplicated type B dissection leaves room for further uncertainty: in particular, the question on how to identify patients who might actually benefit from pre-emptive TEVAR. Specific imaging features such as total aortic diameter, false lumen size and thrombosis, and tear size and location may play a role in this selection process.

Conclusion

As illustrated in this overview, knowledge regarding the management of acute aortic dissection is predominantly derived from retrospective series and registries such as the IRAD. Only two major randomised trials have been conducted, the ADSORB and the INSTEAD trial, but the questions they aimed to answer continue to be a matter of debate. In brief, the current recommendations and guidelines for the management of acute aortic dissection are:

- Medical therapy remains of major importance in all patients with aortic dissection.
- In complicated type B dissection, TEVAR is recommended as treatment in addition to medical therapy.

- In uncomplicated type B dissection, medical management is still the first-line treatment, but pre-emptive TEVAR may be considered. Patients who may benefit from early intervention in the absence of complications are yet to be identified.

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Chapter 9

What to Do with The Aortic Root in Type A Acute Aortic Dissection

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"Ut desint vires, tamen est laudanda"

Introduction

Surgery represents the best therapeutic option for patients with type A acute aortic dissection (TAAAD). Basically, the primary aim of the operation is to save the patient's life, usually by excision of the intimal tear in the ascending aorta, followed by supracoronary ascending aortic replacement up to the hemiarch. Repair of the dissected aortic root, including commissural resuspension, reapproximation of the layers with or without Teflon felt and biological glues, and potential aortic valve replacement (AVR) usually concludes the procedure.

The evolution of surgical techniques as well as cerebral and end-organ protection strategies has fuelled an increasing debate regarding more aggressive strategies [1], including aortic root and arch replacement during surgery for TAAAD, without achieving a consensus [2-4]. In fact, the idea of extensive aortic repair, including aortic root replacement, is not recent. Thirty years ago, Massimo et al. suggested a total aortic repair strategy, from the valve to the bifurcation in the setting of TAAAD [5]. Thirty years later, the question remains unanswered regarding both the aortic root and arch in the setting of TAAAD.

When the aortic root is preserved, late aortic root events, such as aortic regurgitation, dilatation and formation of pseudoaneurysms, have been reported to occur in 9% to 27% of TAAAD patients after the primary surgery [6]. Root repair at the time of TAAAD repair, by avoiding late aortic dilatation and re-dissection, and by lessening recurrence of aortic insufficiency, is in fact expected to reduce late mortality and reintervention but is also perceived to carry higher immediate mortality [6]. In order to address this issue, one must answer the concerns regarding the fate of the spared aortic root after surgery for TAAAD, the risk of reoperation for late aortic root events after the primary surgery for TAAAD, and whether the root replacement technique impacts the outcomes.

The purpose of this chapter is therefore to discuss the management of the aortic root in the setting of TAAAD, by reporting the experience of a French aortic centre. To put it elegantly, to replace or not to replace, that is the question.

Management of The Aortic Root in Type A Acute Aortic Dissection

Conservative Root Management (CR) Versus Root Replacement (RR)

The current guidelines date back to 2010 and 2014 and partially address the issue of aortic root management during surgery for TAAAD [7,8]. It is recommended to replace the aortic root in the case of extensive root dissection, or if the root is dilated. Otherwise, the root can be preserved and repaired with aortic valve resuspension. In both guidelines, the level of evidence remains poor, and several questions remain unanswered.

In more recent literature, several studies have compared root management strategies in the setting of TAAAD. The International Registry of Acute Dissection (IRAD) in 2014 reported the data of 1995 patients with TAAAD [9]. Conservative root (CR) management was performed in 65% of the patients while 35% of the patients had root replacement (RR). Mid-term analysis revealed comparable in-hospital mortality, supporting a more aggressive approach, especially in younger patients, patients with connective tissue diseases and bicuspid aortic valves. Moreover, it also demonstrated similar results regarding survival and freedom from root reintervention at 3 years.

In a multicentre study by Peterss et al., 74% of patients had a root-sparing technique while 26% underwent root replacement, with comparable in-hospital mortality in 338 patients with TAAAD (15% versus 20% respectively, p=0.31) [15]. They also demonstrated similar 10-year survival, and 92% of freedom from reoperation at 10 years in supra-coronary repairs.

In a retrospective study, Nishida et al. evaluated the aortic root management strategy in 316 patients with TAAAD [6]. A supra-coronary repair was performed in 87.3% of patients, while 12.7% underwent aortic root replacement. In-hospital mortality was higher in the patients with RR (12.5% versus 4.7%, p=0.05). Late aortic root events at 5 years were also more frequent when the aortic root was preserved (11.6% versus 0%, p=0.029), mostly dilatation of the aortic root, requiring reintervention in only 3 patients (1%). The authors also demonstrated that dissection of two or more sinuses at the time of TAAAD surgery was predictive of late aortic root events.

In order to prevent such events, Rylski et al. have suggested a partial repair technique of the aortic root in 489 patients with TAAAD, based on aortic valve resuspension and aortic root neomedia reconstruction using Teflon felt with an in-hospital mortality of 11% [10]. At 15 years follow-up, 17 patients (3%) required proximal reintervention for root events.

Using propensity score analysis, Castrovinci et al. have evaluated 296 patients with TAAAD, with 40% RR and 60% CR [3]. Operative mortality remained similarly high in both groups (21% after root replacement versus 26% in preserved roots, p=0.45). At 7 years follow-up, survival was comparable while freedom from proximal aortic reintervention was higher after a root replacement approach (RR: 98 ± 2% vs CR: 86 ± 6%, log-rank p=0.06).

Finally, in a comprehensive review of the literature in 2016, Leshnower et al. suggested that in the vast majority of patients, a strategy of root repair could be accomplished with acceptable mortality [2]. Although root replacement was not found to increase operative mortality, it was protective against secondary root events.

Root Replacement: Composite Graft or Valve-Sparing Techniques

Replacing the aortic root has more recently opened a new debate, fuelled by the increasing popularity of valve-sparing root replacement techniques (VSSR). The use of composite valve-graft conduits (CVG) may expose patients to a higher risk of endocarditis, high-risk reoperative valve replacement in the case of bioprosthetic aortic valve replacement (AVR), or the burden of lifelong anticoagulation in the case of mechanical AVR. In that case, anticoagulation may also preclude downstream false lumen thrombosis [11].

Several high volume aortic centres have therefore suggested the use of VSRR strategies in selected patients presenting with TAAAD. Although the reports remain limited, and mainly performed by centres experienced in VSRR in elective procedures, the current data suggest durable valve function and no increase in operative mortality in relatively small cohorts of patients, thus emphasising the importance of careful patient selection.

Leshnower et al. reported 43 consecutive David V procedures among 350 patients treated for TAAAD with an operative mortality of 4.7% [11]. With a 40±31 month follow-up, no patient developed endocarditis or required aortic valve replacement, while freedom from 2+ aortic regurgitation was 94%, and freedom from aortic valve replacement was 100%.

Esaki et al. have further suggested that TAAAD was not found to be associated with higher failure of David V procedures [12]. In their cohort of 282 patients treated with VSRR, only 14.9% were treated for TAAAD.

In a comparative study evaluating 135 patients presenting with TAAAD, Yang et al. carried out 95 Bentall and 40 David procedures [13]. Operative mortality was lower in the David cohort without achieving statistical significance (3% versus 13% for the Bentall group, p=0.1). At 10 years, the VSRR cohort also demonstrated superior survival: 98% (95% confidence interval [95% CI], 84-99%) for the David group and 57% (95% CI, 42-70%) for the Bentall group.

Equally, Subramanian et al. have compared the outcomes of VSRR (David and Yacoub procedures) and CVG techniques (Bentall procedure) for root replacement in the setting of TAAAD [14]. Overall, 208 patients underwent aortic root procedures for TAAAD, including 130 Bentall, 51 Yacoub and 27 David operations. The authors reported comparable outcomes regarding in-hospital mortality and no difference in the need for aortic valve replacement for aortic regurgitation at mid-term follow-up. Five-year survival estimates were also equivalent.

Fate of the Spared Aortic Root After TAAAD Surgery

The main dilemma when approaching the aortic root during TAAAD repair focuses on the fate of the spared root over time. The risk of secondary root events, including aneurysmal evolution, aortic regurgitation, formation of pseudoaneurysms and recurrence of root dissection must be weighed against the additional technical complexity of root replacement, and the potential challenge to mobilise and anastomose acutely dissected coronary artery buttons [15].

Several studies have therefore evaluated the fate of spared aortic roots after surgery for TAAAD. Peterss et al. have evaluated and followed-up 338 patients undergoing surgery for TAAAD, including 74% of CR procedures and 26% of RR [15]. Total population mean age was 60.7 ± 13.5 years. Both strategies had equivalent operative mortality (15% for CR and 20% in RR, p=0.31) and survival rates at 10 years. Freedom from root events after 5 and 10 years

of follow-up was 97 and 92% in the CR group, and 100% in RR group. In practical terms, less than 10% of the preserved aortic roots developed significant disease at 10 years. Upon follow-up, the authors also demonstrated the slow growth of the aortic root after TAAAD repair, with an average 0.40 ± 0.13 mm/year.

These findings were consistent with the outcomes reported by Dell'Aquila et al. over a 23 years follow-up in 319 patients undergoing surgery for TAAAD with preservation of the aortic root with a 34% in-hospital mortality [25]. Among the surviving population, freedom from reoperation on the proximal aorta was 97%, 92%, and 82% patients at 5, 10, and 23 years, respectively.

Rylski et al. reported 97 TAAAD treated with supracoronary aortic repair [16]. At 4.4 years, 27% of the patients presented with new onset root disease, with 10% requiring reoperation. Survival at 10 years was, however, similar regardless of the aortic root evolution. The authors also identified the dissection of all aortic sinuses as a predictive factor for root reintervention.

Outcomes of Secondary Reintervention on the Preserved Aortic Root

In 2017, Wang et al. reported 129 aortic reinterventions on patients previously operated on for TAAAD [17]. Most initial reoperations were performed in the elective setting (83.1%), including 52% of proximal reoperations. In-hospital mortality for all reoperations was 7%. The authors suggest, therefore, that reoperation after TAAAD repair is associated with acceptable rates of mortality and morbidity, supporting more limited index repair, because reoperations if needed can be performed safely in reference aortic centres.

Previously, Estrera et al. reported comparable outcomes for proximal reinterventions after primary repair for TAAAD in 63 patients with a 30-day mortality of 11.1% [18]. The authors concluded their work suggesting that the concern for proximal reoperation should not dictate the initial procedure choice during acute type A aortic dissection.

Management in Patients with Connective Tissue Disorders and Bicuspid Aortic Valves

This is probably the less debated question in this topic. In patients presenting with connective tissue disorders (mainly Marfan and Loeys-Dietz syndrome), more aggressive strategies are recommended due to the nature of the aortopathy and the frequent rapid evolution of the untreated aortic segments.

Evaluating 74 patients with Marfan syndrome, including 85% with TAAAD, Rylski et al. reported a 3% in-hospital mortality with a median population age of 37 years [19]. Most importantly, the authors demonstrated a 40% rate of reintervention after supracoronary repairs for root disease at 10 years. Given the high chance of reintervention, the authors strongly advocate for systematic root replacement (CVG or VSRR) in patients with Marfan syndrome in the setting of TAAAD.

Similarly, patients with Loeys-Dietz syndrome (LDS) present an aggressive aortopathy, requiring multiple re-interventions for untreated aortic segments, as suggested by two studies [20,21]. In these reports, patients with LDS presented with acute aortic syndromes at a young age and smaller aortic diameters. In both studies, the authors advocated for

more aggressive strategies regarding root replacement and meticulous clinical and imaging follow-up given the rapid evolution of the aortopathy and the frequent need for re-interventions.

Although not considered as a connective tissue disorder, bicuspid aortic valve (BAV) is frequently associated with aortic disorders, and BAV predisposes to the development of ascending/root dilatation and subsequent TAAAD [22,23]. Consequently, the IRAD registry authors have suggested that patients with BAV undergoing surgery for TAAAD should undergo root replacement [9]. There is, however, limited data regarding the evolution of BAV after primary repair for TAAAD.

Results of a French Aortic Centre

In this second part, we report our experience regarding the management of the aortic root in the setting of TAAAD. Most importantly, we highlight the main characteristics and features that we take into consideration in managing the aortic root in such a setting.

Between 2000 and 2017, 303 patients underwent surgical repair for TAAAD at our institution with 62% of patients undergoing supracoronary repair and 38% root replacement. Mean age was 63±13 years with an operative mortality of 23%. Our management of the aortic root during repair for TAAAD is summarised in Figure 1. The following criteria strongly advocate for root replacement:

- entry tear inside the aortic root,
- dissection involving all 3 aortic sinuses,
- involvement of the coronary ostia,
- age under 65 years old,
- or a history of connective tissue disorder.

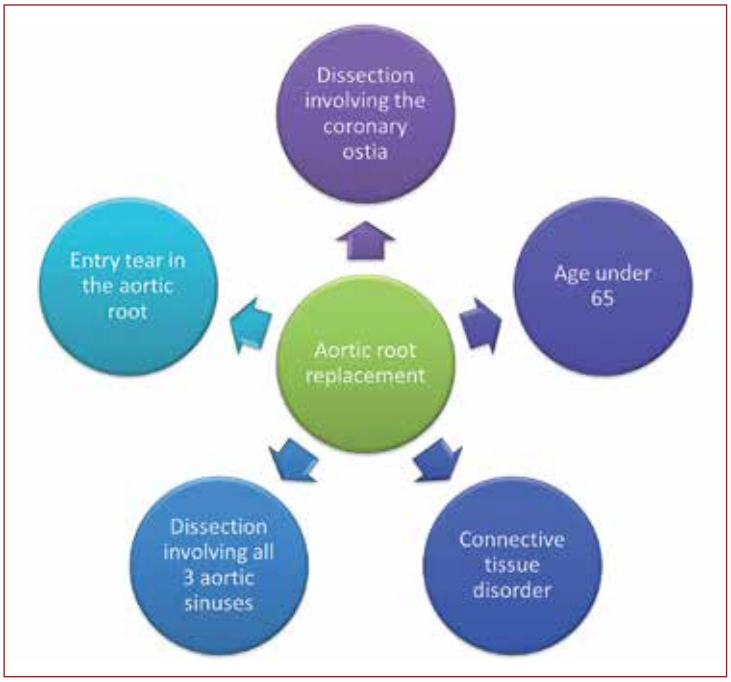

Figure 1: Management of the aortic root in the setting of type A acute aortic dissection. We systematically consider root replacement if one or more criteria are present.

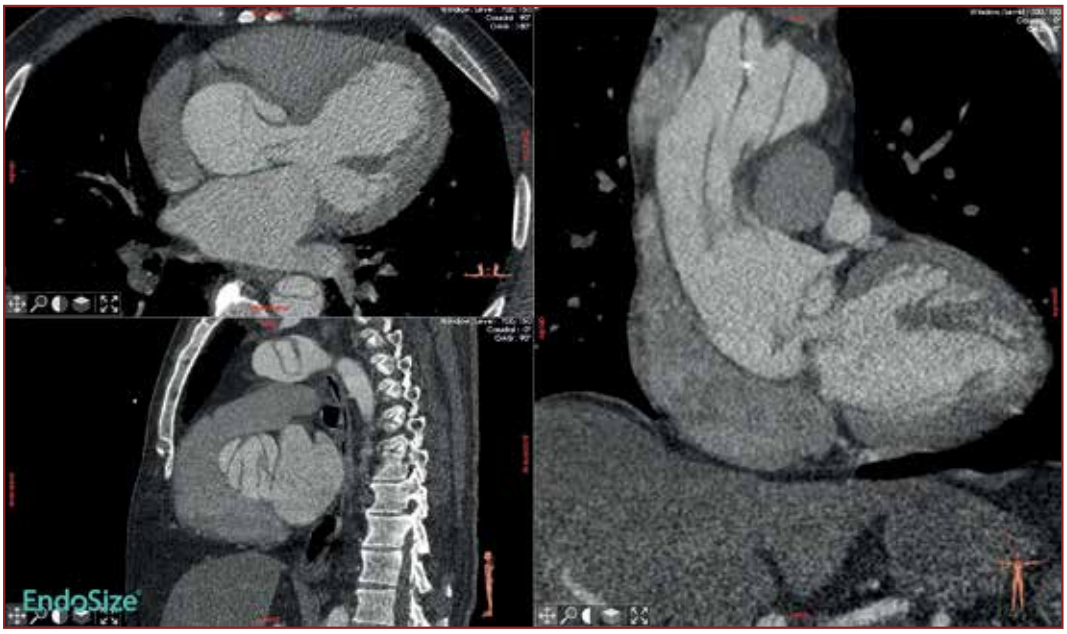

Figure 2: A 65-year-old patient presenting with TAAAD with an entry tear in the aortic root. The root was preserved due to major perioperative haemodynamic instability. Five days later, the patient re-dissected the aortic root and required root replacement.

Otherwise, in the case of older age (75-80 years old), major haemodynamic instability, neurological presentation (coma or stroke), absence of root involvement in the aortic dissection, or two or less dissected sinuses, our approach tends towards root repair.

