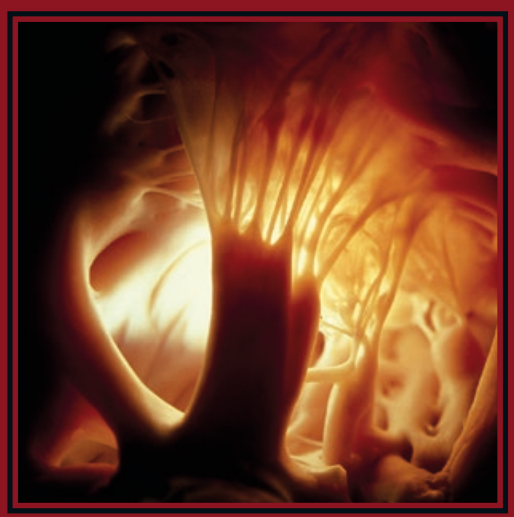
Society for Cardiothoracic Surgery in Great Britain and Ireland

# Perspectives in Cardiothoracic Surgery

## The SCTS Ionescu University Volume V



Series Editor
Bilal Kirmani

Invited Editor
Marian Ion Ionescu

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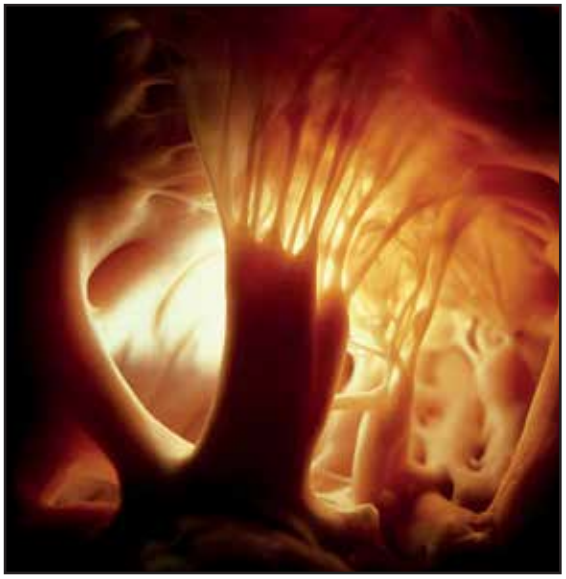


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Perspectives in Cardiothoracic Surgery: The SCTS Ionescu University, Volume V

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# Perspectives in Cardiothoracic Surgery

## The SCTS Ionescu University
## Volume V

*Edited by* Bilal Kirmani

*Invited Editor* Marian Ion Ionescu

### Section I: Cardiac Surgery

*Guest Editor* *Benjamin Adams, London, UK.*

### Section II: Thoracic Surgery

*Guest Editor* *Michael Shackcloth, Liverpool, UK.*

Society for Cardiothoracic Surgery
in Great Britain and Ireland

SCTS Ionescu UNIVERSITY

# Preface

*"Quidquid praecipies esto brevis"*

*Quintus Horatius Flaccus. 65 - 8 BC*

The book you are holding in your hands is the fifth in the series of "Perspectives" and summarises the presentations made by experts from all parts of the globe at the March 2019 SCTS-Ionescu University, which was held in London. As always the chapters are a distillation of the presentations which provide an update for the current situation in the ever-expanding speciality of cardiothoracic surgery. The work is comprehensively referenced and beautifully illustrated (especially the intra-operative photographs) and I know will be appreciated by all SCTS members. Many of the chapters present the dilemmas of management within our practice and are usefully both provocative and didactic in helping the reader understand the often very difficult decisions which have to be made by our patients when facing cardiothoracic surgery. A consistent theme of "Perspectives" is to ensure that the advice we give to patients is based on evidence when available, but if not that it originates from the special knowledge of cardiothoracic surgical experts and their teams whom we have been privileged to invite to join the Faculty of SCTS-Ionescu University.

In the current digital age to have a printed book such as this is always invaluable, especially given that most text-books become rapidly out of date by the time they are published. This never happens with "Perspectives" given the rapid turnaround time, for which the authors and the guest editors deserve full credit and our thanks. Bil Kirmani deserves our particular thanks as chief editor. He has seamlessly taken on the role this year and has lead the project with his usual energy, effectiveness and diplomacy, with the result that the work has been completed well ahead of schedule, despite the need to work with dozens of colleagues throughout the world.

This project would not have been possible without the vision and long-term support of Mr Marian Ionescu, not only for the SCTS-Ionescu University and the resulting "Perspectives" publications but all he does to support STCS Education. Perspectives Volume 5 is another superb example of his enthusiasm for all things educational and therefore the major part of our thanks go to him.

*Richard Page*
President 2018-20

*Simon Kendall*
President elect 2020-2022

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# Section 1

## Cardiac Surgery

*Benjamin Adams*

*"Nemo sine vitio est"*

*Lucius or Marcus Annaeus Seneca the elder. 54 BC - 39 AD*

SECTION 1 CARDIAC SURGERY

# Coronary Artery Surgery

*"Malum consilium quod mutari non potest"*

*Publius Syrius. 85 - 43 BC*

Chapter 1

# MIDCAB and Robotic CABG

*Jonathan M Hemli and Nirav C Patel*

*"Mus uni non fidit antro"*

*Titus Maccius Plautus. 254 - 184 BC*

## Introduction

Robotic-assisted cardiac surgery has enjoyed a relentless progressive evolution, ever since the first coronary and mitral valve procedures were performed in the late 1990s. Repeated advancements in technology have resulted in enhanced three-dimensional stereoscopic visual systems, improved ergonomic instruments with greater flexibility, dexterity and multiple degrees of freedom of movement, programmable instrument carts with integrated energy sources, and the ability for the surgeon to improve their skills on a simulator.

The da Vinci system (Intuitive Surgical, Inc., Sunnyvale, CA) remains the most commonly utilised commercial robot in cardiac surgery. In addition to providing all of the standard advantages of a robotic platform, as outlined in Table 1, the current da Vinci systems are able to integrate multiple video consoles, thereby facilitating the training of the next generation of robotic surgeons.