Usually, our strategy for root repair includes reapproximation of the dissected layers using Bioglue® (Cryolife, Kennesaw, GA, USA) and two running 4-0 polypropylene sutures. Inner and/or outer Teflon felt may be added to strengthen the repair. Commissural resuspension, using U-shaped 4-0 polypropylene sutures on Teflon pledgets, usually completes the repair. In case of a diseased aortic valve, aortic valve replacement is performed, preferably using a tissue valve. This strategy aims at avoiding the postoperative (and lifelong) burden of anticoagulation with its haemorrhagic complications, and favours false lumen thrombosis. Moreover, in case of CVG implantation, we favour bioprostheses with greater diameter, in order to promote better haemodynamic outcomes after valve-in-valve implantation.

In this setting, consideration of a potential future valve-in-valve implantation procedure must be taken into account during reimplantation of the coronary ostia. Thus, we use aortic grafts with Valsalva sinuses, such as the Gelweave Valsalva® (Vascutek, Glasgow, UK) and try to implant the coronary buttons as high as possible, in order to prevent potential coronary obstruction following valve-in-valve procedures. Our strategy also requires the availability of a senior aortic surgeon, from the decision-making process through to potentially assisting in more challenging cases: arch replacement (usually by a Frozen Elephant Trunk (FET) procedure), VSRR, endovascular or hybrid completions.

In our experience, this strategy favours a simplified approach to TAAAD, with a more standardised technique and thus more reproducible outcomes. Our results are consistent with the current literature regarding operative mortality and emphasise that surgery for

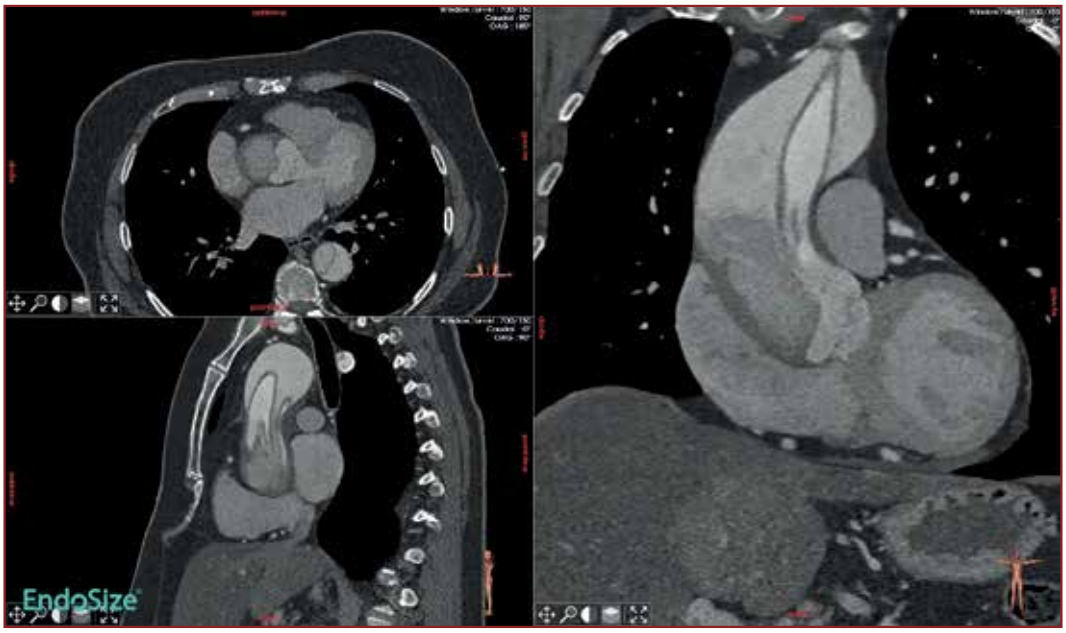

Figure 3: A 59-year-old patient presenting with TAAAD (top) underwent supracoronary repair. At the time of the initial procedure, the entry tear was located in the aortic root. Two days after the initial procedure, she presented with an acute coronary syndrome.

TAAAD still carries a high mortality. During follow-up, 7 patients (3% of the surviving population) required proximal re-intervention (3 root TAAAD, 1 aortic valve endocarditis, and 3 aortic regurgitation with root dilatation).

Figures 2, 3 and 4 illustrate two cases of patients presenting with TAAAD that underwent supracoronary aortic replacement, with subsequent complications in the preserved aortic root. Both cases illustrate the requirement for root replacement in the presence of an entry tear inside the aortic root.

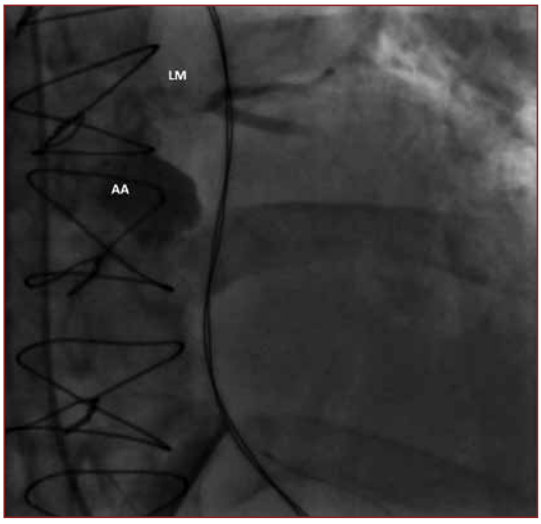

Figure 4: A coronary angiogram of the figure 3 patient revealed dissection of the left main due to a re-dissection of the aortic root. (LM = left main, AA = ascending aorta)

This also emphasises the need for rigourous imaging and clinical follow-up. At our institution, we perform a discharge CT scan for baseline assessment of the aortic root and the downstream aorta; patients thereafter undergo an annual CT scan. In this setting, we also carried out 12 FET procedures during the follow-up of chronic TAAAD, with 0% mortality. In our experience, the aortic arch can almost systematically be repaired without the need for arch replacement in the acute setting.

Our management of the aortic root in the setting of TAAAD may be summarised by the "live to fight another day" paradigm [24]. While this approach is currently challenged, we believe it offers a standardised approach aimed at lowering operative mortality and morbidity. Close imaging and clinical follow-up is mandatory to identify proximal or downstream aortic evolution.

Conclusions

- Type A acute aortic dissection remains a condition with high operative mortality, frequently over 20%.
- Both root replacement and conservative root management can be performed with comparable in-hospital outcomes.
- While conservative root management approaches may lead to secondary root events over time, less than 10% of patients will require proximal reoperation for root disease at 10 years.
- A patient-tailored approach may provide the optimal outcomes: reduced operative mortality and low rate of aortic re-intervention.
- Our criteria advocating root replacement include connective tissue disorders, entry tear in the aortic root, dissection of all aortic sinuses, coronary artery involvement, bicuspid aortic valve, and age under 65 years old. Otherwise, the root can be repaired, usually by layer reapproximation and commissural resuspension.
- When aortic valve replacement is necessary, we favour bioprosthetic valve replacement to avoid anticoagulation-associated complications and promote downstream false lumen thrombosis.
- Valve-sparing root replacement may represent a suitable strategy in selected patients, usually young haemodynamically stable patients with normal aortic cusps and presenting criteria for root replacement.
- Rigorous imaging follow-up is mandatory to monitor the aortic evolution and, when required, perform re-intervention electively by senior aortic surgeons with optimal case planning and with acceptable outcomes.

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Chapter 10

Chronic Dissection in Thoracoabdominal Aortic Aneurysm - The Cleveland Clinic Experience

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"Rapiamus, amici, occasionem de die"

Introduction

Chronic aortic dissections deserve special consideration. Many of these patients (25-35%) develop late complications, including subsequent dissection, malperfusion, ischaemic events and, in some cases, thoracoabdominal aortic aneurysm (TAAA). One of the common anatomic findings characterising TAAAs is the involvement of visceral and lumbar arteries along the thoracic and infrarenal aorta. Complex anatomy, debilitated patients, spinal protection and bleeding are more complex than with other aortic surgeries. Therefore, it is well recognised that management of TAAAs remains a challenge. Over the last three decades, refinements in techniques have continued to reduce complications and broaden the scope of patients than can be offered surgery. Historically, open surgery had long been the only treatment approach. More recently, endovascular advances have been made that have somewhat modified this. Consequently, in assessing the treatment strategy, the surgeon must take into account the broad options available whilst acknowledging the patient's frequent comorbid illnesses. We address some of the Cleveland Clinic's traditional open as well as more recent endovascular and hybrid surgical treatments and provide insights about differential management and outcomes of chronic dissection in TAAA.

History

In retrospect, by today's standards, TAAA management options were limited and had disappointing results with frequent complications as well as high morbidity and mortality. First introduced by Crawford, Gross, and Etheridge, many important factors for success were learned during this era that are often used today. The paradigm shift toward the modern era of surgical treatment of TAAA began with E. Stanley Crawford. His pioneering results, documented in 1974, were strikingly successful: significant reductions in mortality and paraplegia rates without assisted circulation [1]. Dr. Crawford set the standard for a generation of surgeons – overall mortality of 8% and paralysis of 16% in over 1500 TAAA repairs [2,3].

Epidemiology

The incidence of TAAA is approximately 10.4 per 100,000 and is increasing with an aging population, greater awareness of the disease, and better diagnostic tests [2,4]. Most cases occur in the elderly, with the highest incidence in the fifth to seventh decades (Table 1), and are more common in men [2], with a male-to-female ratio of about 1.7:1. There has been some controversy over a possible increase in the incidence of TAAAs. Population-based incidence data from the Swedish National Healthcare Registry has demonstrated a significantly increasing incidence of TAAAs [2,5]. The most common cause of death from TAAA is rupture. Indeed, aortic rupture is the 19th leading cause of death in the United States, accounting for approximately 13,000 deaths annually [6].

Table 1: Risk Factors for TAAA

Risk Factors for TAAA
• Degenerative (associated with atherosclerosis)
• Dissections
• Connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Takayasu disease)
• Infection, Syphilis, Tuberculosis
• Mycotic aneurysms
• Aortitis
• Non-specific variety of giant cell aortitis
• Rheumatoid aortitis, Ankylosing spondylitis, Reiter syndrome
• Relapsing polychondritis
• Postoperative pseudoaneurysms
• Associated with unrepaired and repaired aortic coarctations
• Traumatic

Modified from Rutherford's Vascular Surgery and Endovascular Therapy, 9th edition. Philadelphia: Elsevier; 2019. p. 970-986.e5 [1]

Anatomic Classification

The standard classification for TAAAs was described by Crawford, based on therapeutic implications and risk of complications. Crawford found that different aneurysm extents each have different levels of risk. Extent I TAAA, the second most common type, involves the left subclavian to above the most proximal renal artery. Extent II TAAA, the most common type, involves the left subclavian artery to below the renal arteries. Extent III TAAA involves the sixth intercostal space to below the renal arteries, and Extent IV TAAA is limited from T12 to below the renal arteries.

Indications for Intervention

A chronic dissection itself is not an indication for surgical intervention. In general, surgical decision making for a symptomatic chronic dissection progressing to a TAAA is straightforward; operative repair is nearly always appropriate because of the high mortality associated with rupture. For those with an asymptomatic chronic dissection progressing to a TAAA, published guidelines have provided assurance that the TAAA can be safely monitored until the aneurysm diameter is 5.5 cm or twice the diameter of the normal contiguous aorta, and the rate of growth is less than 1 cm during a 1-year period [6,7]. However, a lower threshold is often used for patients with connective tissue disorders, including Marfan, Loeys-Dietz, and other familial aortic syndromes. As expected, considerable variation in operative risk occurs between individual patients and depends on specific risk factors. Therefore, the individual risk of rupture under observation, operative risk of repair, and assessment of life expectancy must be considered to determine the optimal threshold for intervention. Surgeons should not adopt a one-size-fits-all policy for treating patients with TAAAs.

Preoperative Evaluation

Accurate preoperative evaluation for a TAAA requires a thorough history, physical examination, and basic laboratory data. These factors are important and can be translated into metabolic equivalents for estimating perioperative risk and subsequent life expectancy. Assessments of cardiovascular, pulmonary, and renal diseases not only influence the decision to operate, but they may focus preoperative management to reduce modifiable risk. Pulmonary function testing, echocardiography and cardiac catheterisation are indispensable as disturbances in one organ system often have repercussions for other systems.

Most patients undergo preoperative imaging using computed tomography angiography (CTA). Rapid advances in technology have put CTA at the forefront of aortic imaging at our institution, and it is particularly accurate at size measurements, relationships to visceral and renal arteries, aortic neck and iliac artery anatomy and tortuosity. Furthermore, CTA can be reformatted digitally with the most popular display arrangement being three-dimensional imaging. Magnetic resonance imaging or angiography (MRI/MRA) is another mapping technique used for preoperative imaging. While comparable with CTA in terms of measurement accuracies, MRI/MRA is more expensive and time consuming.

Surgical Treatment Algorithms

The primary indications for any surgical approach to TAAAs are the same with regard to the size of the aneurysm and its rate of growth. Choosing the approach can be quite complex and is influenced by a number of factors including: the patient's age, performance status and comorbidities; the TAAA extent; underlying connective tissue disease, anatomy, and prior aortic surgery; the comfort level of the surgeon; and the experience of the team. Open surgical interventions for TAAAs date back centuries and had become the mainstay of treatment. Although excellent results have been obtained at the Cleveland Clinic, open surgery remains a complex, challenging operation. Contemporary endovascular methods, including hybrid techniques, enable the exclusion of the aneurysm through an endograft with less morbidity. The visceral segments can also be addressed endovascularly with either debranching from a remote location or custom-designed fenestrated or branched endovascular aortic repair (F/BEVAR) devices [7]. Similarly, hybrid procedures also allow for

endograft completion of the descending thoracic aorta with an open elephant trunk by providing proximal anchorage in the distal aortic arch/proximal descending aorta.

There are cardinal approaches that allow the repair of the vast majority of TAAAs. These can be simplified into three groups: 1) open surgery alone, 2) endovascular surgery alone, and 3) a hybrid approach - staged open surgery combined with endovascular completion. While the approach can often be modified to the individual patient's clinical status, underlying anatomy, and the institution's experience, these modifications nonetheless remain variations on the main three corridors.

Building on decades of efforts with open and endovascular techniques, the Cleveland Clinic has transformed TAAA management (Table 2). For Extent I and IV, an endovascular approach may be a consideration. Thus, the subset of patients with aneurysms that were previously considered "prohibitive" has become smaller. However, for an aortic dissection with Extent II, III and IV aneurysms, open surgery is our preferred repair method. For TAAAs involving the aortic arch, for example from prior aortic dissection, a hybrid, staged approach - open surgery (elephant trunk) with endovascular completion - is our preferred repair method. During the elephant trunk procedure, cardiac pathology and aneurysmal disease of the ascending aorta and aortic arch can be concomitantly treated. Similarly, the lower thoracic or upper abdominal aorta can be wrapped to convert a thoracoabdominal aneurysm to a thoracic one, and the second-stage endovascular procedure using a thoracic endograft can be undertaken [7]. Next, patients at high risk for open second-stage procedures (comorbid disease, lung pathology, or adhesions) can undergo less invasive, endovascular completion operations.

Table 2: Cleveland Clinic Surgical Algorithm for TAAA Repair.

TAAA Extent	Repair
I	Endovascular
II	Open
III	Open
IV	Open
Aortic Arch Involvement	Hybrid

The management of debilitated patients with Extent II, III and IV TAAAs continues to draw some controversy. Although open surgery for these patients does not present much of a dilemma, the decision to proceed with endovascular intervention is more complicated. We reserve endovascular treatment with F/BEVAR for extent II, III, and IV TAAAs for debilitated patients considered prohibitive for open surgical repair.

Open Repair

Anaesthesia

The anaesthetic management for TAAA repair is complex and has unique considerations. Close cooperation and continuous communication between the surgeon and anaesthetic team is crucial. The maintenance of organ perfusion, selective right lung ventilation, and preventing spinal cord ischaemia demands vigilant monitoring and timely intervention. Hypotension and hypoxia must be avoided to prevent secondary insults.

Preoperative intravenous antibiotics are administered to reduce the risk of prosthetic graft infection. The patient is intubated with a double-lumen endobronchial tube or a single-lumen tube with a bronchial blocker, allowing collapse of the left lung [8]. Ample intravenous access, arterial pressure recording (bilateral radial and right femoral arterial lines), and a Foley catheter are inserted. Pulmonary artery catheters are used for haemodynamic monitoring (cardiac index, central venous pressure, pulmonary pressures). Transoesophageal echocardiography (TOE) can be useful to monitor ventricular volume and function. Nasopharyngeal and bladder temperatures, coagulation parameters and arterial blood gases are continuously monitored through the surgery [2,8].

Other Considerations - Preserving Spinal Cord Function

The morbidity associated with spinal cord ischaemia is well known. Temporary interruption of distal aortic perfusion and sacrificing spinal segmental arteries are the principal contributing factors to spinal cord ischaemia and paraplegia. We have previously reported the spinal protective strategies largely aimed at preventing injury and mitigating spinal cord ischaemia [9-18]. First, cerebrospinal fluid (CSF) drainage during aortic clamping and for at least two days after surgery; CSF drainage lowers intrathecal pressure and improves spinal cord perfusion. Second, maintaining patients hypertensive after surgery. Third, cooling systemically to moderate or, less so, profound hypothermia; hypothermia has long been explored for its neuroprotective effects. Fourth, intrathecal papaverine - our group demonstrated that adding intrathecal preservative-free papaverine enhances spinal cord perfusion and provides additional spinal cord protection. Fifth, minimising intercostal ischaemia time, using a sequential segmental repair approach, and re-attaching all patent and segmental intercostal arteries below T8 for descending thoracic aortic repair and from T7 to L1 for TAAA repairs. Finally, minimising any postoperative hypotension.

Intraoperative Neurophysiologic Monitoring

Intraoperative neurophysiologic monitoring (IONM) is a multimodal technique using a wide array of electrical recordings to monitor both sensory and motor pathways extending from the cerebral cortex to the distant peripheral nerve action potentials. Generally accepted monitoring techniques include somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs). In SEP monitoring, stimulation electrodes excite repetitive action potentials propagating from peripheral nerves eventually to the contralateral sensory cortex. The main disadvantage of SEPs is that only somatosensory pathways are monitored. The more common problem, motor deficits, can be missed. This leads to MEPs where stimulation of the cerebral motor cortex is detected peripherally to discover motor deficits. In patients in whom we use MEPs, a platinum or stainless-steel electrode on the catheter for spinal cord stimulation is used. Of note, we do not routinely use SEPs or MEPs to select intercostals for re-implantation. Following a prospective randomised trial, we stopped using SEPs or MEPs given this added 1-2 hours per case without an apparent benefit.

Surgical Technique

Proper patient positioning provides access to the thoracoabdominal aorta. Positioning is best achieved by placing the patient in a right lateral decubitus position with the left side up, using a beanbag. The pelvis is rotated 45° from the table to further assist access to the aorta. A thoracoabdominal incision is tailored to fit the extent of the aneurysm. An extent II or III TAAA repair requires the full thoracoabdominal incision, whereas for an extent I or IV

TAAA a smaller incision is preferred [2]. The full thoracoabdominal incision begins posterior to the tip of the scapula and proceeds medially along T6, extending inferiorly at the midline toward the umbilicus [19]. The costal margin is then divided and the incision is extended obliquely across the abdominal wall, and the appropriate muscles are divided to the level of the rectus abdominis fascia [4]. The retroperitoneal space is entered without the viscera being exposed. The left lung is then deflated and the pleural cavity is entered. Next, the left inferior pulmonary vein in the pulmonary hilum and aorta proximal to the aneurysm are exposed. The arch vessels are exposed with careful avoidance of injury to the phrenic and vagus nerves, and its recurrent branch [2]. At this point, the diaphragm is incised radially to the level of the aortic hiatus and a retroperitoneal plane can be developed, which allows for complete exposure of the descending thoracic and abdominal aorta with its visceral branches and the iliac arteries [2]. Caution is advised to avoid entering the peritoneal cavity. Next, dissection and exposure of the coeliac, superior mesenteric, and left renal arteries is performed. Of note, preservation of the inferior mesenteric artery (IMA) is not a concern unless the patient had prior surgery or if the IMA is large and patent.

Heparinisation (1 mg/kg) and cannulation of the left femoral artery with an 8-mm graft and left inferior pulmonary vein are now performed. Partial bypass is established with flows between 750 and 1500 mL/min/m^2 to maintain a mean arterial pressure in the lower circulation of 60 to 70 mmHg while normal arterial and central venous pressures continue in the upper circulation [4]. From there, lidocaine is given, the patient actively cooled to a bladder temperature of 29°C to 30°C, and specially prepared intrathecal papaverine solution is administered. A segmental clamp is applied proximal to the diseased segment and distally in the mid-thoracic aorta [4]. This will maintain perfusion of the lower intercostal arteries, kidneys, abdominal organs, and lower extremities. The aneurysm is opened and intercostal vessels from below T6 down to and including L2 need to be reattached. The proximal aorta is completely divided and a Dacron graft sutured in end-to-end fashion. The anastomosis is reinforced with felt strips.

The distal clamp is moved to the infrarenal abdominal aorta, the upper abdominal aorta is opened and the visceral arteries are exposed. The kidneys are perfused with cold renal perfusion solution (180 ml each of 4°C lactated Ringers solution) [2]. The viscera are attached either as a Carrel patch or with a side-branched thoracoabdominal aortic graft that we designed. The Carrel patch is narrowed to avoid future patch aneurysms [2]. However, if the vessels are spaced too far apart, then they are attached individually to avoid a large visceral patch prone to aneurysmal dilatation over time. This concept is especially important in patients with connective tissue disorders. When a dissection flap is encountered, the flap can be excised to create a common channel. Next, the distal anastomosis is completed either at the level of the distal aorta or individually to the iliac arteries. In the latter case, a bifurcated aortic graft is sutured to the proximal graft and the distal anastomoses sutured to the iliac arteries. After completing the distal anastomosis, the graft is de-aired and the clamps released.

Endovascular Repair

Procedures are performed in a hybrid operating room with high-quality fixed imaging under general anaesthesia. Patients may first undergo extra-anatomic bypass (carotid-subclavian) or distal branched grafts (iliac branched devices) to preserve the left subclavian artery and pelvic circulation [20]. Cerebrospinal fluid drainage is used when the region of aortic coverage is >20 cm. The spinal drain is inserted preoperatively and maintained for 48 to 72 hours with a CSF pressure ≤10 cm H_2O. The endografts are sized to the aorta

proximal to the dissection with a 10% to 15% oversizing (not tapered) to accommodate any changes in the true lumen dimensions. The access is transfemoral and the arteries must generally be approximately 7mm in diameter and free of obstructing plaque to accommodate 18 to 20 Fr delivery systems for F/BEVAR [2]. In the case of small or calcified iliac arteries, iliac conduits with a 10-mm Dacron graft are anastomosed to the common iliac artery in end-to-side fashion. The conduit is then either ligated distally or converted to an ilio-femoral bypass. This is performed as a staged procedure. Fenestrated or branched TEVAR is performed using custom-made Zenith branched and fenestrated endografts and standardised bifurcated iliac branch devices (Cook Medical Inc, Bloomington, IN, USA). For dissected lesions involving an aneurysmal arch, a total arch endovascular repair using a custom arch branched graft (Cook Medical) incorporating two arch vessels (brachiocephalic and left common carotid artery) is used.

Bilateral femoral artery access is achieved and 20F to 24F sheaths are placed over a stiff guide wire into the infrarenal aorta. Intravascular ultrasound and transoesophageal echocardiography are used to ensure placement of the endovascular graft in the true lumen. Aortography is then performed and the landing zones that were determined preoperatively are confirmed. With F/BEVAR the seal length should be 20 to 40 mm in a relatively straight segment of aorta. However, in the case of angulations, a longer seal zone may be preferable to decrease endoleaks and migration and protect from late aneurysmal degeneration [2]. The F/BEVAR device is prepared and oriented extracorporeally with the fenestrations/branches oriented properly. The device is introduced into the aorta over a stiff wire, situated in the ascending aorta and unsheathed slowly. Next, the target vessels are cannulated using a 6 or 7 Fr guiding sheath, via the contralateral sheath. After an angiogram confirms the graft fenestrations correspond to the target arteries, the stent grafts are delivered but not deployed. Covered stents are then placed into the target arteries, with 3 to 4 mm of fabric overlapping the fenestration into the aortic endograft. The proximal aspect of each covered stent is then flared to maximise apposition of the stent and endograft fabric. Next, the contralateral and ipsilateral limb are extended, if necessary. After all devices are deployed, completion angiography is performed to confirm the absence of type I and III endoleaks. If either are observed, additional balloon inflation or insertion of extension pieces may be necessary. The large sheath is then removed and an iliofemoral angiogram is performed while maintaining wire access. Heparin is reversed and arteriotomies are closed. Completion CT angiography hopefully shows a sealed aneurysm.

Hybrid repair

Stage I - Conventional Elephant Trunk

An 8mm side graft is attached to the right subclavian or axillary artery. This provides arterial inflow during cardiopulmonary bypass and selective antegrade brain perfusion during circulatory arrest. After median sternotomy and pericardiotomy, a multistage venous cannula is placed and cardiopulmonary bypass commences with cooling. The aortic arch is exposed from the left anterolateral surface to approximately 2cm beyond the left subclavian artery. Preservation of the vagus and recurrent laryngeal nerves should be maintained by keeping the plane of dissection close to the aorta and avoiding mobilisation of the head vessels.

While cooling, attention is turned toward preparing the elephant trunk. A stay suture on a haemostat is placed on the proximal end of a tube graft, typically less than 32 mm, and the graft is inverted. The distal portion should be kept approximately 10-15 cm in length [21].

Moreover, placement of two large clips and a pacing wire loop on the distal end will facilitate finding the opening of the elephant trunk for endovascular grafting. In case of future kinking or accordioning of the elephant trunk, a wire can be passed endovascularly through the looped pacing wire, making it technically feasible to remove any kinks from the elephant trunk.

When a nasopharyngeal temperature of 20° C is reached, circulatory arrest begins. At this point, cardiopulmonary bypass is stopped and the patient is placed in a steep Trendelenburg position to prevent air accumulating in the arch vessels [21,22]. Carbon dioxide is also insufflated into the surgical field at 10 L/min [22]. The aneurysm is then entered in the mid-ascending aorta, opened along the arch, and distally to an anterior lateral position above the subclavian artery origin. With a chronic aortic dissection, the septum is excised as far as possible in the descending thoracic aorta, so that true and false lumens are perfused distally by the elephant trunk [21,22]. Perfusion of either the true or false lumen alone may result in paraplegia or renal failure. The inverted graft is placed in the descending aorta, preferentially the true lumen, and an anastomosis between the inverted edge of the elephant trunk graft and aorta just beyond the subclavian artery is then performed. We make a concerted effort to have the anastomosis distal to the left subclavian artery. Once the anastomosis is completed, the stay suture is gently tugged upon to remove the inverted proximal graft from the distal elephant trunk and the arch vessels are then ready to be re-anastomosed. By withdrawing the inverted graft from inside the elephant trunk, this will tighten the anastomosis and improve haemostasis. Next, an opening is made in the graft opposite the arch vessels and reattachment of the arch vessels is performed. The graft is flushed, clamped and checked for haemostasis. Cardiopulmonary bypass is restored and warming commenced. Finally, the proximal ascending aorta anastomosis and/or aortic valve or root procedure is completed.

Stage I - Frozen Elephant Trunk

Right subclavian/axillary cannulation with an 8mm side graft and a multistage cannula in the right atrium is a fundamental step. After initiating cardiopulmonary bypass and systemic cooling, the proximal arch and branch vessels are individually dissected, with care taken to preserve the vagus and recurrent laryngeal nerves. After the appropriate temperature is reached (20°C nasopharyngeal), the innominate and left common carotid arteries are snared and selective antegrade cerebral perfusion is commenced. The aorta is transected obliquely in a hemiarch fashion, starting from the base of the innominate artery to the underside of the aortic arch [24,25]. The left subclavian artery is cannulated with a 9Fr occlusion balloon to avoid steal from the left vertebral system. The stent-graft is deployed antegradely into the true lumen and positioned across the aortic arch. In the presence of complicated anatomy, a transfemoral wire may be used to deliver the stent graft. Once the graft is positioned to cover the left subclavian artery ostium, the graft is secured to the lesser curve of the aortic arch to prevent migration. Then, a handheld cautery is used to create an opening in the stent-graft at the level of the left subclavian artery. A bridging branch stent-graft (2.5cm length) is directly positioned through the main stent graft and deployed into the left subclavian artery. It is typically necessary to expand the branch stent graft opening with a clamp and 9Fr occlusion balloon. Next, the main stent-graft is directly sutured to the transected aortic wall. Care must be exercised to ensure apposition of the stent graft and aorta to prevent migration and endoleaks. Once securing the stent graft has been completed, a surgical hemigraft, ideally the diameter of the sinotubular junction, is used for the open distal anastomosis. It is particularly critical that all three layers are

incorporated in the suture line - the hemigraft, transected aorta and stent-graft. At this point, innominate and left carotid flows are resumed, the graft deaired and cardiopulmonary bypass is re-instituted. Lastly, the aortic valve and root are addressed, and proximal aortic reconstruction with the proximal end of the surgical graft is completed.

Stage II – Endovascular Graft Completion of Elephant Trunk

Endovascular repair of chronic dissections is most successful when disease is limited to the descending thoracic aorta and both the proximal and distal landing zones are stable segments of aorta for fixation and sealing [26,27]. There are several options for performing the second-stage endovascular elephant trunk procedure (Table 3). While the proximal landing zone for the placement of a stent graft can be achieved with the stage I elephant trunk, many patients with chronic dissection have a distal landing zone which is not ideal [26,28]. Our institution described a novel hybrid technique involving an elephant trunk procedure with open fenestration of the distal landing zone in the first stage, followed by TEVAR extending from the ET to the modified fenestrated segment. Prior to arch reconstruction, the descending aorta is exposed and about 5 to 6 cm of septum is excised.

Table 3: Options for Performing Second-Stage Endovascular Elephant Trunk Procedure

Stent graft from the elephant trunk to the celiac artery.
Stent graft from the elephant trunk to below the celiac artery, with separate either covered or noncovered side stents into the visceral vessels through openings in the aortic stent.
Premanufactured stent graft with spiral endovascular branched tube grafts into the visceral vessels.
Stent graft into an infrarenal elephant trunk and then distally into the iliac arteries: - For patients with prior thoracoabdominal aneurysm resection with debranchedvisceral arteries from separate tube grafts originating on the left iliac artery. - The elephant trunk is left below the renal artery bypasses to facilitate infrarenal and iliac artery stenting. - The elephant trunk is stented all the way to the aortic bifurcation.

With micropuncture, the ipsilateral common femoral artery is accessed and a flexible guidewire advanced into the suprarenal aorta. As the flexible guidewire is advanced into the proximal thoracic aorta, it is essential to confirm true lumen location with intravascular ultrasound (IVUS), which can also precisely define the relation of the flap and vessel origins. After being positioned in the ascending aorta, the flexible guidewire is exchanged for a Super Stiff™ wire. The contralateral femoral artery should then be accessed to introduce a marker catheter. This will allow for aortography performed in a left anterior oblique projection [2]. Intravenous heparin is then administered to achieve an activated clotting time (ACT) of 250 to 300 seconds. A large introducer sheath for the delivery device stent-graft can then be introduced under fluoroscopic control. It is helpful to properly orient the endograft device prior to insertion. The main device should be advanced, carefully, across the iliac artery and abdominal aorta to the target region under fluoroscopic guidance.

Next, an aortogram is performed by the use of a power injector injecting 20 ml of contrast at 10 ml/sec (imaging at two frames per second). Every attempt should be made to ensure the stent-graft is in the optimal position; hence care should be taken to reposition or rotate the graft, as necessary. The device is deployed according to the recommendations of the manufacturer. If more than one device is needed, the smaller one is deployed first [2]. With the device deployed, a digital subtraction aortogram is performed, which confirms proximal and distal endograft landing zone apposition and absence of types I and III endoleaks. It is important to recognise type I or III endoleaks as they should be treated with balloon dilation, realigning or insertion of extension pieces. Type II endoleaks are not treated given their relatively benign course as the majority will spontaneously resolve [2]. Finally, the sheath is removed and iliofemoral angiography confirms vessel integrity, while wire access is maintained. A CT scan of the completed repair shows a sealed aneurysm.

Outcomes

The heterogeneity of chronic dissection in TAAAs make generalisation of prognosis difficult. Surgical advances that include frozen elephant trunk and branched/fenestrated endografts have led to marked changes in management. As a preamble to the evaluation of the impressive outcomes for open, endovascular and hybrid TAAA repair from the Cleveland Clinic, it may be important to note that TAAA repair is a considerable surgical undertaking that carries substantial risk.

From 1960 to 1991, surgical pioneers reported a series of 1509 patients with thoracoabdominal aortic aneurysms who underwent a total of 1679 aortic repairs [3]. The authors achieved a 30-day survival of 92%. They noted that poor prognostic indications were increasing age, preoperative creatinine level, concurrent proximal aortic aneurysms, coronary artery disease, chronic lung disease, and total aortic clamp time. Spinal cord injury – paraplegia or paraparesis – developed in 16% (234/1509) of cases, with worse outcomes associated with total aortic clamp time, extent of aorta repaired, aortic rupture, patient age, proximal aortic aneurysm, and history of renal dysfunction. Other complications included renal failure in 18% (269/1509) of patients and gastrointestinal complications in 7% (101/1509) of patients.

The results of open surgical repair at our institution remain excellent.[29] We reported 169 patients treated at the Cleveland Clinic with open repair of descending thoracic and thoracoabdominal aortic aneurysms. Many patients had undergone previous ascending, arch, and first-stage elephant trunk reconstructions. Event-free survival differed between descending aneurysm repair (80%, 69%, 51%) and TAAA repair (69%, 62%, 47%) at 1, 2, and 5 years, respectively (Figures 1 and 2). Operative mortality was 8% and neurologic complications occurred in 2.4% of patients [1,29]. Moreover, actuarial survival at 1, 2, and 3 years was 74%, 67%, 55%, respectively. With regard to freedom for vascular reintervention after TAA repair, this was 89%, 85% and 79% at 1, 2, and 5 years, respectively.