*Table 1: Advantages of robotic instruments vs. conventional surgical instruments*

| | Conventional Instruments | Robotic Instruments |
|---|---|---|
| Degrees of freedom | 4 | 12 |
| Tremor filter | No | Yes |
| Motion scaling | 1:1 | 1:1 or 1:3 or 1:5 |
| Hand-eye alignment | Misalignment / unnatural | Natural |
| Fulcrum effect | Reverse motion | Not impactful |
| Vision | 2-dimensional (2D) | 3-dimensional (3D) |
| Ergonomics | Unfavourable | Favourable |

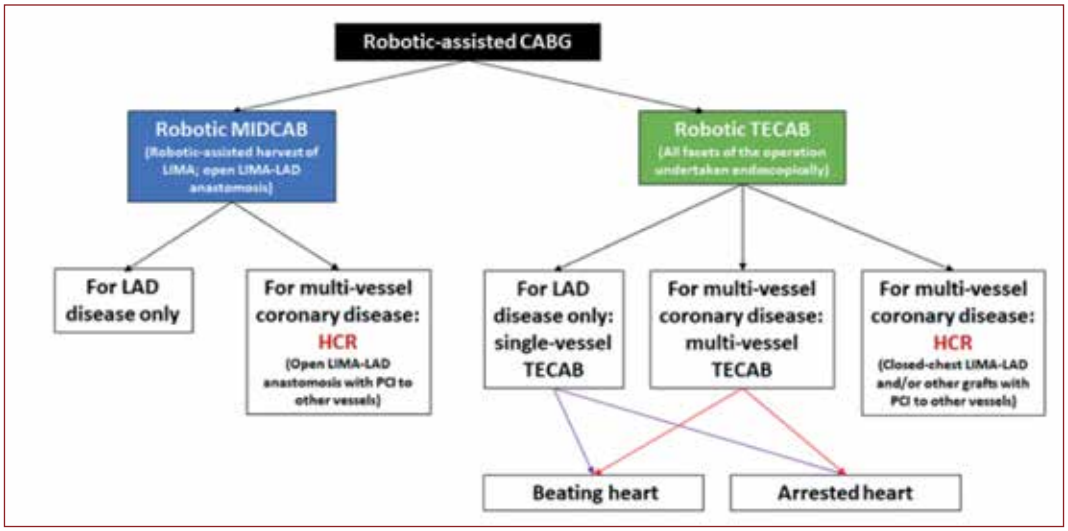
Between 2007 and 2009, there was a 75% increase in the number of da Vinci systems purchased in the United States alone[1]. Similarly, recognising the inherent benefits afforded by the technology, over a four-year period, robotic-assisted cardiac surgery increased six-fold[2]. Despite this, however, robotic coronary revascularisation procedures only constitute a small minority of all coronary artery bypass grafting (CABG) performed in the United States each year.

Of all robotic cardiac surgical procedures performed worldwide, approximately half are robotic coronary artery bypass operations. Robotic mitral valve surgery constitutes almost the entirety of the remainder, whereas atrial septal defect (ASD) repair and resection of intra-cardiac tumors comprise less than 1% of all robotic-assisted cardiac cases[3].

## Robotic Coronary Surgery

Robotic techniques for coronary artery bypass have now been consistently employed for more than two decades. The term, 'robotic-assisted coronary surgery,' however, can refer to a number of different procedures (Figure 1).

*Figure 1: Types of robotic-assisted coronary revascularisation.*




## Robotic MIDCAB

Minimally-invasive direct coronary artery bypass (MIDCAB) is, by far, the most commonly performed robotic-assisted CABG procedure performed worldwide, despite its relatively low adoption in the United States as compared with conventional sternotomy CABG techniques. The LIMA is harvested utilising robotic instruments, with a subsequent open anastomosis to the LAD being fashioned, off-pump, via a small left anterior mini-thoracotomy.

### Patient selection

Robotic MIDCAB can be offered to patients with isolated disease of the LAD, or, alternately, it can be used in patients with multi-vessel coronary stenoses, whereby the robotic LIMA

to LAD graft is coupled with percutaneous coronary intervention (PCI) techniques to all diseased non-LAD vessels, thereby constituting a hybrid coronary revascularisation (HCR) strategy.

The 2012 *ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease* suggests a Class IIb recommendation for HCR, stating that it may be a reasonable alternative to CABG or multi-vessel PCI, so as to improve the risk-benefit ratio of the procedures[4]. The 2014 ESC/EACTS Guidelines on Myocardial Revascularisation mentions HCR as an option when multi-vessel PCI is deemed to be unsuitable, or when traditional CABG is considered to be at prohibitive risk[5]. The more recently published 2018 ESC/EACTS Guidelines state that minimal-access CABG is a reasonable alternative to traditional CABG, in experienced centers, either for patients with sole disease of the LAD, or as a component of a hybrid approach for those with more diffuse lesions[6].

Robotic MIDCAB is not an appropriate technique to use in an emergency setting or in haemodynamically unstable patients. Individuals with limited pulmonary reserve who are unable to tolerate single-lung ventilation are also not ideal candidates for a MIDCAB operation. Significantly impaired left ventricular systolic function has been regarded by some as a relative contraindication to a robotic procedure, although favourable results in this setting have been reported[7]. A robotic MIDCAB is undoubtedly technically more challenging in the obese patient, and has been associated with longer operative times[8]. However, a higher body mass index (BMI) should not necessarily preclude a minimal-access approach, and, indeed, satisfactory outcomes have been described in this patient cohort[9]. Patients who have had previous cardiac surgery can also potentially be offered a reoperative robotic MIDCAB[10].

## Surgical technique

The patient is intubated in such a manner as to allow for selective lung isolation. A padded support is typically placed underneath the left scapula to facilitate access to the left chest. The left arm hangs below the surgical table, with the left shoulder angled downwards; particular attention has to be paid to avoid undue traction on the brachial plexus or ulnar nerve (Figure 2).

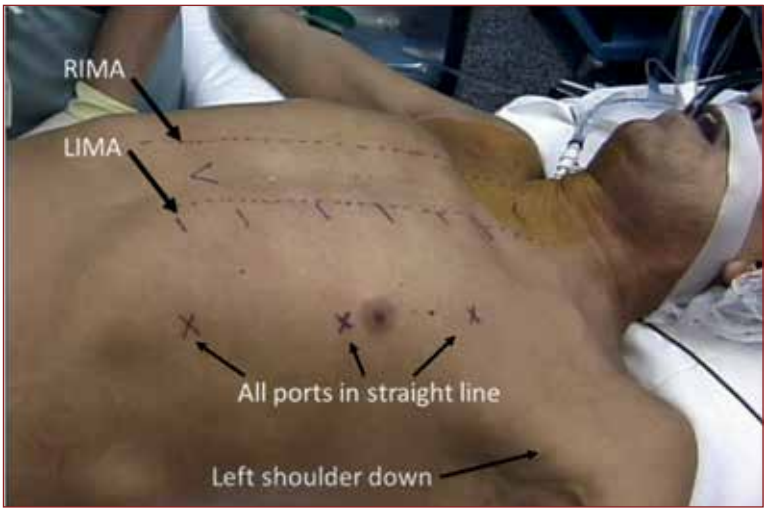



*Figure 2: Positioning of the patient for robotic MIDCAB.*

After deflation of the left lung, three ports are introduced into the left pleural cavity, under vision, typically in the second, fourth and sixth interspaces (Figure 3). The pleural cavity is insufflated with carbon dioxide.

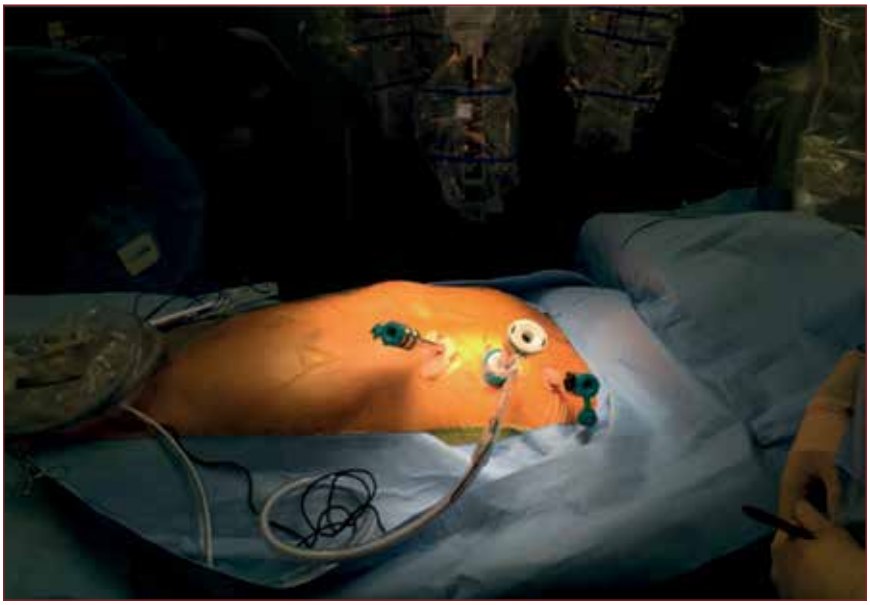


*Figure 3: Ports are introduced into the left chest for the robotic instruments.*

The left internal mammary artery is harvested as a skeletonised vessel, in its entire length, using the robotic instruments only (Figure 4). Utilising the robot to harvest the LIMA not only allows the entire length of the vessel to be mobilised with excellent visualisation, even in patients with more challenging body habitus, but it also facilitates easier skeletonisation of the LIMA conduit, as opposed to taking it down as a pedicle, a technique that has been associated with more favorable outcomes, particularly in higher-risk patient subgroups[11].

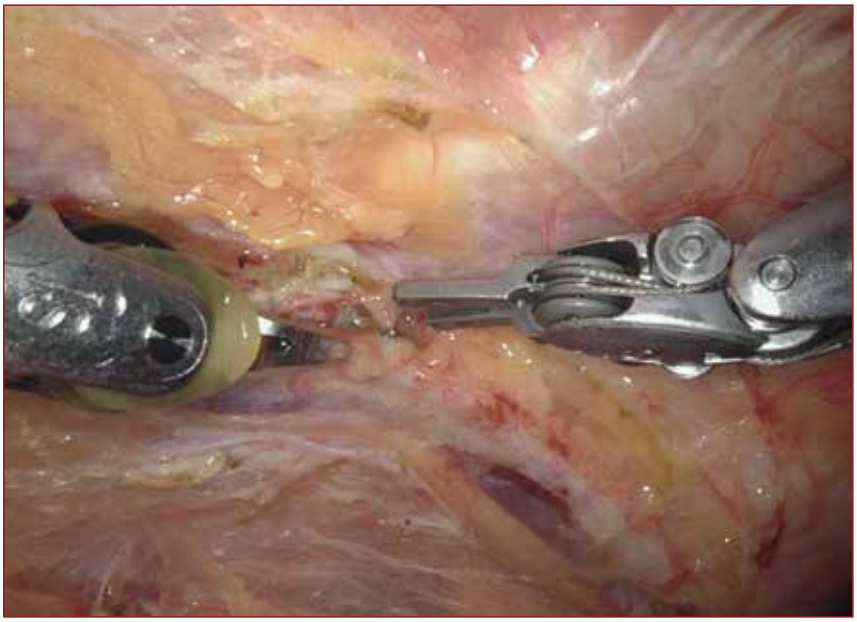


*Figure 4: Robotic harvesting of the left internal mammary artery.*

After the LIMA has been divided, the pericardium is opened, once again utilising the robotic instruments, typically over the right ventricular outflow tract, and the LAD is identified (Figure 5). This guides the surgeon as to the best place for the subsequent thoracotomy incision to be made so as to maximise exposure of the LAD.

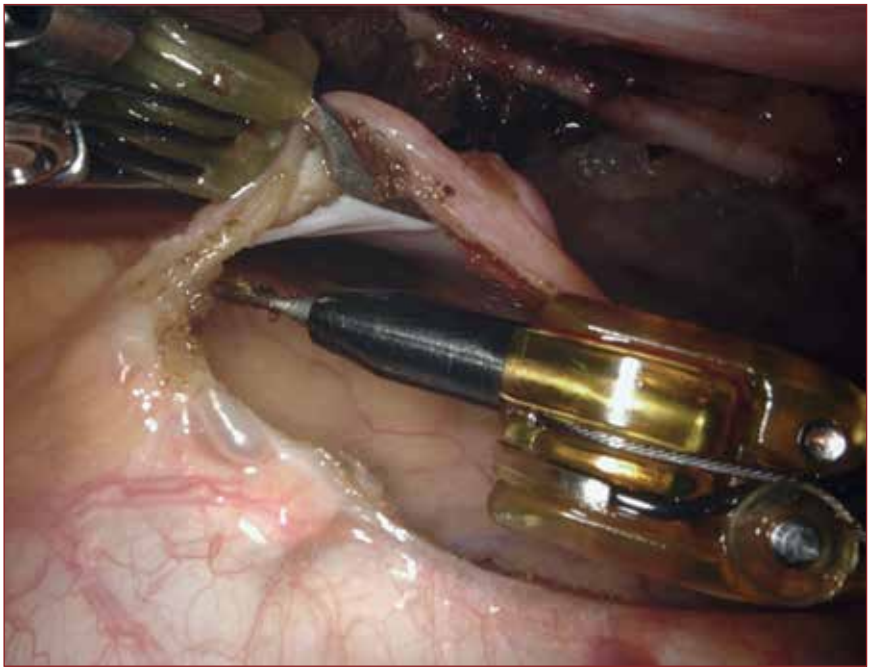


*Figure 5: The pericardium is opened using the robotic instruments.*

The robot is undocked from the operating table, the patient is systemically heparinised, and a left anterior muscle-sparing mini-thoracotomy is performed, most commonly by extending the middle (robot camera) port incision. Rib trauma is minimised, and a soft-tissue wound protector is used to provide circumferential, atraumatic exposure (Applied Medical, Rancho Santa Margarita, CA) (Figure 6).