Most often, prospective comparative trials are needed to determine the therapeutic benefits of a new regimen. In a landmark prospective trial, our group reported a comparison of 330 patients undergoing descending thoracic aneurysm and TAAA repairs with or without the addition of intrathecal papaverine (IP) to modern neuroprotective adjuncts [9]. This led to a significant decrease in unadjusted transient or permanent lower limb paralysis or paraparesis in the group of patients who received IP (6% vs 19%, $p=0.0006$). The addition of IP reduced permanent deficits from 14% to 5.2% ($p=0.01$) and renal failure necessitating dialysis from 16% to 6.8% ($p<0.05$). Although not statistically significant, there appeared

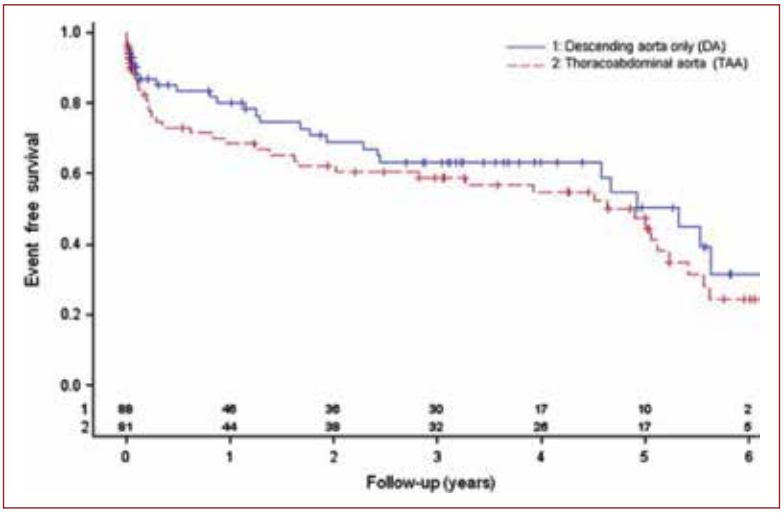

Figure 1: Kaplan–Meier estimate of event-free survival (freedom from all-cause mortality and vascular reintervention) by extent of repair, expressed as probability with number at risk.[29]

to be a trend toward improved long-term survival in the IP group; actuarial survivals at 1, 3, and 5 years were 87%, 81%, and 76% for the IP group versus 80%, 73%, and 67% for the non-IP group. Propensity-matching analysis showed a clear advantage in terms of neurological outcomes and overall survival with IP. This trial marked the potential for IP to have an impact on spinal cord protection as a component of treatment for patients undergoing descending thoracic aneurysm and thoracoabdominal aortic aneurysm repair.

More recently, our institution analysed 354 high-risk patients with extent II (n=128 (36%)) and III (n=226 (64%)) TAAA who underwent F/B-EVAR [30]. Technical success was achieved in 94.1% of patients. The perioperative mortality was 4.8%. When compared to those undergoing extent III repair, mortality was higher in extent II repairs; the overall perioperative morbidity was 40%. However, this could be explained by the patients' significant underlying comorbidities. The 3-year freedom from aneurysm-related mortality was high at 91% [26,28]. Spinal cord injury developed in 8% of patients, but with symptoms resolving in nearly half of the patients before discharge from the hospital [30]. As previously mentioned, we have shown that spinal cord injury rates were comparable with those

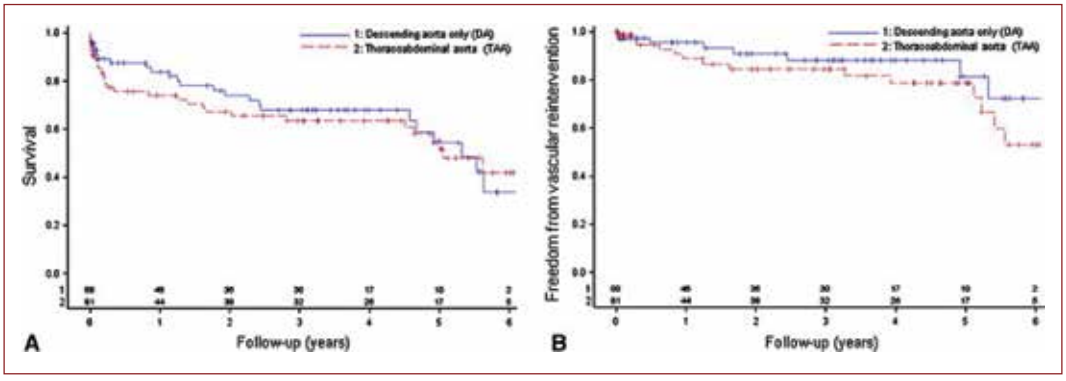

Figure 2: A, Actuarial survival by extent of repair, expressed as probability with number at risk. B, Kaplan–Meier estimate of freedom from vascular reintervention by extent of repair, expressed as probability with number at risk.[29]

observed with open repair – F/B-EVAR: 19% (type I) and 5% (type III), versus open repair: 22% (type I) and 10% (type III). Perhaps most important was the finding that in a high-risk subset of patients, mortality was low and morbidity high, as expected, but long-term branch patency was excellent – better than anticipated.

Our institution reported a comparison of endovascular and open techniques for descending thoracic and thoracoabdominal aneurysm repair [31]. Of 724 patients, 372 underwent open surgery and 352 underwent endovascular procedures with thoracic and branched endografts. The mean age was 67±12 years and patients with endovascular repair were on average 8.6 years older (71.3±12 versus 62.7±13 years, $p<0.001$) than open repair.[31] Endovascular repair was more commonly used to treat extent I and IV TAAA, with open repair more frequently used to treat extent II and III TAAA, of which chronic dissections were more frequently treated (113 open versus 44 endovascular, $p<0.001$) [31]. There were no intraoperative deaths, the 30-day mortality rate was 8.3% in open and 5.7% in endovascular patients ($p=0.2$). One-year mortality rates were 15.9% in open and 15.6% in endovascular repair patients. There were no ruptures during follow-up. Spinal cord injury – paraplegia or paraparesis – occurred in 15 endovascular patients (4.3%) and 28 open patients (7.5%, log-rank $p=0.08$). Spinal cord injury was linked to the extent of the required aneurysm repair, which was highest for extent II aneurysms in both groups, followed by extent I, III, and then IV, with the lowest incidence noted for patients with isolated thoracic aneurysms; the repair technique was not associated with risk of spinal cord injury. Moreover, the severity of the spinal cord injury and potential for recovery did not differ between the groups. Of note, spinal cord injury was more likely to occur in chronic dissection patients treated with open (11 of 113, 10%) compared to endovascular (0%) repairs, but the extent of aneurysm treated precluded any definitive conclusions.

Summary

Surgical approaches to the TAAA are challenging and the risks of neurologic deficit are significant. Advances in spinal cord protection, open and endovascular surgical techniques, and perioperative care have led to promising outcomes. Concomitantly, the morbidity and mortality rates associated with these procedures have decreased significantly. Although better technology and techniques have allowed improved surgical outcomes, appropriate patient selection and the experience of the surgical team cannot be overstated. The key to success during TAAA repair is the planning that leads up to it. There are multiple facets to the planning stage: rigorous medical risk evaluation, evaluating preoperative imaging, and the timing and design of the surgical procedure itself. Finally, because TAAA repair is a team sport, a multidisciplinary surgical team is required.

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Section 2

Thoracic Surgery

Steven Woolley

"Omnia mutantur, nihil interit"

Publius Ovidius Naso (43BC-17AD)

Chapter 11

Surgical Treatment of Small Cell Lung Cancer

Vignesh Raman, Oliver K. Jawitz and David H. Harpole

"Acta est fabula, plaudite"

Gaius Octavius Augustus (63BC-14AD)

Introduction

The American Cancer Society (ACS) estimates that in 2018 about 234,000 new cases of lung cancer will be diagnosed, and that about 154,000 lung cancer deaths will occur in the United States [1]. Small cell lung cancer (SCLC) represents about 15% of all lung cancer and portends a poor prognosis [2]. Risk factors for SCLC are the same as for non-small cell lung cancer (NSCLC), and include smoking, pollution, and exposure to carcinogens like asbestos and radon. Over 95% of patients with SCLC have a history of tobacco use. Its incidence has been decreasing over the past several decades, but all-stage median survival has remained constant at about seven months. The five-year overall survival for patients with stage I, II, III, and IV SCLC is 31%, 19%, 8%, and 2%, respectively [1].

Staging

The Veterans Administration Lung Study Group (VALG) initially designated SCLC as either limited or extensive based on the ability to provide radiation therapy through a single treatment port [3]. Limited SCLC is defined as disease confined to a single hemithorax, including nodal metastasis. Extensive disease is generally defined as involving more than one hemithorax or systemic involvement. The VALG staging has been historically the most popular in describing SCLC. In 1989, the International Association for the Study of Lung Cancer (IASLC) recommended inclusion of contralateral mediastinal and supraclavicular nodal metastases, as well as ipsilateral pleural effusions under limited disease stage [3]. While the American Joint Committee on Cancer's (AJCC) TNM staging is increasingly used to describe SCLC, the National Comprehensive Cancer Network (NCCN) guidelines still define SCLC as either limited-stage, including any M0 tumor that can be safely treated with a radiation plan, or extensive-stage, including M1 tumors and T3-4 tumors too large to be encompassed in a radiation plan [4].

Historical Treatment

Historically, surgery has not played a role in the management of SCLC. Instead, chemotherapy and radiation have been the mainstay of treatment. Two prospective clinical trials have

examined the role of surgery in SCLC. Between 1966 and 1973, the Medical Research Council reported a trial comparing surgery and radiotherapy for primary treatment of small or oat-cell lung cancer [5-7]. The trial enrolled 144 patients with biopsy-proven SCLC without extrathoracic metastasis who were deemed to be candidates for surgical resection. They were randomly assigned to either surgery with intention to treat or radiation therapy. There were no survivors at 10 years in the surgery group, while three patients in the radiation group were alive at 10 years. The mean survival for patients who underwent surgical resection was 199 days, while patients who underwent radiation therapy had a significantly higher mean survival of 300 days, leading the authors to conclude that surgery did not have a role in the treatment of SCLC. The trial had important limitations:

(1) the surgery group had 37 patients (total 71) who underwent a thoracotomy without resection, but due to intention to treat analysis, these patients were all included in the trial.

(2) the stage information for patients in each arm was not provided.

(3) the kind of radiation used in the radiation arm was also not detailed.

In 1994, the Lung Cancer Study Group reported a prospective trial comparing surgery with no surgery after chemoradiation in SCLC patients [8]. In this trial, 328 patients underwent chemotherapy and radiation, after which 146 patients with at least a partial response to chemotherapy were randomized to surgery vs. no surgery. The median survival for patients who underwent surgery was 15 months, compared to 19 months for those who did not undergo surgery. There was no significant difference in survival between both arms, prompting the conclusion that surgery did not provide a benefit in the multimodal treatment of SCLC. This study was limited by a small number of patients. Therefore, as the only prospective data available demonstrated no clear benefit to surgery, the treatment of SCLC has largely been confined to chemoradiation.

The biggest advances in the treatment of SCLC have been in the development of more effective chemotherapeutic regimens. In the 1970s, combination anthracycline-based chemotherapy was found to be superior to monotherapy, and in the 1980s platinum-based chemotherapy was developed and combined with thoracic radiation for limited disease SCLC [9]. In the 1990s, concurrent chemoradiotherapy was devised, and prophylactic cranial irradiation (PCI) was offered to patients with good performance status and complete response to chemoradiation. In the 2000s, hyperfractionated thoracic radiation regimens were developed, and the use of PCI extended to those with extensive disease with good performance status.

Current Management

The development of platinum-backbone chemotherapy and potentially improved survival for limited disease SCLC renewed interest in surgery. In a prospective single-arm study in 1999, Eberhardt et al. enrolled 46 consecutive patients with stage IB to IIIB SCLC after mediastinoscopy to undergo chemoradiotherapy followed by surgery [10]. They found an all stage median survival of 36 months and a five-year survival of 46%, which is higher than the survival reported in the literature for chemoradiotherapy alone, suggesting a possible benefit for surgery in SCLC.

Several national and population-based observational studies have since also indicated a survival benefit in patients with SCLC who undergo surgery. In 2010, Sawabata et al. described the outcomes of over 1300 patients with SCLC and found on multivariable analysis that patients who underwent surgery were more likely to survive compared to

those receiving chemotherapy or radiation alone; however, this survival benefit was not seen when compared to patients receiving both chemotherapy and radiation [11]. Four studies using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry have demonstrated a survival benefit for patients undergoing surgery for early and limited stage SCLC, although with the important limitation that the SEER database does not contain information about receipt of chemotherapy [12-15]. Schreiber and colleagues examined patients with localized (T1-T2Nx) and regional (T3-T4Nx) disease and found that the median survival for patients with local and regional disease undergoing surgery was 42 and 22 months, respectively, compared to that of patients not undergoing surgery (15 and 12 months, respectively) [14].

Weksler and colleagues studied patients with stage I and II SCLC and found that patients undergoing surgery had a median survival of 34 months compared to 16 months in non-surgical patients [13]. The SEER analyses also found that even wedge resections are associated with a survival benefit compared to no surgery, but that lobectomy and pneumonectomy are associated with the best outcomes. Three studies using the National Cancer Database (NCDB) have studied the long-term survival of patients with SCLC treated with surgery [16-18]. Yang and colleagues found that surgery for N0 and N1 SCLC is associated with a survival benefit compared to definitive chemoradiation, with a five-year overall survival of 48% (compared to 30%) in N0 disease and 31% (compared to 26%) in N1 disease [16,17].

As the evidence for including surgery in the multimodal therapy for SCLC mounts, the NCCN currently recommends surgery in limited stage T1-2N0 SCLC for patients with negative mediastinal staging. The NCCN recommends the addition of adjuvant chemotherapy for N0 patients, and chemotherapy with mediastinal radiation for patients with N1 and N2 disease. The NCCN does not recommend surgery for limited stage disease in excess of T1-2N0, or for extensive stage disease, where chemotherapy with or without radiation remains the mainstay [4].

Future Directions

The landscape of medical therapy for lung cancer is evolving rapidly with the promise of molecular and immunotherapeutic agents targeting genes differentially expressed in subsets of tumours. A new trial has demonstrated a survival benefit for patients with extensive stage SCLC receiving immunotherapy in the form of a programmed death ligand-1 (PDL1) inhibitor, atezolizumab, in combination with systemic therapy compared to systemic therapy alone [19]. The role of surgery in multimodal therapy of SCLC including systemic therapy, molecular and immune therapy, and radiation needs to be further elucidated. New prospective randomised controlled trials are needed to examine the utility of surgery in both limited and extensive SCLC, given the limitations of the existing older trials and the significant advancements in systemic and radiation therapy.

Summary

Chemotherapy and radiation remain the mainstay of treatment for SCLC. Recommendations from the National Comprehensive Cancer Network currently advocate the use of surgery in patients with limited stage T1-2N0 SCLC with negative mediastinal nodes, followed by adjuvant chemotherapy with or without radiation. The guidelines do not recommend offering surgery to patients with limited stage SCLC beyond T1-2N0 disease, or with extensive stage disease. New prospective, randomised trials are needed to fully elucidate the role of surgery in the treatment of SCLC.

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Chapter 12

Recent Advances in Radiation Oncology in the Management of Lung Cancer

Anoop Haridass

"Aeque pars ligni curvi ac recti valet iqui"

Introduction

Lung cancer remains one of the leading causes of cancer mortality in the UK [1]. In keeping with the population shift to an older age group in developing and developed nations, the demographic of the patients presenting to the cancer clinic is also changing. This has commonly resulted in the average lung cancer patient being older with attendant comorbidity which has always had an impact on the feasibility, tolerability and safety of cancer treatment.

After surgery, which remains the gold standard for curative treatment of lung cancer, radiotherapy (RT) is the second most common modality used in a curative setting for lung cancer. Following rapid evolution in the imaging, computing and treatment delivery aspects of RT, there has been a perceptible shift over the last decade in the therapeutic ratio of this treatment modality with a decrease in toxicity and improvements in reducing cancer mortality.

Fundamentals of Radiotherapy

At its most fundamental, RT involves treatment of lung tumours with high doses of high energy photons or X-rays or other forms of ionising radiation. Ionising radiation by definition creates ions in the cells when it penetrates through the tissues, mostly in the form of hydroxyl ions from water molecules. These ions in turn cause damage to the DNA in the cancer cells (and normal cells) which causes cell death by various pathways like apoptosis, necrosis, etc. The selectivity of radiation and its therapeutic ratio arises from the ability of normal cells to correct such DNA damage caused by radiation using DNA repair mechanisms, which are deficient in cancer cells [2]. In newer RT techniques, like Stereotactic Ablative Body Radiotherapy (SABR/ SBRT), the significantly higher (biological equivalent) doses of radiation used can cause other types of cell injury like microvascular injury and immune-mediated cell death as well. It is notable that these repair mechanisms, even in normal cells, are not absolute in their ability to repair the damage caused and these are responsible for the late/permanent side effects of radiation on normal tissues.

The doses of (conventional) radiation required to treat lung cancer with curative intent are high and most radiotherapy schedules for non-small cell lung cancer (NSCLC) deliver 55 to 70 grays (Gy) of radiation split in to multiple sessions called fractions (usually 2 to 3 Gy per fraction) delivered daily over several weeks. In SABR treatment, the dose delivered per fraction is higher (typically 8 to 18Gy per fraction for lung cancer treatment). To put these doses in context, a 3 Gy dose delivered to the whole body would be lethal, hence the need for accurate delivery of the radiation [3].