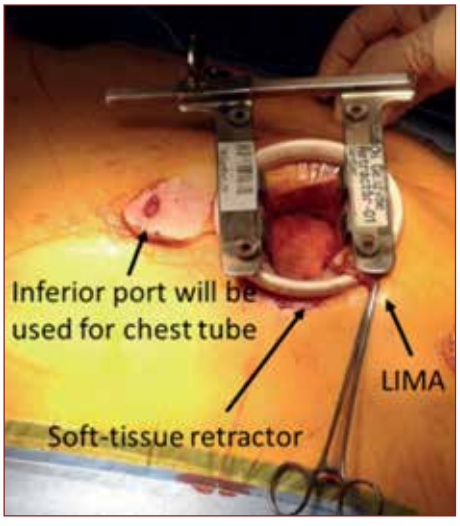



*Figure 6: Left mini-thoracotomy for subsequent coronary grafting.*

The LIMA-LAD anastomosis is undertaken under direct-vision, using standard off-pump coronary grafting techniques, typically incorporating a low-profile compression myocardial stabiliser (Figure 7). An intra-coronary shunt is utilised in all cases.

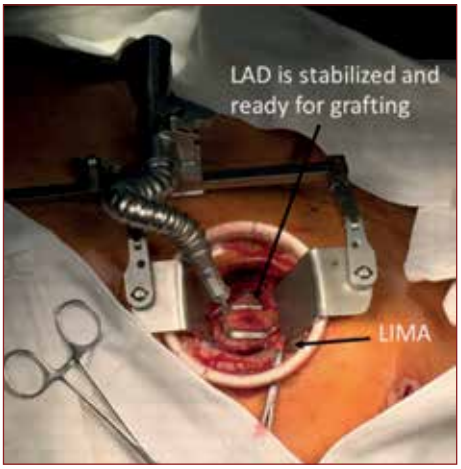



*Figure 7: Off-pump stabilisation of the LAD.*

Graft flow and patency is assessed using a transit-time flow measurement system (Medistim VeriQ, Medistim USA Inc., Plymouth, MN) prior to pleural drainage and wound closure.

## Results

There is a wealth of data now available that affirms the advantages of robotic MIDCAB, both as a stand-alone procedure for patients with isolated LAD stenosis, and as part of a more global HCR strategy for patients with multi-vessel disease. Numerous studies detail the admirable results of a robotic-assisted LIMA to LAD graft, with or without PCI to non-LAD vessels, confirming low perioperative mortality and morbidity, as well as excellent mid to longer-term graft patency[12-15]. When compared to sternotomy CABG, robotic MIDCAB procedures (and HCR overall) have been consistently associated with shorter intensive care and hospital stays, a reduced perioperative transfusion requirement, less postoperative pain, and faster recovery[16-27]. Of course, a sternal-sparing robotic MIDCAB completely negates the risk of sternal wound infection.

Despite the well-recognised advantages of robotic MIDCAB (and HCR), an analysis from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database revealed that HCR represented only 0.48% of all CABG volume in the United States between 2011 and 2013[28]. Indeed, there is little doubt that a MIDCAB can be a somewhat technically challenging operation, and this may explain, at least in part, the hesitancy amongst surgeons to routinely adopt it as part of their coronary grafting repertoire.

A definite learning curve inherent to robotic MIDCAB has been well described. Oehlinger and colleagues noted a steady decrease in LIMA harvest time over the course of 100 consecutive procedures[29]. Bonatti and associates similarly described improvements in LIMA harvest times after 38 cases, while Kappert and co-workers noted better operative times after 35 cases[30,31]. Our group not only found that LIMA harvest times progressively decreased with increasing surgical experience, we also noted that other components of the operation tended to become faster as well, including port-placement time, and total

robotic-use time (Figure 8)[32]. We demonstrated that a 10% decrease in operating times could be expected for each doubling of the number of cases performed, although the greatest improvements are most consistently achieved within the first 20 cases.

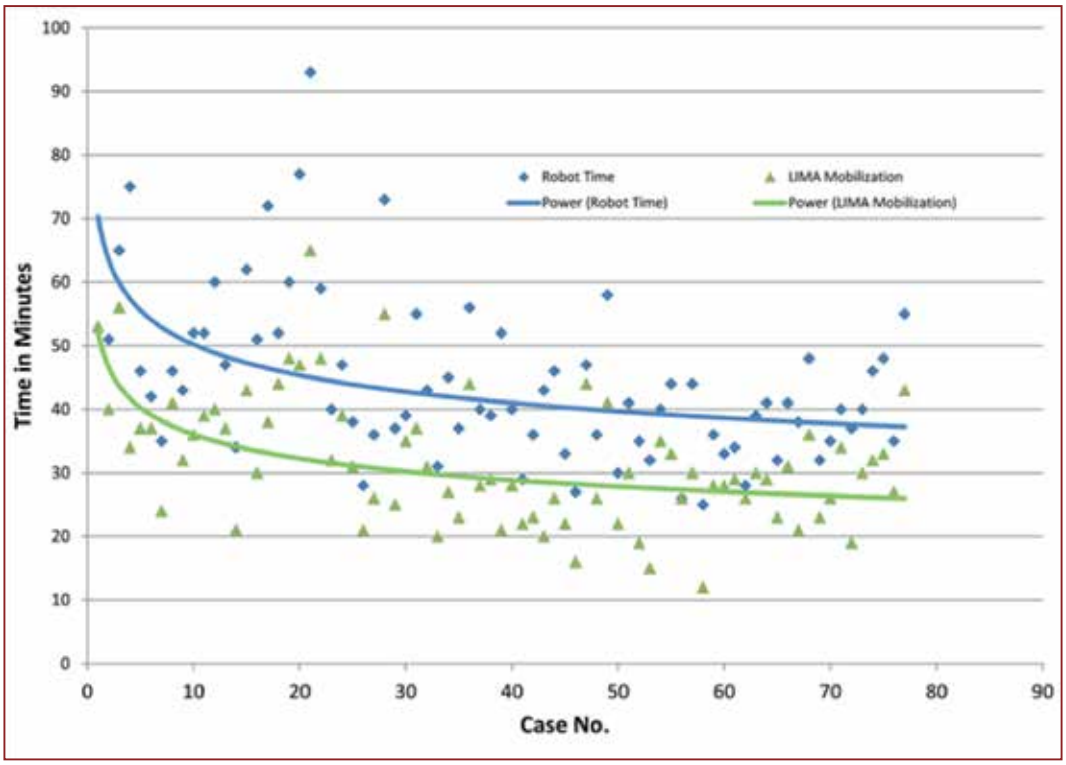



*Figure 8: Learning curves for LIMA harvest time and total robotic-use time in robotic MIDCAB. LIMA, left internal mammary artery. (From Hemli JM, Henn LW, Panetta CR, et al. Defining the learning curve for robotic-assisted endoscopic harvesting of the left internal mammary artery. Innovations (Phila) 2013; 8: 353-8; with permission).*

The learning curve for robotic MIDCAB may, in fact, be shorter than would be otherwise expected, particularly for those surgeons who are already comfortable with typical off-pump surgical techniques.

## HCR: MIDCAB or PCI first?

For patients undergoing robotic MIDCAB as part of an HCR management algorithm, a MIDCAB-first approach is typically adopted, followed by interval PCI, typically within 4 to 6 weeks of surgery. This allows the surgical revascularisation to be performed without concern for any potential bleeding that may be associated with the dual antiplatelet therapy that is mandatory after PCI with drug-eluting stents (DES). MIDCAB procedures have, in fact, been undertaken in patients taking dual antiplatelet agents without undue bleeding, although these findings have not necessarily been consistent amongst all surgical groups[33,34]. More importantly, the MIDCAB-first approach allows the patency of the LIMA to LAD bypass graft to be interrogated during the subsequent PCI procedure.

A PCI-first strategy is typically employed in those patients who present with an acute coronary syndrome in which the culprit vessel is not the LAD, or in those individuals in whom the angiographic severity and/or clinical import of at least one of the non-LAD stenoses is deemed to be greater than that of the disease within the LAD itself. In these patients, subsequent LIMA to LAD grafting is undertaken on uninterrupted dual antiplatelet therapy. Alternately, simultaneous MIDCAB and PCI has been adopted by some centers[35-37].

## Robotic TECAB

The first robotic total endoscopic coronary artery bypass (TECAB) was performed by Loulmet and associates in 1998[38]. In some respects, robotic TECAB may represent the ultimate in minimally-invasive CABG, as the entire operation is performed through port access, within the closed chest (Figure 9). Not only is the internal mammary harvested endoscopically, but the coronary anastomoses themselves are constructed wholly within the chest using robotic instruments (Figure 10).

*Figure 9: Final clinical result after a robotic TECAB.*

In contrast to robotic MIDCAB, which only revascularises the LAD, a TECAB procedure can be used to graft multiple arterial territories. Moreover, unlike a MIDCAB operation, which is almost invariably completed off-pump, TECAB procedures can either be performed on the beating heart or on the arrested heart. Arrested-heart TECAB utilises peripheral cannulation strategies to establish cardiopulmonary bypass and it incorporates endoscopic techniques to occlude the ascending aorta and administer cardioplegia.

The adoption of robotic TECAB by cardiac surgeons has been even slower than that of MIDCAB, undoubtedly, in large part, due to the technical complexity inherent to the procedure, the challenges related to working entirely within the closed chest, and the longer learning curves associated with the operation. Although it is not widely practiced, robotic TECAB is nevertheless carried out on a routine basis by a limited number of dedicated centers across the globe.

In a recent review of the literature, Gobolos and colleagues analyzed the outcomes of 2397 TECAB cases and reported a perioperative mortality of 0.8% (slightly higher in beating-heart cases than in arrested-heart cases), a stroke rate of 1.0%, and an incidence of new renal failure of 1.6%[39]. These favourable clinical results have tended to be achieved at the expense of longer operating times, a not insignificant conversion rate to larger incisions, and a higher re-exploration rate for bleeding. Leonard and co-workers conducted a meta-analysis of all TECAB studies from 2000 to 2017[40]. They also reported encouraging results, with low operative mortality (0.8%), infrequent stroke (1.5%), an incidence of perioperative myocardial

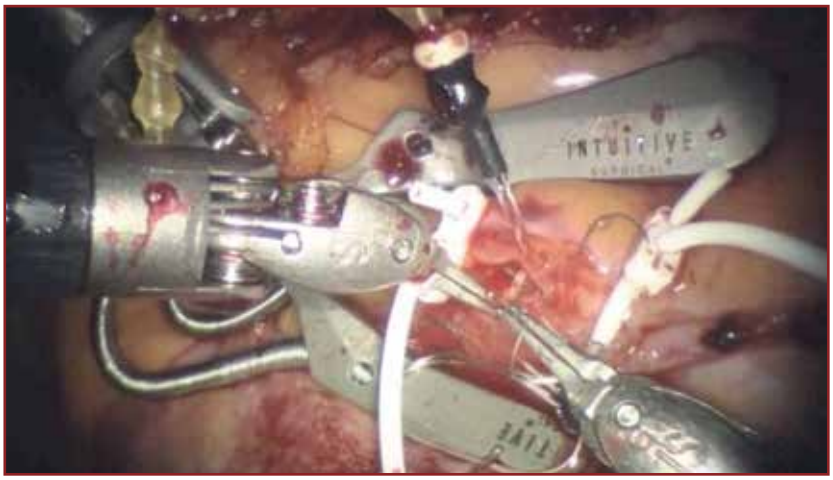



*Figure 10: Coronary anastomosis performed within the closed chest using the robot in a TECAB.*

infarction (MI) of 2.28%, and 94.8% graft patency at a mean follow-up of just over 10 months. Bonaros and associates described their multi-center experience of 500 TECAB cases, performed between 2001 and 2011[41]. Intraoperative conversion to larger incisions was required in 10% of patients, and operating time was again on the longer side. The investigators found that independent predictors of procedural success included a less-technically challenging operation (such as a single-vessel or an arrested-heart TECAB, as opposed to a multi-vessel beating-heart TECAB) and a non-learning curve case.