Patient Pathway for Radiotherapy

The patient's journey through radiotherapy is usually in a series of discrete steps. The first and perhaps the most important is the decision to treat the lung cancer with radiotherapy. This decision is taken in the context of the patient's performance status, stage at presentation, histology, tumour location, and underlying comorbidity - especially pulmonary function and alternative treatment options available. Due to these factors and the different expertise required to make these decisions, this is usually done in the setting of a multidisciplinary team meeting in the UK (tumour boards in other parts of the world) which usually include a respiratory physician, pathologist, surgeon and oncologist. The different approaches are usually discussed and written information provided to the patient before a finalised radiation treatment plan is put in place after obtaining informed consent for the procedure. The exact inclusion and exclusion criteria for radiotherapy will be discussed in further detail in later sections addressing the different stages of lung cancer presentation, but baseline lung function tests which show a forced expiratory volume in the first second (FEV1) of at least 40% of predicted levels and a transfer factor for carbon monoxide (TLCO) of at least 40% predicted are requisite for feasible delivery of curative radiotherapy. At present, these apply for conventional radiotherapy but not for SABR treatment which, possibly due to the lower volumes of lung treated, appears to have less impact on the physiological reserve of the patient. Therefore, there is no lower threshold for lung function for patients being treated with SABR for lung cancer.

Once a joint decision with the patient is made regarding the need for radiotherapy, the next step is to 'plan' the radiotherapy which entails the patient undergoing a CT scan of the area of interest (chest for lung cancers). This treatment planning scan serves multiple purposes:

(a) accurately measure the electron density (required to accurately calculate amount of dose deposited by ionising radiation in tissue) of the tissues in the patient's anatomy.

(b) determine the size and depth from surface of the tumour to allow accurate radiotherapy delivery.

(c) map the patient to a coordinate system - usually involving intersecting laser lights on the treatment scanner which is replicated on the radiotherapy treatment machine-usually a linear accelerator (LinAc).

(d) accurately measure the extent of movement of the tumour during each phase of respiration in 3 dimensions, this is then linked to measurement of the respiratory cycle (regularity, amplitude, etc.) as a visual trace – analogous to an ECG to create a 4-dimensional CT scan.

Once these images have been obtained and processed by the computerised radiotherapy planning system, the oncologist delineates the tumour (called GTV – gross tumour volume), expands the tumour volume to a clinical target volume (CTV) to cover areas at

risk of microscopic spread of disease and subsequently expands this again in 3 dimensions (usually 5-10mm) to a planning target volume (PTV) based on measured uncertainties in treatment delivery specific to the machine treating the patient.

The oncologist also contours the organs at risk (OAR) of damage from high dose RT (spinal cord, oesophagus, normal lung, heart, brachial plexus, skin etc.). The dataset of the scans, target volume and organs at risk are used by the radiotherapy planner to calculate a radiation plan on the computerised system to cover the PTV in high dose while simultaneously ensuring the OARs are getting a lower dose of radiation than the tolerance threshold of that organ based on pre-defined constraints or as per the oncologist's requests.

The oncologist reviews the plan and approves it if satisfactory and the treatment is delivered by the LinAc over many fractions. The typical curative radiotherapy dose in the UK would be 55-60Gy in 20-30 fractions delivered 5 days a week for 4-6 weeks. In contrast, SABR is delivered on alternate days in a smaller number of fractions e.g.: 55Gy in 5 fractions over 7-10 days.

The patient is regularly reviewed during the treatment to assess side effects and manage them as required. Common side effects of RT include fatigue, dermatitis, oesophagitis, pneumonitis, cough, breathlessness and chest wall aches dependent on the areas/volumes of lung treated. With high dose SABR, in addition to lung fibrosis other side effects like insufficiency fracture of the ribs (~4% incidence), bronchial collapse (1%) and oesophageal strictures (<1%) can also occur months to years after the treatment. The patient is subsequently followed up with interval imaging to gauge response to treatment and manage the late side effects of radiotherapy like lung fibrosis.

Radiotherapy in Early Stage NSC Lung Cancer (AJCC v8.0 Stage I and IIA)

Surgery remains the gold standard in the curative management of early stage NSC lung cancer. There unfortunately remains a significant number of patients, mostly due to pulmonary and/or cardiovascular comorbidity, that are not medically fit enough to undergo surgical resection. It is in the curative management of these patients that radiotherapy has commonly played a role. Conventionally, fractionated radiation as detailed in the previous section has produced inferior results [4]. The advent of stereotactic radiotherapy in this setting with higher rates of local control has changed the utility of radiotherapy.

This will be discussed under three scenarios:

(a) Peripheral* early stage NSC lung cancers in medically inoperable patients.

(b) Central* early stage inoperable NSC lung cancers.

(c) Peripheral* early stage NSC lung cancers in medically operable patients.

* defined as per the IASLC as tumours within 2cm of the proximal airways, mediastinal organs and brachial plexus [5].

(a) Peripheral Early Stage NSC Lung Cancers in Medically Inoperable Patients

This is the commonest scenario in which radiotherapy is used in early lung cancer in most lung cancer clinics. The options for this cohort of patients include conventional RT, SABR

and surveillance. Retrospective comparisons of 497 propensity-matched patients treated with conventional RT or SABR for lung cancer have shown SABR to be superior in terms of local failure rates (34% vs 13.6%) and overall survival (39% vs 53% at 3 years) [6]. Recently, a prospective trial (CHISEL) comparing SABR with modern conventional radiotherapy techniques has shown improved freedom from local failure (HR=0.29, p=0.002) and longer overall survival (HR=0.51, p=0.02) for the patients treated with SABR [7]. However, in another prospective trial (SPACE) comparing SABR with escalated doses of conventional RT, there was no significant difference in overall survival at 3 years (54% in the SABR arm vs. 59% in the conventional RT arm) or local control (86.4% vs. 85.7%) [8]. These trials, in addition to SABR retrospective series (Table 1), have shown high rates of local control with very low levels of late toxicity (2 to 10% > Gr3) and acceptable overall survival [9-15].

Table1: Primary Non-Small Cell Lung Cancer SABR cohorts

Author	No of pts	Local control	Survival
Onishi et al 2007 [9]	257	86% @3yrs	56% @3yrs
Lagerwaard et al 2008 [10]	206	93% @2yrs	64% @2yrs
Bongers et al 2011 [11]	500	90.4% @3yrs	53.1% @3 yrs
Senthi et al 2012 [12]	676	10.5%LRR @ 5yrs	Not available
Gillespie et al. 2015 [13]	320	95% @2yrs	64.3% @ 2 yrs
Murray et al 2015 [14]	273	95.7% @3yrs	38.6% @3yrs
Chiang et al 2016 [15]	192	89.3% @ 3yrs	72.4% @3yrs

As a result, SABR is now considered standard of care in medically inoperable NSCLC worldwide. Due to concerns surrounding toxicity to the mediastinal structures (proximal airways, pulmonary vasculature, oesophagus, heart) by the high radiation dose, this treatment is offered mainly to peripheral lung cancers although this is an area of contention. The inclusion criteria for SABR are largely standardised and listed below.

Inclusion Criteria:

- T1a/b/c or T2a/b (≤5cm) N0 M0 NSCLC with histological diagnosis or FDG avid lesion on PET-CT scan and/or growth on serial CT scan when predictive models indicate a >70% risk of malignancy.
- Not suitable for surgery because of medical comorbidity, technically inoperable or patient choice after surgical assessment.
- WHO performance status 0-2.
- Peripheral lesions, defined as outside the IASLC 'central' zone (Figure 1).
- Able to lie flat for up to 30 minutes in the treatment position.
- Radiologically definable lesions – i.e. discrete lesions with discernible edges.

Although pulmonary fibrosis and significant (non-correctable) respiratory movement of the tumour are relative contraindications to treatment, these must be taken in context with the risk of excess toxicity the SABR treatment could entail in these circumstances weighed against the potential lack of other treatment options in these patients.

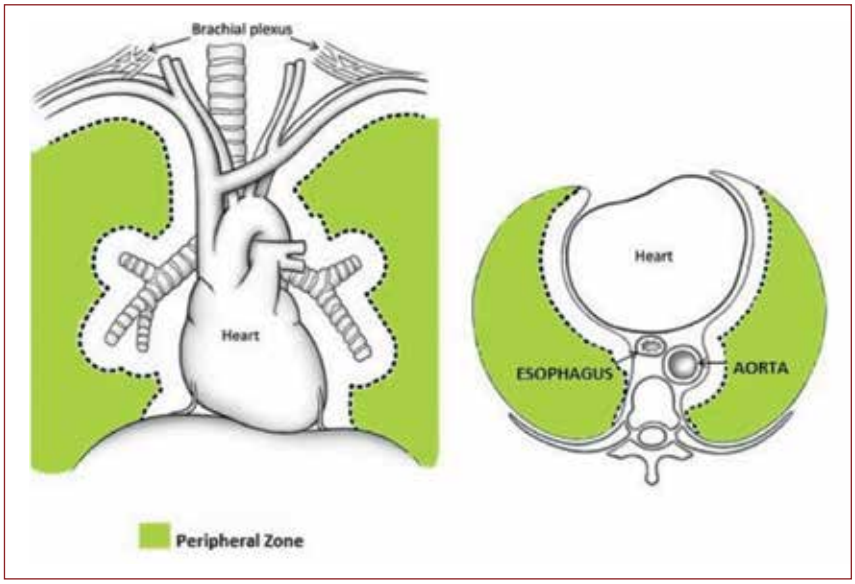

Figure 1: IASLC lung peripheral zone 2cm from mediastinal structures

IASLC, International Association for the Study of Lung Cancer.

(b) Central Early Stage Inoperable NSC lung cancers

Central tumours which are inoperable have been treated with fractionated conventional radiotherapy with similar rates of control as peripheral tumours and slightly more toxicity largely related to mediastinal structures like the oesophagus. Concerns of toxicity with SABR to central early stage lung cancer were initially raised by a differential rate of freedom from >gr3 toxicity in central (54%) and peripheral (83%) lung cancers treated to the same dose of SABR (66 Gy in 3 fractions) in a phase II study by Timmerman et al [16]. Risk-adapted (lower) SABR doses treated over more fractions (e.g. 60Gy in 8 fractions & 45Gy in 5 fractions) has been reported in retrospective series to achieve high rates of local control (>92%) without significant level of grade 3 and above toxicity (7%) [17,18]. This was also reported in larger retrospective series from several centres but was different from the prospective trial data provided by the Nordic HILUS trial which showed similar local control rates but with high levels (28%) of high grade (>gr3) toxicity [19]. The RTOG 0813 trial was a dose escalation study looking at treating central lung tumours with SBRT and, at the highest dose levels achieved in the trials (60Gy in 5 fractions), there was 21% Gr3 and above toxicity including 4% incidence of fatal pulmonary haemorrhage. The authors concluded that the higher toxicity of the central lung cancer SABR could be mitigated by lower doses of RT with more prolonged fractionation regimes. Further trials (LungTECH, Sunset) testing this hypothesis are currently in progress and at present the best way to treat this cohort of patients would be within the context of these trials.

(c) Peripheral Early Stage NSC Lung Cancers in Medically Operable Patients

The high rates of local control provided by SABR in the cohort of inoperable patients has led to interest in the use of SABR in the cohort of patients who have operable disease, especially in the subset of patient in whom surgical resection is considered high risk due to

comorbidity. Retrospective comparisons of surgical and SABR cohorts are confounded by the difference in survival between operable and inoperable patients but have consistently shown improved survival with anatomical surgical resection. The meta-analysis carried out by Zheng et al. analysed 63 SBRT and surgical studies which included over 11,000 patients treated between 2000 and 2012 with either SBRT or surgery [21]. This analysis showed that lobectomy (LR) had improved survival in comparison to SBRT with a 5-year observed survival rate of 66.1% for LR vs. 41.2% for SBRT, with no statistically significant differences in local control (80% LR vs. 83.9% SBRT) or disease-free survival rates (74.8% LR vs. 65.8% SBRT) at 5 years. In an attempt to remove confounders inherent in such analyses, a propensity-matched analysis of 864 matched patients across 6 studies by Zhang et al. has shown the superiority of surgery over SBRT in terms of 3-year overall survival (OR=1.82, 95% CI 1.38-2.40, p <0.0001), with no difference in local control, disease-free survival or cancer specific survival.

Multiple prospective trials (ROSEL, STARS, ACOSOG, RTOG Z4099 and SABRTooth) to address this question have failed to recruit due to a lack of equipoise. A pooled analysis of two of the closed trials (ROSEL and STARS) showed a 3-year survival of 95% for SBRT vs. 79% for surgery (HR 0.14; p=0.037) but with 10% of SBRT patients having grade 3 toxicity and no grade 4 or 5 toxicity [22]. This compared favourably to 4% grade 5, 4% grade 4 and 15 % grade 3 toxicity seen in patients who had surgery. The credibility of this analysis is questionable, given that the recruitment of both these trials was 4% of their respective targets. Further prospective trials like the VALOR trial are in progress and are recruiting patients with innovative pathways to obtain level one evidence to answer this question about the utility of SABR in the setting of operable lung cancer.

Based on current evidence, surgery should be considered as the first option for operable early lung cancer. In cases where the surgical risk is considered high by the multidisciplinary team, an informed discussion with the patient about the utility of SABR in this context would be appropriate.

Radiotherapy in Locally Advanced Lung Cancer (AJCC v8.0 stage IIB to IIIC)

In locally advanced lung cancer, multimodality treatment is generally required to obtain control over lung cancer. Surgery followed by (adjuvant) chemotherapy, chemotherapy concurrent with radiotherapy, and sequential (induction) chemotherapy followed by radiotherapy are the options available to treat these stages of lung cancer. Overall survival at 5 years despite multimodality treatment remains poor at 53% for stage IIB, 36% for stage IIIA, 26% for stage IIIB and 13% for stage IIIC [23].

In stage IIB and III NSC lung cancer patients who are not surgical candidates, a combination of platinum-based chemotherapy and radiation would be the primary treatment option. This does require the patient to have adequate pulmonary reserve as discussed previously. Patients with WHO performance status (PS) of 0 to 1 could be considered for concomitant chemoradiation and those with a PS of 2 could be considered for sequential chemotherapy followed by radiotherapy as a potentially more tolerable curative regime.

A meta-analysis of 1205 patients across six trials showed significant benefit of concomitant chemoradiotherapy over sequential chemoradiotherapy on overall survival (HR 0.84, p=0.004), with an absolute benefit of 4.5% at 5 years [24]. Concomitant radiotherapy was

not superior to sequential treatment in reducing distant progression (HR 1.04, p=0.69). Concomitant chemoradiotherapy however increased acute oesophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (p<0.001).

As lung cancer has a dose response relationship, escalation of the dose of RT delivered with concurrent chemotherapy was tested in the RTOG 0617 trial [25]. Median overall survival was 28.7 months (95% CI 24.1-36.9) for patients who received standard-dose radiotherapy (60Gy) and 20.3 months (95% CI 17.7-25.0) for those who received the escalated dose (74Gy) radiotherapy (HR 1.38, p=0.004). Higher doses of radiotherapy appeared to be detrimental to survival and were hypothesised to be secondary to the longer treatment time which allows tumour repopulation (a well-documented effect in category 1 solid tumours like NSCLC) and possibly cardiovascular effects of the higher doses of RT. To address these problems with dose escalation, the IDEAL CRT trial escalated the dose delivering it over a shorter time frame and used novel RT planning methodology by escalating the dose of RT simultaneously keeping the dose constraints of the organs at risk (e.g. lung and oesophagus) to a trial-derived minimum [26]. This trial showed higher rates of overall (68%) and progression-free survival (48.5%) at two years without increasing the rates of high grade (gr 3 to 5) oesophageal toxicity (6%). This concept of 'isotoxic' dose escalation is likely to be the way forward in improving the therapeutic ratio in this group of patients.

In the sequential chemotherapy followed by radiation group, similar attempts to improve the therapeutic ratio have used various methods, like isotoxic dose escalation, accelerated regimes of RT along with treating with larger doses of RT per session and completing the treatment before repopulation of the tumour cells becomes a limiting factor such as treating with multiple fractions per day continuously. As all of these approaches have shown some degree of benefit in this patient population in various small-scale trials, a phase 2/3 larger scale 'pick the winner' type trial called ADSCAN has recently opened and is currently recruiting patients to determine which of these approaches (if any) produced the largest therapeutic gain compared to standard radiotherapy after chemotherapy [27]. As the majority of lung cancer patients present with locally advanced or metastatic disease, even small increments in survival made in this cohort of patients can have a big impact at the larger population level.

Radiotherapy in Metastatic Lung Cancer (AJCC Stage IV)

Radiotherapy has been extensively used in metastatic disease for palliation of symptoms, both in an emergency situation like metastatic spinal cord compression and routine situations like control of bony pain and haemoptysis. Radiotherapy has been quite effective in the control of bone pain with rates of pain control around 60% for most RT schedules and in studies which used SABR to bony metastases, up to 90% pain control has been reported, with up to a third of patients reporting complete pain control [27]. There is also consensus that single session radiation treatment (e.g. 8Gy in 1 fraction) is as effective at controlling pain and achieving local control as longer fractionated courses (e.g. 30Gy in10 fractions). As a result, most of the palliative radiation delivery for bony pain has moved to single session treatment that can be planned and delivered on the same day. In the context of patients in a metastatic setting with a limited life expectancy, a short effective treatment would be the ideal intervention. The utility of SABR to bony metastases in improving pain control is being explored in clinical trials but has yet to gain traction due to the significant amount of extra resources required to plan and deliver SABR compared to conventional palliative RT.

Thoracic symptoms from lung cancer (e.g. haemoptysis, pain, cough, airway obstruction, etc.) can be reliably improved by short courses of palliative thoracic radiotherapy. As with bony metastases, delivering higher doses of RT over longer time frames did not appear to give better or more durable control of symptoms compared to shorter regimes [28].

Brain metastases develop in about 30% of all lung cancer patients. Symptoms arising from intracranial metastases can be relieved by radiotherapy to the whole brain; however, this is achieved at the expense of permanent detriment to the cognitive function in up to a third of patients having whole brain radiotherapy. The QUARTZ trial has shown that there does not appear to be any benefit in treating patients with brain metastases from NSCLC with whole brain radiotherapy either in terms of survival or quality of life [29]. In order improve this, in selected patient with a limited number of brain metastases, approaches like stereotactic radiosurgery (and/or surgical resection) achieves intracranial disease control without the consequent effects on cognition. In a selected subset of younger fit patients with controlled extracranial disease, this can improve survival.

There is increasing interest in the management of oligometastatic lung cancer. Although this is not precisely defined yet, this is considered a stage when there is limited spread (1-5 metastases) of the cancer from the primary site. There is early molecular evidence that the early metastases serve as a source for further metastatic spread of the disease and the hypothesis is that ablative treatment of these limited metastases could improve disease control and improve survival. Metastasectomy and high dose conventional radiation have been used in the past with good local control but with attendant toxicity, which was not always justifiable in the setting of disease that relapsed shortly after these interventions. The use of SABR in ablating the metastases with a non-invasive, relatively low toxicity radiation-based treatment which achieved a high rate of local control (80-90%) was of considerable interest [30]. A recently published trial, SABR-COMET has shown an improvement in median overall survival from 28 to 41 months with the use of SABR in addition to standard of care treatments in the oligometastatic population [31]. Other trials like SARON [32] and CORE [33] are examining the utility of this treatment in the lung cancer setting in the UK and will guide the future use of this novel treatment.

Radiotherapy in Postoperative Patients

Since the publication of the meta-analysis in 1998 and a further update in 2016 by the Cochrane systematic review database, the use of post-operative radiotherapy (PORT) is limited to specific indications and within the confines of clinical trials [34]. Analysis of data from 2,343 participants across 11 trials showed a significant adverse effect of PORT on survival, with a 18% relative increase in the risk of death. This was equivalent to an absolute detriment of 5% at two years, reducing overall survival from 58% to 53%. Although these were trials that used old radiotherapy techniques with very little consideration to cardiac and pulmonary toxicity, these results have restricted the use of PORT largely to patients with N2 disease in the context of the LungART trial [35]. Patients with involved bronchial margins where re-resection is not an option are also referred for adjuvant radiotherapy, though in the context of postoperative chemotherapy treatment, which has become standard of care in locally advanced lung cancer patients, the utility of this is unknown.

Conclusion

Radiotherapy has an important role to play in most stages of lung cancer. Newer technologies and toxicity mitigation strategies have helped to improve the therapeutic

ratio of this treatment. The increasing use of stereotactic radiotherapy which offers high rates of local control with low levels of long-term toxicity is a promising development in primary lung cancer treatment. The results of randomised trials will provide an expanding evidence base for the use of this treatment modality in the management of primary and oligometastatic lung cancer.

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Chapter 13

Pushing the Boundaries in the Surgical Management of Lung Cancer

Lawek Berzenji and Paul E Van Schil

"Auribus teneo lupum"

Introduction

Lung cancer is the most common malignancy worldwide and the leading cause of cancer deaths in the last decade [1]. Although lung cancer rates vary around the world, an overall increase in new cases can be seen, mainly due to a rising incidence in developing nations [2]. In a large number of developed nations, tobacco control policies have caused a decline in lung cancer death rates in men; however, worldwide rates of female lung cancer and lung cancer death seem to be rising, even in most first world countries [1,3-5]. In recent years, an increasing number of treatment modalities and approaches have been proposed, especially since the development of targeted therapies [6]. Despite these trends, complete surgical resection remains the gold standard for the majority of patients with stage I-II, and even in some patients with more advanced stages of non-small cell lung cancer (NSCLC) [7].

The first successful pneumonectomy for lung cancer was performed in 1933 by Evarts Graham in St. Louis [8]. In the 1950s, anatomical studies and clinical research concerning the vascular and bronchial anatomy resulted in the introduction of the lobectomy and segmentectomy as surgical treatment modalities [9]. In the following decades, advances in thoracic anaesthesia and surgical instruments further aided the progress of making lung cancer surgery safer, more effective and more efficient [10]. Furthermore, clinicians began to acknowledge the importance of lymph node involvement and oncological staging in the assessment of disease prognosis [11]. In the last two to three decades, there has been an exponential growth in technological advancements, especially since the introduction of video-assisted and robot-assisted thoracic surgery (VATS and RATS, respectively) [12,13]. At the same time, more research is being performed and new data being published regarding optimal surgical approaches and treatment. In this chapter, we seek to explore the boundaries in the surgical management of lung cancer by reviewing the most recent literature on this subject.

Early Stage Lung Cancer

Recently, the International Association for the Study of Lung Cancer (IASLC) published the eighth edition of the tumour, node, and metastasis (TNM) classification. In this latest classification, a number of changes have been proposed regarding the different

components. For the T descriptors, a few recommendations have been made, primarily regarding early stage NSCLC - T1 disease is now described as a tumour with a maximum diameter ≤3 cm surrounded by lung/visceral pleura, but without involvement of the main bronchus. In the previous edition of the TNM staging system, T1 disease was subclassified into T1a and T1b with cut-off values of ≤2 cm and >2 to ≤3 cm, respectively. In the latest edition, the staging committee has proposed to subclassify T1 into T1a, T1b, and T1c with cut-off values of ≤1 cm, >1 to ≤2 cm, and >2 to ≤3 cm respectively as the survival curves nicely separate between these diameters.

According to the Fleischner Society Guidelines, accurate diagnosis of pulmonary nodules can best be obtained by performing measurements on high-spatial-frequency (sharp) filter of reconstructed thin-section computed tomography (CT) images displayed in lung window and in the axial plane. Furthermore, a differentiation should be made between solid lesions and subsolid lesions with ground-glass components in order to obtain a more accurate risk stratification [14]. The Fleischner Society guidelines have also made a number of recommendations for follow-up and further management of small pulmonary nodules. The recommendations are based on whether there is a single nodule or multiple nodules, whether the nodules are solid or subsolid, whether the patient is classified as low or high risk, and on the size of the nodule(s) [14,15].

In general, lobectomy with hilar and mediastinal lymph node dissection is considered to be the first line of therapy for stage I NSCLC that is functionally operable and technically resectable. However, an increasing number of studies and meta-analyses performed in more recent years have concluded that sublobar resections comprising segmentectomies and wide wedge resections, result in similar oncological and survival outcomes [16-18]. The majority of these studies are single-institution, retrospective analyses. Nevertheless, a growing body of evidence suggests a trend towards less radical surgery for early stage NSCLC <2cm. Until now, there has only been one published randomised trial which directly compared lobectomy and sublobar resection for T1N0 NSCLC. This study by the Lung Cancer Study Group (LCSG) was published in 1995 and updated a year later [19,20]. Diagnosis of the pulmonary nodules was based on chest X-rays and randomisation was performed intra-operatively. Thin-section CT-images and positron emission tomography (PET) were not available as standard diagnostic tools at that time. Furthermore, limited resection was not strictly defined and could be a segmentectomy or a wedge resection. In this trial, a higher death rate and locoregional recurrence rate was found for limited resection when compared to lobectomy [21]. This set lobectomy as the gold standard for the years to come. At the moment, there are two ongoing randomised, controlled trials that will address the same question: the Japanese JCOG0802/WJOG4607L trial which has included 1000 patients from 71 Japanese institutions and the American CALGB 140503 phase III trial which has enrolled 701 patients from institutes in Australia, Canada and the USA [22,23]. The results of these trials are eagerly awaited by clinicians and will hopefully give more insight into whether sublobar resection is equivalent to lobectomy for small early-stage NSCLC.

Another discussion that has simultaneously attracted more attention in the last few years is around the optimal approach for operable NSCLC. The rise of minimally invasive techniques has changed the surgical landscape over the last two decades as it has often proven to result in fewer complications, less pain and faster recovery [12]. In thoracic surgery, VATS lobectomy has indeed become the gold standard approach for operable lung cancers in early stages. There is an increasing amount of evidence that VATS resection

provides many potential advantages over open thoracotomy. Outcomes such as survival rates, complication rates, post-operative pain, hospital length of stay, chest tube duration, and post-operative quality of life all seem to be similar or better with VATS lobectomy when compared to open thoracotomy [24-28]. Even lymph node dissection and oncological efficacy seem to be similar to open surgery. Although several studies have indicated that open thoracotomy results in higher lymph node upstaging rates and, possibly, more radical lymph node dissections, overall survival (OS) does not seem to be better after open surgery. Furthermore, in propensity-matched studies, these differences in nodal upstaging seem to be diminished, possibly indicating that there is a selection bias and that the differences are also partly determined by the surgeon's experience with VATS lobectomy [12,29,30].

Currently there is only one randomised trial that compares the outcomes of thoracoscopic surgery and open surgery in early-stage lung cancer [31]. This is the first large trial that directly compares these two approaches in a multi-institutional, randomised setting. For this study, 508 patients were recruited of which 425 were eligible for analysis. Recently, the short-term outcomes have been published and results have shown significantly shorter median operating times for VATS lobectomy compared to open surgery (150 versus 166 minutes, $p=0.009$) and less intraoperative blood loss ($p=0.001$). Length of hospitalisation, postoperative pleural drainage, and rates of morbidity and mortality were not different. Residual margins and lymph node yields were similar for both groups as well. These short-term outcomes suggest that VATS lobectomy is a safe approach and provides similar, if not superior, results when compared to open thoracotomy for early-stage lung cancer. The results from the long-term follow-up are expected by the end of 2019 and will shed more light on the oncological and survival outcomes of VATS lobectomy [31].

Locally Advanced Disease

Locally advanced NSCLC represents a heterogeneous group of tumours and covers a large spectrum of diseases. In the most recent revision of the TNM-classification, stage III disease includes tumours with limited sizes and occult mediastinal nodal involvement on one hand, and large tumours with extensive nodal disease on the other. According to current guidelines, concurrent chemoradiotherapy (CRT) is recommended for those patients with locally advanced disease [32,33]. However, there is a large grey area of potentially resectable disease that may benefit from bimodal or trimodal therapy regimens that include surgery. The optimal treatment strategy and the use of surgery for this group of patients is hotly debated among clinicians [34].

A number of studies have addressed and investigated this matter over the years. One of the randomised trials that has compared surgical resection with radiation therapy (RT) after induction chemotherapy is the European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial [35]. In this trial, these bimodal treatment approaches were analysed in patients with clinical N2 (cN2) lung cancers of a non-squamous histological subtype. A total of 582 patients with stage IIIA and N2 disease were enrolled in this trial. Staging was performed using chest CT scans and abdominal ultrasound as PET scans were not available as diagnostic tools at the time. Induction chemotherapy consisted of three cycles of platinum-based chemotherapy and patients with response to treatment were randomised to either RT or surgery. Median and 5-year survival rates for the surgical arm were 16.4 months and 15.7% versus 17.5 months and 14% for the CRT arm ($p=0.596$). Mortality rates 30 days post-surgery were 4% for all resections and 7% for patients that underwent a pneumonectomy. In total, 72 patients (47% of patients in the surgical arm)

required a pneumonectomy. In this study regarding bimodal treatment approaches, surgical resection did not improve overall or progression-free survival (PFS) compared to RT.

Another randomised phase III study aimed at comparing surgery with RT after induction chemotherapy is the Radiation Therapy Oncology Group 89-01 (RTOG 89-01) trial. In this study, no significant difference in median survival time (19.4 months for the surgical arm versus 17.4 months for the RT arm, p=0.46) was found when comparing both treatment arms. However, patient recruitment was only 73 while the target was set at 224 patients, thus resulting in an underpowered study [36].

In the last two decades, the concept of trimodal therapy for resectable locally advanced NSCLC has gained more attention. The Intergroup Trial 0139 was one of the first randomised trials that compared definitive CRT with induction CRT followed by surgical resection. A total of 429 patients were enrolled in this study, of which 396 received treatment in one of both arms. In the definitive CRT group, 194 patients received initial treatment with cisplatin/etoposide and 45 Gy RT and further treatment with uninterrupted RT until a total dose of 61 Gy was administered. In the surgical arm, the same regimen of induction chemotherapy and RT was given, followed by a surgical resection. The extent of the surgery varied between wedge resection (3 patients), lobectomy (98 patients) and pneumonectomy (54 patients). No significant difference was found for the overall survival (OS) when comparing the bimodal and trimodal treatment arms (23.6 versus 22.2 months, p=0.24). However, PFS was better with trimodality treatment group compared to the bimodal group (12.8 months versus 10.5 months, p=0.017). Further statistical analysis showed that OS was significantly better for patients who underwent lobectomy instead of pneumonectomy as surgical treatment. In general, these results indicated that surgery, preferably lobectomy, could indeed provide a valuable addition to the standard treatment regimen of CRT [37].

A few years later, the phase III ESPATUE trial also attempted to evaluate the outcomes of trimodal therapy by randomising patients with potentially resectable stage III disease to either definitive CRT or surgical resection after induction CRT [38]. Inclusion criteria differed from the Intergroup trial as patients with N3 disease were also enrolled in the ESPATUE trial. In total, 246 patients were recruited against a target of 300 with an improvement of 15% in the 5-year survival rates after trimodal therapy. After induction therapy, 161 patients with resectable tumours were randomly assigned to either surgical resection (81 patients) or definitive CRT (80 patients). After a median follow-up period of 78 months, no statistical difference was found between the surgical and definitive CRT arm regarding 5-year OS (44% versus 40%, p=0.34) and PFS (32% versus 35%, p=0.75). Both treatment strategies were deemed acceptable for patients with resectable locally advanced NSCLC.

In recent years, there have been a number of meta-analyses that have attempted to bundle the data of these randomised trials to evaluate and compare the different combinations of treatment modalities. One of these meta-analyses combined data from six bimodality and trimodality trials to compare surgery with RT after induction treatment [39]. The two trimodality trials that were included in this analysis were the Intergroup trial and the Scandinavian phase III trial from the group of Sorensen et al. For both bimodality and trimodality treatments, no significant difference was found in OS between patients randomised to surgical resection or RT after induction treatment. Although no conventional levels of statistical significance were reached (p=0.068), the authors concluded that there seemed to be a trend toward improved OS for patients that underwent surgery in a trimodal treatment setting [39].

In the recent meta-analysis by Pötggen et al., six randomised trials including 1322 patients were analysed comparing surgery with definitive RT in a multimodality treatment setting [40]. Overall survival and PFS were not significantly different between the surgical and definitive RT arms, except for the Intergroup trial in which PFS was better in the surgical arm. Over all trials, treatment associated mortality was higher in the surgical treatment arms as was excess early mortality before six months of follow-up in the concurrent CRT trials [40]. In both meta-analyses, the authors concluded that multidisciplinary evaluation and careful selection of individual treatment strategies with either bimodal or trimodal therapy are important steps for treating this heterogeneous group of patients [39,40].

Oligometastatic Disease

In 1995, Hellman and Weichselbaum published a theory regarding the oligometastatic hypothesis for certain types of cancer that seem to progress in a step-wise manner [41]. The prefix "oligo" originates from the ancient Greek word for "few" and is used in the term oligometastasis to describe patients with a limited metastatic burden. In recent years, there has been a paradigm shift regarding treatment options for patients with metastatic disease, especially with the introduction of targeted therapies and immunotherapy. Regarding NSCLC, an increasing amount of evidence suggests that aggressive treatment of patients with oligometastatic disease may indeed improve outcomes. However, clear definitions of oligometastatic disease and treatment guidelines for this group of patients are still lacking [42]. Analysis of the database of the IASLC has shown that the prognosis of patients with a single extrathoracic metastasis is significantly better than patients with multiple metastases in one or several organs. This has resulted in a revision of the M descriptors in the eighth edition of the TNM classification. In the seventh edition, no differentiation was made between the number of extrathoracic metastases and all were staged as M1b and grouped as stage IV disease. In the latest revision, a single extrathoracic metastasis is staged as M1b (stage IVa) and multiple extrathoracic metastases in one or several organs are staged as M1c (stage IVb). This revision highlights the growing importance of the oligometastatic state in lung cancer progression [43].