The concept of a robotic-assisted total endoscopic cardiac operation, as epitomised by TECAB, has since been broadened, and other, non-coronary procedures, have been completed with the aid of the robot entirely within the closed chest, including in the paediatric population[42].

## Other Considerations

One of the main concerns that remains regarding robotic surgery is its cost. Most studies have demonstrated that the financial cost of a robotic procedure exceeds that of a non-robotic one, due to a multitude of factors. Purchasing the robotic unit, in itself, is expensive. The limited effective life-span of the robotic instruments (and the use of single-use consumable items) necessitates continual repetitive purchases, a cost that is unavoidable. The longer operating times reported with some robotic procedures can further reduce the overall efficiency of the operating suite and reduce the institution's capacity to perform other, potentially more financially attractive, cases.

Nevertheless, there remains a definite potential for the cost of robotic coronary procedures to decrease. As surgeons become more comfortable with the procedures, and as case volume increases, operating time would be expected to consistently improve, and the surgeon should also become defter at minimising and managing perioperative complications. Higher in-hospital costs of the robotic operation may also be somewhat offset by the patient's shorter hospital stay, faster postoperative recovery, and earlier return to work.

Other limitations of the robotic approach have included the lack of proprioception and the absence of tactile feedback provided by the robotic instruments. Further incremental advances in robotic technology may address some of these issues.

## Conclusions

Although its adoption thus far has been relatively limited by the wider cardiac surgical community, robotic-assisted coronary revascularisation has been consistently shown to be safe, reproducible, associated with excellent short-term outcomes and longer-term graft patency, and the patients tend to enjoy less postoperative pain and faster functional recovery. As the underlying robotic technology continues to improve over time, one would expect that more surgeons will incorporate these techniques into their armamentarium of management options for myocardial revascularisation. Higher resolution optics, smaller instruments with lower profiles allowing for finer motor control and coordination, and the incorporation of a haptic or tactile feedback system into the robotic arms, will all combine to facilitate faster, smoother operations, with shorter learning curves, and reduced cost.

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Chapter 2

# Optimal Medical Management Post-CABG

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*"Medio tutissimus ibis"*

*Publius Ovidius Naso. 43 BC - 17 AD*

## Introduction

Despite the recent advances in percutaneous intervention (PCI) for coronary revascularisation, coronary artery bypass graft surgery (CABG) remains the mainstay of treatment for a considerable number of patients. Cardiac surgery is a major undertaking for patients and it is usually an opportunity to increase patient awareness to the nature of the disease, optimal medical therapy (OMT), as well as lifestyle changes to improve quality of life. Adherence to OMT maintains graft patency and reduces the risk of recurrence of adverse cardiac events and furthermore, improves patients' wellbeing and quality of life. Unfortunately, in a significant number of patients, post-CABG medical management is suboptimal. A post-hoc analysis of the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial showed that the use of OMT remains low among patients revascularised percutaneously and even lower among CABG patients. Only 41% of patients were optimally medicated at the time of discharge after revascularisation. At 5-years, only one-third of patients in both treatment groups were taking OMT (PCI 40% and CABG 36%)[1]. Numerous reasons may explain this shortcoming in management. These reasons may include: the misconception that once bypass surgery is performed then the patient has reached the ceiling of treatment, resulting in medical therapy and lifestyle management being overlooked; occasionally medications ceased preoperatively are not reinstituted at the time of discharge; poor patient awareness of their condition and secondary prevention may result in poor compliance; and, finally, poor tolerance to medications may result in a poor compliance.

# What is Optimal Medical Therapy?

Optimal management of post CABG patients is a combination of pharmacological and non-pharmacological interventions that aims to reduce the risk of further cardiovascular events and improve wellbeing and quality of life. OMT consists of:

A. Antiplatelet Therapy

B. Lipid lowering agents

C. Beta blockers

D. Renin-Angiotensin Aldosterone System Antagonists

E. Blood pressure control

F. Diabetes management

G. Smoking cessation

H. Cardiac rehabilitation

I. Depression screening and management

J. Influenza vaccination

## A. Antiplatelet therapy

### *i. Aspirin (Acetylsalicylic Acid)*

Aspirin irreversibly inhibits platelet cyclooxygenase-1 and blocks the formation of thromboxane $A_2$, a potent vasoconstrictor and platelet aggregant. By inhibiting platelet aggregation it reduces the risk of stroke, myocardial infarction, and vascular death in patients with ischaemic heart disease[2]. Aspirin is generally commenced at the first diagnosis of angina or acute coronary syndrome (ACS). Its preoperative use is safe and has been shown to reduce CABG operative morbidity and mortality rates. Inhibition of platelet function after CABG helps maintain graft patency and prevent major adverse cardiovascular events. Aspirin significantly improves vein graft patency rates, particularly during the first postoperative year[3,4]. A systematic review of 7 studies showed that administration of Aspirin within 6 hours of CABG was associated with improved graft patency without an increased incidence of bleeding complications[5]. Aspirin should, therefore, be started as soon as possible after CABG allowing for bleeding risk. It is worth noting that the practice of stopping aspirin 5 days preoperatively and replacing it with low molecular weight heparin during that time increases bleeding risk and is therefore not recommended[6].

### *ii. $P2Y_{12}$ Inhibitors*

Clopidogrel, a thienopyridine derivative, is an antiplatelet agent that irreversibly inhibits the platelet $P2Y_{12}$ adenosine diphosphate receptor. It inhibits platelet aggregation for 7-10 days. Ticlopidine, also a thienopyridine, has a similar effect to Clopidogrel. However, Ticlopidine has an unfavourable risk factor profile including neutropenia and rash[7,8]. Prasugrel and Ticagrelor, newer drugs in the same family, inhibit the platelet $P2Y_{12}$ adenosine diphosphate receptor but they have a more rapid onset of action and more consistent and pronounced platelet inhibition than Clopidogrel, at the expense of a higher bleeding risk[9-11].

Current guidelines recommend dual antiplatelet therapy (DAPT) for all patients with ACS regardless of revascularisation treatment[12,13]. DAPT reduces the risk of thrombotic complications after ACS in contrast to treatment with Aspirin alone[9,10,14], especially following PCI. Although DAPT after CABG has been associated with reduced all-cause mortality and better vein graft patency[15,16], the evidence is conflicting with the benefits being outweighed by the increased risk of bleeding. Various trials have evaluated the impact of Clopidogrel on the process of vein graft disease and graft occlusion after on-pump CABG. The first of these, involving 192 CABG patients showed no significant difference in graft patency when isolated Clopidogrel treatment was compared with DAPT after CABG through the use of computed tomography angiography at 1 month or 1 year (1 month: 98.1% versus 98.2%, P=0.73; 1 year: 93.5% versus 96.3%, P=0.25, Clopidogrel versus Clopidogrel plus Aspirin)[17]. Although no significant differences were noted, some studies have suggested that Clopidogrel on its own may be insufficient as a sole antiplatelet agent early after CABG.