The most common sites of distant NSCLC metastasis are brain, adrenal glands and bone. Treatment of patients with oligometastatic NSCLC often involves a combination of therapeutic modalities such as surgery, RT and systemic therapy. Two meta-analyses that have combined and analysed retrospective data on patients with oligometastatic disease found that there is indeed a subset of patients with oligometastatic disease that may benefit from aggressive local therapy. In both these meta-analyses, oligometastatic disease was defined as five or fewer sites of disease [44,45]. There have been a number of randomised trials that have attempted to further evaluate the effects of local ablative therapy. A prospective phase II trial published by Downey et al. included 23 patients who were treated with induction chemotherapy with mitomycin, vinblastine, and cisplatin followed by surgical resection of all disease sites and consolidation therapy with vinblastine and cisplatin [46]. Although only 12 patients completed induction chemotherapy, a median overall survival of 11 months was reported. Another prospective phase II trial was performed by De Ruysscher et al. who included 40 patients with five or fewer metastatic disease sites, 39 of which were evaluable. Radical local treatment consisted of surgery or RT and 37 patients (95%) received prior treatment with chemotherapy. The reported 1- and 3-year survival rates were 56.4% and 17.5% respectively. Despite the limited amount of prospective data, the results seem to suggest a possible role of surgery for a selected group of patients [47].

In the more recent randomised phase II trial published by Gomez et al., patients with three or fewer metastatic disease lesions and an Eastern Cooperative Oncology Group performance status of 2 or less were randomised to either local consolidative therapy (LCT) with or without subsequent maintenance treatment or to maintenance treatment alone [48]. Local consolidative therapy could be (chemo)radiotherapy or surgical resection of all lesions and maintenance treatment could be observation only. A total of 74 patients were enrolled for this study, of which 49 patients were randomised (25 in the LCT group and 24 in the maintenance therapy group). The study was terminated early after an interim analysis showed that local consolidative therapy extended the PFS time by 8 months. A significant difference in PFS was found when comparing the LCT arm with the maintenance arm (11.9 versus 3.9 months, p=0.0054). Furthermore, time to the appearance of a new lesion was significantly longer in the LCT arm compared to the maintenance arm (11.9 months versus 5.7 months, p=0.0497). At the American Society for Radiation Oncology (ASTRO) 2018 conference, the authors reported that OS was also significantly better in the LCT arm. They concluded that the results seem to strongly imply that there is a benefit for local therapy in limited metastatic disease for NSCLC and that LCT can possibly alter the natural history of oligometastatic disease. Two potential explanations are that LCT alters the systemic anticancer immune responses or that it works by limiting further spreading of metastatic disease. Although these results seem very promising, the question remains whether there is an overall survival benefit for aggressive local therapy [48]. Further testing in larger phase III trials are necessary to answer this question and to define which subgroups are most likely to benefit from LCT.

Salvage Surgery

For a selected group of patients with relapse after definitive CRT for locally advanced NSCLC, salvage surgery is an option. Prospective large-scale data regarding oncological efficacy, survival rates and morbidity for patients receiving salvage lung surgery after CRT are lacking. Furthermore, there is limited evidence regarding which patient selection criteria should be used when considering salvage surgery. In general, high-dose RT induces radiation fibrosis which increases surgical risk and compromises dissection planes and wound healing. For this reason, surgical resection becomes technically demanding and patients will be exposed to higher perioperative and postoperative risks. Until now, only a few studies have been published in order to clearly determine the feasibility and possible risks for surgery after longer intervals after radiotherapy [49]. A number of retrospective studies have been performed in recent years to evaluate local control and prognosis. Shimada et al. published a study of 18 patients with stage IIIA or IIIB (according to the seventh TNM classification) who underwent lobectomy or pneumonectomy after relapse or residual disease following initial therapy with definitive CRT [50]. Complete resection was obtained in 16 patients with 5 patients showing complete pathological response. There were no perioperative deaths and postoperative complications occurred in 5 patients. Furthermore, 3-year survival and recurrence-free rates were acceptable as well (78 and 72%, respectively).

Casiraghi et al. performed a similar study examining 35 patients with recurrence after definitive CRT for locally advanced NSCLC [51]. A total of 29 patients underwent lung cancer resection (11 lobectomies, 1 bilobectomy and 17 pneumonectomies), and six other patients underwent an exploratory thoracotomy. Extended resection was performed in 13 patients (45%): intrapericardial pneumonectomy (n=5), vascular or bronchial sleeve resection (n=2), atrial resection (n=1), tracheal sleeve (n=1), superior vena cava resection

and reconstruction (n=2, one of these with a tracheal sleeve resection), and chest wall resection (n=2). Complete resection was obtained in 27 patients (77%). Postoperative two- and three-year survival rates after surgical resection were 46% and 37%, respectively, with a median follow-up of 13 months. There were 2 perioperative deaths and 9 patients experienced major complications.

A very recent retrospective study performed by Schreiner et al. evaluated long-term survival after salvage surgery for patients with recurrence after definitive CRT. A total of 13 patients who were treated between 2011 and 2016 were analysed for 5-year survival rates, perioperative morbidity and mortality. Median postoperative survival and estimated 5-year survival rates were 29.7 months and 46%, respectively. Furthermore, the 5-year postoperative survival and 5-year recurrence-free survival were 46% and 44%, respectively. These results suggest that salvage lung surgery after definitive CRT is feasible with acceptable long-term survival and complication rates. However, patients should be carefully selected and evaluated by an interdisciplinary team of specialists, preferably in a thoracic reference centre [52].

Conclusion

The evolution of diagnostic and surgical techniques in the last two decades has immensely expanded the range of possibilities in the management of lung cancer. Undoubtedly, this evolution will continue in the coming years as our understanding of the pathophysiology and management of lung cancer increases. Currently, there are many exciting developments that will change the landscape for clinicians worldwide. Recently, at the IASLC 19th World Conference on Lung Cancer (WCLC), the results of the NELSON trial were presented which showed lower mortality rates for high-risk men and women that underwent CT screening (26% reduction, p=0.0003 and 39% reduction, p=0.0054, respectively) [53]. Already, current diagnostic tools allow earlier diagnosis and treatment of pulmonary nodules than in the past. If low-dose CT scans are applied as a screening tool, an even greater shift from late to early stage lung cancers will be seen in the future. This will have implications for surgeons as well, resulting in less radical surgical treatments and an increase in the use of minimally invasive techniques. In addition to screening, developments in minimally invasive approaches such as robotic surgery will provide surgeons with better tools for managing early stage lung cancers.

For locally advanced diseases, more studies are necessary to evaluate the long-term oncological efficacy and survival outcomes of bimodal and trimodal therapy. In the near future, immunotherapy will most likely be a part of multimodal strategies as well. Currently, the phase II exploratory NADIM-study is investigating the outcomes of combining chemotherapy and immunotherapy (nivolumab) as neoadjuvant treatment before surgical resection in patients with resectable stage IIIA NSCLC [54]. This is the first study that uses chemo/immunotherapy in a neoadjuvant setting. The results were presented at the WCLC and 24 out of 30 operated patients showed major pathological response. This was defined as <10% viable tumour cells in the resected specimen. In total, 18 of these 24 patients showed a complete response and none of the patients suffered recurrence at a median follow-up of 4.1 months. The preliminary results of this trial seem very promising and the complete results are eagerly awaited.

Regarding oligometastatic and recurrent disease, there is still a lot of ongoing debate. Although an increasing amount of studies are being published, there is a lack of level A evidence. The general consensus regarding treatment of these patients is that

interdisciplinary discussion and referral to thoracic specialist centres are the best option. Furthermore, careful selection and preoperative evaluation are necessary.

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Chapter 14

Endobronchial Valves: Current Evidence and Tips

Jorine E Hartman and Dirk-Jan Slebos

"Qui audet adipiscitur"

Introduction

Emphysema is characterized by an irreversible destruction of alveolar tissue and is a progressive incurable disease. Despite optimal medical therapy (like drugs, long term oxygen therapy and pulmonary rehabilitation), patients with severe emphysema still remain severely disabled and, for a small group of patients, lung volume reduction or lung transplantation can be an option. Lung volume reduction surgery is, in a carefully selected group of patients with severe emphysema, a beneficial treatment [1,2]. Due to high complication and mortality rates, less invasive bronchoscopic alternatives were developed. One of these is the bronchoscopic treatment with endobronchial one-way valves (EBV).

Endobronchial Valve Treatment

Like lung volume reduction surgery, EBV treatment is aimed at removing less-functional and hyperinflated areas of the lung. The treatment is aimed at patients with severe emphysema with severe hyperinflation of the lung. The proposed improved lung mechanics of lung volume reduction are: removal of dead space, relief of alveolar pressure, improvement of elastic recoil, improvement of chest wall motion and diaphragmatic function, and restoration of the tethering effect.

Currently, there are four different type of valves: The Zephyr one-way EBV (PulmonX Corp, CA, USA), Intrabronchial valve (IBV) (Spiration/Olympus, United States), MedLung EBV (MedLung, Barnaul, Russian Federation) and Endobronchial Miyazawa valve (Novatech, La Ciotat, Cedex, France). Results of randomised controlled trials (RCTs) are currently only published for the Zephyr one-way EBV and this is the only Food and Drug Administration (FDA)-approved valve and therefore we will focus in this chapter on this type of valve.

The Zephyr endobronchial valve is an implantable device that consist of nitinol and silicone (see Figure 1). It is a one-way valve and therefore allows for expiration of air from the treated lobe but does not allow re-inflation (see Figure 2). The valves are placed bronchoscopically in all airways leading to the target lobe preferrably under general anaesthesia [3]. Currently, there are three valve sizes for differing bronchial airway sizes. Table 1 shows the procedure

Figure 1: Zephyr one-way valve

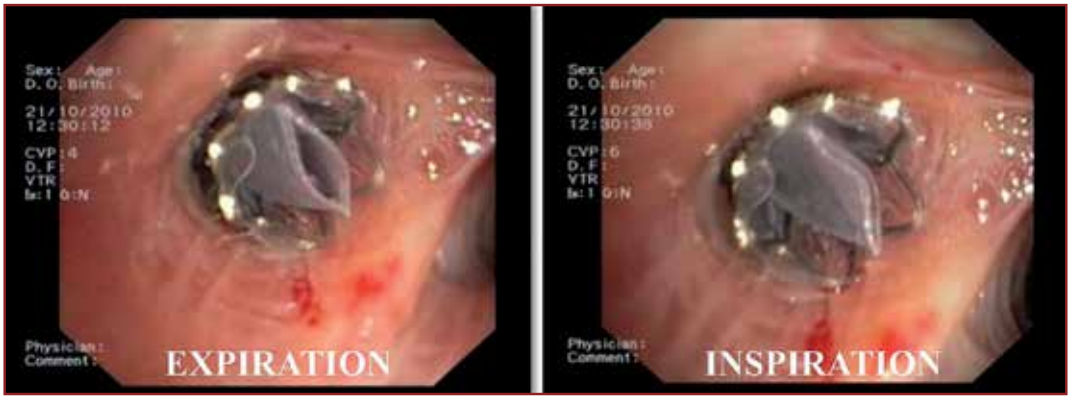

Figure 2: Picture of open valve at expiration and closed valve at inspiration

Table 1: Procedure characteristics of four RCTs investigating EBV treatment

	STELVIO (2015)	IMPACT (2016)	TRANSFORM (2017)	LIBERATE (2018)
n	34	43	65	128
Procedure time (mins)	18 (6-51)	NR	NR	29 (4-123)
Valves used, number	4 (2-7)	4	4 (2-8)	4 (2-8)
Hospital stay (days)	1 (1-13)	6 (3-40)	4 (1-49)	NR

Data are presented as median (range), EBV=Endobronchial valve group, NR= not reported, RCT = randomised control trial.

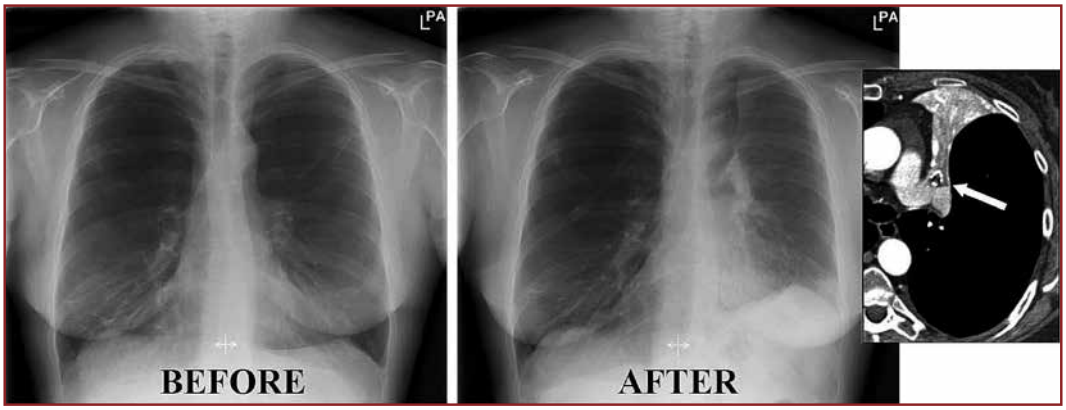

Figure 3: X-ray before and after EBV treatment and visible atelectasis after treatment on HRCT

characteristics of the four published RCTs investigating the Zephyr valve showing a median of four valves per patient (range 2-8) in a median procedure time of 18-29 minutes (range 4-123). Air only flows out of the lung and not back in, so the treated lobe will collapse (atelectasis) and this will reduce the hyperinflation of the lung. Figure 3 shows an X-ray before and after treatment and visible atelectasis on HRCT.

The decreased hyperinflation of the lung will potentially lead to relief of alveolar compression of adjacent tissue, improvement of elastic recoil, improvement of diaphragm function and restoration of airway tethering. These physiological improvements will lead to improvements in breathlessness, exercise capacity and quality of life.

The Evidence

The first-in-human treatment was performed in 2001 [4]. The first clinical trials showed the feasibility of EBV treatment using the Zephyr valve which is still used today, but it has gone through different developmental stages [5,6]. In 2010, the results of the first randomised controlled trial (RCT), the VENT trial, were published [7]. This trial showed that intact interlobar fissures, as a surrogate for absence of interlobar collateral ventilation, are a crucial predictor of success and important in patient selection. The CHARTIS trial, that validated the CHARTIS system (PulmonX Corp, CA, USA) that functionally measures collateral ventilation during bronchoscopy, confirmed this [8]. Before treatment, the CHARTIS balloon catheter is placed at the orifice of the target lobe to occlude it and the volume of air from the target lobe is then measured. In cases where collateral ventilation is absent, the flow will decrease (Figures 4 and 5).

The results of the BELIEVER-HIFI trial also showed that the CHARTIS measurement in patient selection is important besides visually scoring the intactness of fissures on CT [9]. Four RCTs have been published that used the CHARTIS measurement to include patients who had no collateral flow between target lobe and adjacent lobe. These were the STELVIO, IMPACT, TRANSFORM and LIBERATE trials that included in total 448 patients [10-13]. The results of these 4 trials are discussed below.

Figure 4: CHARTIS console and balloon catheter

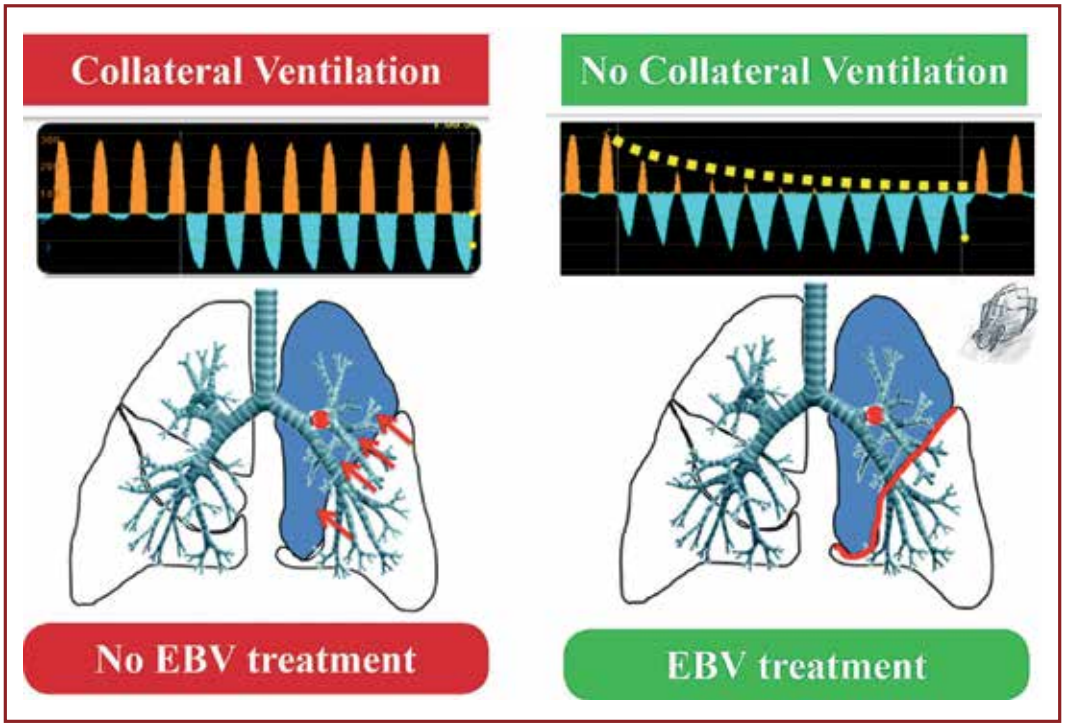

Figure 5: Flow measurement during CHARTIS measurement

Efficacy

These trials all showed significant and clinically relevant improvements in favour of the EBV treatment group compared with Standard of Care (SoC) in important outcome variables like lung function, exercise capacity and quality of life (Table 2). In these trials, the FEV1 improved by 17-29% compared to the SoC group, residual volume by -480ml to -831mL, 6-minute walk distance by 39-79 metres and St George's Respiratory Questionnaire -6.5 to -14.7 points. Furthermore, the STELVIO trial showed that treated patients also significantly improved their physical activity level compared to the SoC group (+1340 steps per day (57% increase)) [14].