In comparison to Aspirin which has a more rapid onset in the first 5 days after surgery[18], the platelet inhibitory effects of Clopidogrel do not fully manifest until days 9 to 28 after CABG[19].

Off-pump surgery avoids the cardiopulmonary bypass during surgery, hence, reducing the systematic inflammatory response after CABG and improving haemostasis by averting the activation and consumption of clotting factors and platelets associated with bypass. This, however, may have undesirable effects on graft anastomosis sites as these clotting disorders and platelet dysfunction induced by cardiopulmonary bypass may, in fact, have a protective effect on surgical anastomoses and prevents graft thrombosis. Several reports have documented the existence of a relative hypercoagulable state after off-pump surgery, associated with higher levels of postoperative platelet activity and a decrease in platelet sensitivity to Aspirin after off-pump CABG[20-27]. Recent trials noted that combined therapy with Aspirin and Clopidogrel was associated with a significant reduction in the rate of vein graft occlusion as assessed by thromboelastography studies and by computed tomography angiography[28,29]. These finding have been reproduced on a meta-analysis evaluating the role of dual antiplatelet therapy after CABG surgery in which the benefit of combined Clopidogrel and Aspirin treatment was most pronounced after off-pump CABG, reducing vein graft occlusion by 55% compared with Aspirin alone[16].

*Table 1: Antiplatelet Therapy Recommendations* [51,52]

| | |
|---|---|
| 1. | Aspirin should be restarted as soon as possible postoperatively (preferably within 6 hours after CABG. It should then be continued indefinitely to reduce graft occlusion and adverse cardiac events) |
| 2. | After off-pump CABG, dual antiplatelet should be administered for 1 year with combined Aspirin and Clopidogrel daily to reduce graft occlusion. |
| 3. | Clopidogrel 75 mg daily is a reasonable alternative after CABG for patients who are intolerant or allergic to Aspirin. It is reasonable to continue it indefinitely. |
| 4. | In patients who present with ACS, it is reasonable to administer combination antiplatelet therapy after CABG with Aspirin and either Prasugrel or Ticagrelor (preferred over Clopidogrel), although prospective clinical trial data from CABG populations are not yet available. |

## B. Lipid Lowering Agents

Statins, as lipid lowering agents, have traditionally been prescribed for both primary and secondary prevention in the context of ischaemic heart disease. They have been shown

to improve survival and reduce the risks of adverse cardiovascular events. In addition to reducing progression of native coronary artery atherosclerosis[30-33] they have been demonstrated to inhibit the development of saphenous vein graft disease[34,35] by reducing neointimal formation and smooth muscle proliferation[36-38]. A target reduction in low-density lipoprotein (LDL-C) of 50% in patients with coronary artery disease (CAD) is recommended, achieved by intense or maximally tolerated statin therapy.

The Treating to New Targets (TNT) trial, showed that intense lowering of LDL-C (mean 2.05 mmol/l) with Atorvastatin 80mg daily in previous CABG patients reduced major cardiovascular events by 27% and the need for repeat revascularisation by 30%, as opposed to less intensive lowering of the cholesterol level to a mean of 2.61 mmol/l with Atorvastatin 10 mg daily[39]. Statins also appear to have beneficial non lipid related effects including improved endothelial function, antioxidant activity, and nitric oxide levels, in addition to inhibition of anti-inflammatory responses, vasoconstriction, platelet aggregation and thrombosis[40-45]. Small scale randomised controlled trials and observational studies have suggested that administration of preoperative statin therapy before cardiac surgery reduced mortality, postoperative atrial fibrillation and acute kidney injury[46,47]. The Statin Therapy in Cardiac Surgery Trial involving 1922 patients undergoing elective cardiac surgery concluded that initiation of Rosuvastatin therapy (20mg/day) did not prevent perioperative myocardial damage or reduce the risk for postoperative atrial fibrillation and reported that acute kidney injury was significantly more common among patients who received Rosuvastatin than among those who received a placebo[48]. Recent data, therefore, does not support immediate preoperative initiation of statins in statin-naive patients undergoing cardiac surgery. Although no data is available regarding continuation of statins preoperatively, common practice is to continue them. The evidence base for their continuation post operatively, however, is unequivocally supportive. The European Atherosclerosis Society has developed a scheme for statin re-exposure in patients with statin intolerance[49].

Alternatives to statins such as fibrates, bile acid sequestrants and niacin should be considered in the occasional patient who is unable to take statins [33,50]. In post CABG patients in whom maximum tolerated statin dose does not achieve target LDL C (1.8mmol/l) adding a cholesterol absorption inhibitor (Ezetimibe) should be considered. This has been shown

*Table 2: Lipid lowering therapy recommendations[51,52]*

| | |
|---|---|
| 1. | Unless contraindicated, all CABG patients should receive statin therapy, starting in the preoperative period and restarting early after surgery (avoid starting in the period shortly prior to surgery). |
| 2. | High-intensity statin therapy (Atorvastatin 40–80 mg, Rosuvastatin 20–40 mg) should be administered after surgery to all CABG patients. |
| 3. | Moderate-intensity statin therapy should be administered after CABG for those patients who are intolerant of high-intensity statin therapy and for those at greater risk for drug-drug interactions (i.e. patients >75 years of age). |
| 4. | Discontinuation of statin therapy is not recommended before or after CABG unless patients have adverse reactions to therapy. |
| 5. | In patients after CABG, if a target LDL-C of 1.8 is not achieved consider adding a cholesterol absorption inhibitor (e.g. Ezetimibe). |
| 6. | In patients after CABG surgery who have a persistently high LDL (3.6mmol/l) despite treatment with the maximal tolerated statin dose (in combination with Ezetimibe), a PCSK9 inhibitor should be considered. |

to achieve a substantial reduction in cardiovascular events compared to statin alone[53]. No evidence exists for the use of the recently introduced proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor after CABG, however, they have been shown to reduce cardiovascular events in high cardiovascular risk patients who have not achieved LDL- C target despite maximum tolerated statin dose on follow-up[54]. PCSK9 inhibitors should therefore be considered in selected post CABG patients[55,56].