The four trials also investigated the responder rates after EBV treatment (number of patients who reach a certain established minimal important difference) and these are shown in Table 3. The percentage of responders in the different trials for FEV1 were 40-72%, for RV 44-71%, for 6MWD 42-79% and for SGRQ 50-87%.

Table 2: Efficacy results of 4 RCTs with CHARTIS measurement investigating EBV treatment

	STELVIO (2015)	IMPACT (2016)	TRANSFORM (2017)	LIBERATE (2018)
n	EBV:34, SoC:34	EBV:43, SoC:50	EBV:65, SoC:32	EBV:128, SoC: 62
Emphysema distribution	Hetero- & homogeneous	Homogeneous	Heterogeneous	Heterogeneous
Efficacy:				
Target lobe vol reduction, mL	-1366	-1195	-1090	-1142
Between group difference:	6-month FU	3-month FU	6-month FU	12-month FU
FEV1, %	+17.8%*	+17%*	+29%*	+18%*
RV, mL	-831	-480*	-700*	-522*
6MWD, metres	+74*	+40*	+79*	+39*
SGRQ, total score	-14.7	-9.7*	-6.5*	-7.1*
mMRC, change	NR	-0.57*	-0.6*	-0.8*

*Data are presented as mean change between EBV and SOC group. Target lobe volume reduction is the change in the EBV group only. *Intention to treat analyses. EBV= endobronchial valve group, SOC= standard of care. NR=not reported, mL=milliliter, FEV1= forced expiratory volume in 1 sec, RV= residual volume, 6MWD=6-minute walk distance, SGRQ= St. George's Respiratory Questionnaire, mMRC= modified Medical Research Council Scale.*

Table 3: Responder rates of 4 RCTs with CHARTIS measurement investigating EBV treatment

	STELVIO (2015)	IMPACT (2016)	TRANSFORM (2017)	LIBERATE (2018)
n	EBV:34	EBV:43	EBV:65	EBV:128
FEV1	72%	40%	66%	56%
RV	71%	44%	68%	62%
6MWD	79%	57%	66%	42%
SGRQ	87%	50%	65%	56%

EBV: endobronchial valve group, FEV1: Forced expiratory volume in 1 sec, RV: residual volume, 6MWD: 6-minute walk distance, SGRQ: St. George's Respiratory Questionnaire. Responder rates are the percentage of patients who reached the earlier established Minimal important difference (MID). MID: FEV1: ≥12% (STELVIO ≥10%); RV: ≥430 ml (LIBERATE ≥310 ml); 6MWD≥ 25 metres; SGRQ ≥ 4 points.

Longer Term Follow-up and Survival

Until now, only a few studies have shown that EBV treatment is safe and beneficial for patients with intact fissures or a collapsed target lobe up to 1-year post-procedure and some evidence is available showing significant improvement up to 5 years after treatment [13,15-17]. Furthermore, other studies have shown favourable survival after EBV treatment [18-20].

Safety

All trials showed that the major complication of treatment is a pneumothorax, which occurred in 18-34% of patients (Table 4). The LIBERATE trial showed that 76% of the pneumothoraces occurred within 3 days following treatment and 85% within 5 days following treatment [13]. Close monitoring of patients after treatment and a hospital stay of 3-5 days is important and should be recommended. Slebos et al. described a pneumothorax management algorithm regarding EBV treatment [3]. However, recent studies have shown that the occurrence of a pneumothorax does not appear to negatively impact clinical outcomes [12,13,21]. The EBV treatment is reversible and, in all trials, revision bronchoscopies (19-35%) with adjustment or removal of the valves were necessary (Table 4). During the trials, permanent valve removal was necessary in 3-21% of the patients. Furthermore, the STELVIO trial showed that 78% of patients (including patients treated after cross-over) retained the valves after 1 year [15].

The LIBERATE trial reported that, between treatment and 45 days follow up, there were more respiratory serious adverse events in the EBV group compared to the SoC group (35% vs 5%) [13]. However, between 46 days and 1 year after treatment, the respiratory serious adverse events were equal between groups and there was a lower frequency (although not statistically significant) of serious COPD exacerbations, pneumonias and respiratory failures in the EBV group compared with the SoC group.

Table 4: EBV related safety outcomes in 4 RCTs investigating EBV treatment

	STELVIO (2015)	IMPACT (2016)	TRANSFORM (2017)	LIBERATE (2018)
n	EBV:34	EBV:43	EBV:65	EBV:128
Pneumothorax (%)	18%	26%	29%	34%
Valve retainment (%)	79%	93%	97%	94%
Re-bronchoscopy (%)	35%	19%	28%	27%
Deaths (%)	3%	0%	2%	4%

Cost-Effectiveness

Two studies have investigated the cost-effectiveness of EBV treatment [22,23]. Both studies found that the clinical improvements of EBV treatment in the short term are associated with increased cost compared to standard of care. One of the studies showed that reaching a minimal important difference (MID) in 6MWD of 26m would cost €4160 extra in comparison with standard of care, and a MID of 7 points in the SGRQ total score would cost €8687 extra [22]. However, both studies also showed that the treatment has a favourable cost-effectiveness profile in the long term compared with other treatments for severe emphysema patients, like bronchoscopic lung volume reduction with coils or lung volume reduction surgery. Comparable incremental cost-effectiveness ratios (ICER) were found of approximately €40000 per QALY gained over 5 years and €25000 over 10 years. Furthermore, the LIBERATE trial showed that in the longer term, the frequency of serious adverse events is lower in the EBV group compared to SoC and the reduction in the healthcare costs related to these events is positive for the cost-effectiveness in the long term [13].

Treatment Guidelines

Due to the promising results of the RCTs, EBV treatment was included in the COPD GOLD guidelines in 2017 [24]. Furthermore, the US FDA approved the treatment in 2018 and in an increasing number of countries in Europe, like the Netherlands, Switzerland, Germany and the UK, the treatment is considered routine care. Recently, a group of experienced physicians in Europe have published 'best practice recommendations' for EBV treatment[3]. These recommendations include key selection criteria, valve placement procedure recommendations and a pneumothorax management algorithm.

Patient Selection

The key to treatment success is patient selection. The following criteria are important in patient selection:

1) COPD patients with GOLD stage III or IV (FEV1 < 50% of predicted & FEV1/FVC<70%).
2) Patients need to be symptomatic and limited in daily life activities, e.g. have a modified Medical Research Council (mMRC) score ≥2 and 6-minute walk distance (6MWD) <450 meter.

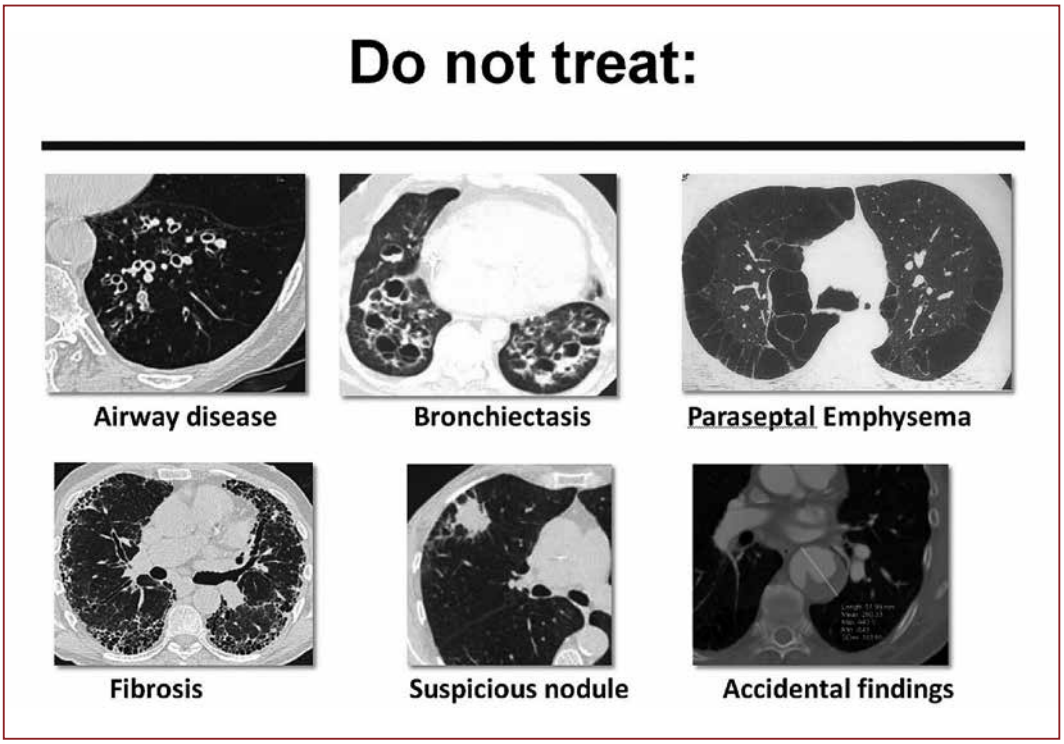

Figure 6: Examples of reasons for exclusion from treatment visible on CT scan

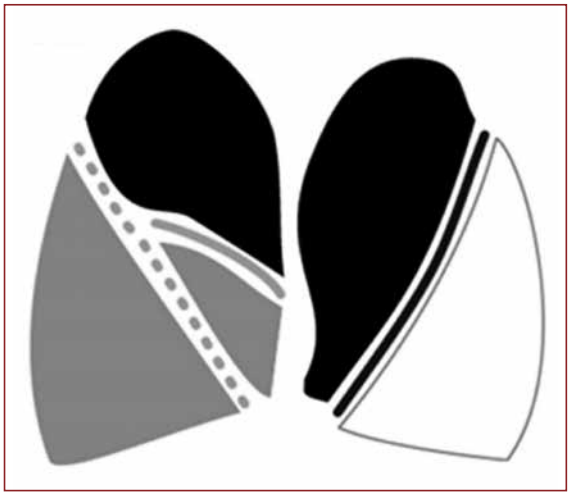

Figure 7: Examples of Quantitative CT image useful for target selection [25]

3) Patients must be on optimal medical management.
4) Severe hyperinflation - the minimal treatment criteria measured by body plethysmography are: residual volume (RV)> 180%, total lung capacity (TLC)> 100% and RV/TLC ratio>58%.
5) Severe comorbidity that would exclude patients from treatment are:
   - $PaCO_2$ >8 kPa (>60mmHg) (on room air).
   - PaO_2 <6.0 kPa (<45mmHg) (on room air).
   - Significant airway disease (asthma, bronchiectasis, severe chronic bronchitis).
   - Unstable or severe cardiac co-morbidity, such as coronary artery disease or congestive heart failure (LVEF<40%).
   - Pulmonary hypertension: RVSP >50mmg Hg.
   - Use of low molecular weight heparin (LMWH), warfarin, direct oral anticoagulants (DOACs) or clopidogrel that cannot be stopped for the procedure.
   - Severe co-morbidity affecting safety and survival.
   - Immunodeficiency (Common Variable Immune Deficiency (CVID); >10mg prednisolone or equivalent, etc).
6) Intact fissures, severe tissue destruction and no other reasons for exclusion seen on CT scan. A visual CT analysis is important to detect fissure integrity, emphysema phenotypes (severity of tissue destruction, heterogeneous or homogeneous emphysema distribution) and reasons for exclusion, like: airway disease, bronchiectasis, parastatal emphysema, fibrosis, suspicious nodule or incidental findings (e.g. aortic aneurysm) (see Figure 6).

Target Selection

Quantitative CT analysis is very helpful in selecting the right treatment target and provides information on fissure completeness, emphysema destruction (either measured at -910 (>50% destruction) or -950 (>30% destruction) Hounsfield Units (HU)) and inspiratory lobar volumes per lung lobe (Figure 7) [25].

Important key factors in treatment target selection are:

- Emphysema destruction (@-910HU) ≥ 50%.
- No collateral ventilation / complete fissure between target and adjacent lobe.
- Most diseased lobe, taking into account:
  - level of heterogeneity (difference between emphysema destruction score between target and adjacent lobe),
  - lowest perfused lung and lobe (measured by perfusion scan),
  - lobar volumes,
  - most air-trapped lobe (seen at expiratory CT scan).
- Absence of the following local factors:
  - pleural adhesions / thickening,
  - bronchiectasis,
  - fibrotic changes,
  - nodules,
  - large bulla adjacent to target lobe.

Conclusions

Bronchoscopic lung volume reduction treatment using endobronchial valves can be seen as a 'bronchoscopic lobectomy'. Currently, there are four published randomised clinical trials that show promising similar results regarding efficacy (in lung function, exercise capacity and quality of life) and safety which led to their inclusion in the GOLD guidelines and FDA approval in the US. Patient selection is key to success and the use of a multidisciplinary team in this process is recommended. Key selection criteria are severe hyperinflation (RV>180% predicted and RV/TLC> 58%) and absence of collateral ventilation measured by the CHARTIS system, and the use of quantitative CT analysis is recommended for treatment target selection. The risk of a pneumothorax is high after treatment (about 20%) and therefore close monitoring of a patient after treatment is recommended. Their inclusion in treatment guidelines and FDA approval, as well as reimbursement of EBV treatment in multiple countries, will lead to an increasing number of patients that can be treated. However, due to the complexity of treatment with respect to patient selection, intervention and follow up, it is recommended to perform the treatment in specialised centres only.

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Postscriptum

"Vi Veri Veniversum Vivus Vici"

From the diary of Aleister Crowley (1875 - 1945) from The Cry of The 4th Aethyr

Each time I began to write something for the Postscriptum I met the same obstacle; how to represent the passage of the short historical time from the publication of one volume to the next, knowing that there is only one year between each of them and that the subject of the books is broadly about the same general topic, Cardiothoracic Surgery, but in progressive evolution.

This fourth volume of Perspectives in Cardiothoracic Surgery begins, as the previous ones, with a mythical representation of the number of the Volume published. This Volume 4 is being printed at the time when the stupendous bird, the Phoenix, was born again this year out of its own ashes, four centuries after its last reincarnation. This volume is comprised of 14 chapters, 10 for cardiac and 4 for thoracic surgery. It is jam-packed with new content, the present and the future of our speciality are on display through the many, varied chapters. These chapters are among the most outstanding presentations made at the 2018 Annual University Meeting. They were specifically prepared to address some of the recent developments in the respective sub-specialties. They were not meant to be exhaustive, but all of them succeeded in combining the advanced, cutting edge of surgery and technology of our speciality with the scholarly description of clear and well documented subjects.

I am certain that all my colleagues will join me in congratulating the authors for so generously giving of their time and above all their knowledge and experience for making the SCTS University and its corollary, this Book on Perspectives, successful events. Congratulations and thanks are extended also to the editors of this Volume. With his knowledge and experience Paul Modi, the Chief Editor, guided and helped his team to produce this scientific and aesthetically pleasing piece of work. Paul Modi has decided to pass the torch of this complex and demanding task after having edited several scientific books (The Pericardial Heart Valve and the first four volumes of Perspectives in Cardiothoracic Surgery).

We all thank him warmly and some of us affectionately for his successful editorial work. As my personal gift to Paul, I conjured the Goddess Fortuna to protect him and his family and to stay close to them now and for evermore. At the same time, I wish his successor who will continue the editorial job courage, perseverance and success in this complex and beautiful endeavour. By perusing the text of this volume, one would realise how well surgical science and practice have adapted to and emulated the transformations which occurred in Cardiothoracic Surgery in the world. Through the variety of subjects which animate this volume, one could discern two significant changes in the direction of future developments in our profession.

Team work is already a reality and it needs to be further encouraged starting with early training of future surgeons. The team Fellowships created by our Society are a good example. Surgeons in training need to learn the Heart Team and the Lung Team approach

from the start but one needs also to allow ample time for developing the maturity of reflection and judgement on which the quality of patient care rest. Team work is a complex but delicate organisation of different personalities. Come together and stand together said the Prophet, but not too close together, the pillars of the temple stand apart and the oak tree and the cypress grow not in each other's shadow.

Super-sub-specialisation is no longer a question but a necessity. In all aspects of surgical education, the training of future cardiothoracic surgeons should prepare them for the years 2030 and beyond. With regret I have to admit that this will push us even farther away from the knowledge and practice of the good old classic medicine and from the general classical education, but humanity has often had to pay a painful price with the decline in humanism for progress in other fields of human endeavour. As always, in life, naught may endure but mutability said Percy Bysshe Shelley and on the opposite side, great writers under various book titles described The World of Yesteryear with all its nostalgia, mystery and grandeur.

In closing, I quote from a recent Skidmore speech given by Robert S. D. Higgins as advice on overcoming barriers to success. *'Define your dream, align those around you with that vision, and motivate them to make it happen no matter what the hurdles or obstacles may be. Never let the challenges you face in life defeat your spirit, remain unconquered through thick and thin'.*

And remember also that we are not born only for ourselves.

Marian Ion Ionescu

February 2019, Portofino.

Society for Cardiothoracic Surgery in Great Britain and Ireland