## C. Beta Blockers

Beta blockers, a group of competitive antagonists of the β-adrenergic receptors work by modulating activation of the adrenergic nervous system. Some beta blockers are selective to β1 receptors while others are non-selective. In addition to the β-receptor blockade some beta blockers have β-receptor blockade effects, intrinsic sympathomimetic activity and a direct vasodilator effect[57]. Consequently beta blockers counter the effects of circulating catecholamines including tachycardia, increased contractility and ventricular hypertrophy[58]. A review of patient data in the Society of Thoracic Surgeons Database from 1996 to 1999 demonstrated that administration of β-blockers before surgery significantly lowered 30-day mortality rates compared to patients who did not receive beta blockers[59]. There is compelling evidence from numerous studies demonstrating the benefits of beta blockers during and after ACS[60,61]. A metanalysis by Freemantle et al showed a 23% reduction in odds of death with beta blocker therapy for long term prevention after MI[62]. Subsequent studies have reiterated this finding in patients with a recent myocardial infarction or reduced left ventricular ejection fraction (<35%)[63,64]. Heng Zhang et al. further assessed the efficacy in post CABG patients with or without previous MI and concluded that the consistent use of β-blockers was associated with a lower risk of long-term mortality and adverse cardiovascular events regardless of a prior history of MI[65].

It is therefore vital that patients remain on a beta blocker long term post CABG as a secondary prevention measure, particularly in patients with a recent myocardial infarction or with reduced ejection fraction. Bisoprolol, Metoprolol succinate, Carvedilol and Nebivolol are all approved for this use [66.]

*Table 3: β-Blocker Therapy Recommendations[51,52]*

| | |
|---|---|
| 1. | Beta blockers should be continued postoperatively in all CABG patients especially for patients with a history of MI or LV systolic dysfunction. |
| 2. | Patients who were not on beta blockers preoperatively should be commenced on this in the postoperative period if no contraindication. |

## D. Renin-Angiotensin Aldosterone System Antagonists

### Angiotensin Converting Enzyme Inhibitors (ACEi) and Aldosterone Receptor Blockers (ARB)

The Renin-Angiotensin Aldosterone System (RAAS) is activated by reduced blood flow to the kidneys resulting in the formation of angiotensin II, a potent vasoconstrictor that reduces renal perfusion, stimulates LV hypertrophy and cardiac remodeling, and causes release of arginine, vasopressin, proinflammatory cytokines, and aldosterone[67]. The resultant effects include increased blood pressure and fluid retention. In pathologic states, such as heart failure, vasoconstriction and fluid retention, RAAS activation results in decompensation. ACEi prevent the conversion of angiotensin I to angiotensin II and inhibits the breakdown of bradykinin, a peptide with beneficial properties including

antihypertensive, antiremodeling, and natriuretic effects. Disrupting the RAAS therefore results in favourable effects[68].

Although the long term symptomatic and mortality benefits of ACEi in patients with reduced left ventricular ejection fraction have been well demonstrated[69-71] there is no evidence to support their use routinely post-CABG with ejection fraction >40%[72]. Their benefit has been demonstrated in diabetic patients as well as patients with chronic kidney disease (both diabetic and non-diabetic)[73,74]. ARB can be used as an alternative to ACEi for patients with prior myocardial infarction or symptomatic heart failure provided there are no contraindications for their use[75-79]. The early postoperative period after CABG can be associated with hypotension as well as acute renal injury. Introduction of ACEi or ARB during this period could have detrimental effects and should therefore be practiced with caution and, preferably, delayed to avoid any adverse effects related to either of these drugs[75].

*Table 4: Recommendations for Renin Aldosterone System Antagonists*[51,52]

| | |
|---|---|
| 1. | Post CABG patients with a previous MI or LV dysfunction should be commenced on ACEi. If intolerant of this ARB should be used as an alternative. |
| 2. | There is no indication for ACEi/ARB routinely post CABG in patients without previous MI, LV dysfunction, diabetes mellitus or chronic kidney disease. |

## E. Blood Pressure Control

Approximately 80 percent of patients proceeding for CABG have a prior diagnosis of hypertension[80]. To date there have been no clinical targets specifically assessing blood pressure targets in post CABG patients in relation to clinical outcomes, however, a reading of less than 140/90 has been suggested as optimal, especially for patients with previous coronary events and a history of hypertension and diabetes mellitus[81,82]. Unfortunately, blood pressure managements among CABG patients remains suboptimal[83]. Several randomised control trials have further assessed the value of a lower diastolic BP target of < 85mmHg and have found this to be safer with improved clinical outcomes in patients with a history of hypertension, diabetes mellitus or multiple cardiovascular risk factors[58,84,85]. The majority of hypertensive post CABG patients are on beta blockers or ACE inhibitors in view of their additional cardioprotective effects[86,87]. There has been no studied method of introducing or escalating antihypertensive therapy in post CABG patients so this should be selected based on individual patient circumstances. Although the antihypertensive effect of beta blockers has not been systemically explored it is preferred that they are introduced as soon as possible after CABG as they improve outcomes in patients with congestive heart failure and LV dysfunction[88] and reduce the risk of atrial fibrillation[89].

Post CABG patients with LV dysfunction, recent MI, diabetes mellitus and chronic kidney disease should be offered ACE inhibitors, often in addition to beta blockers[81,82,90]. Occasionally a diuretic may be required to potentiate the antihypertensive effect of an ACEi since their BP lowering effect is dependent on the patient's volume state. ARBs are suitable alternatives in patients who are intolerant of ACEi. Renal function should be carefully monitored after introduction and with long term administration of either an ACEi or ARB. Calcium channel blockers and diuretics are a suitable next step if a blood pressure target is not achieved despite the use of beta blockers and ACE inhibitors.

Lifestyle measures such as an appropriate limited sodium intake diet, weight management and exercise are important in achieving blood pressure control.

*Table 5: Hypertension Management Recommendations*[51,52]

| | |
|---|---|
| 1. | Although there is no studied ideal BP target in post CABG patients it is reasonable to aim for a BP of <140/85mmHg. |
| 2. | There is no studied method of introducing or escalating antihypertensive therapy in in post CABG patients. Antihypertensive therapy should be selected based on individual patient circumstances. |
| 3. | In the absence of contraindication, beta blockers should be commenced as early as possible post CABG to reduce risk of arrhythmia and facilitate BP control. |
| 4. | Patients with a recent MI, LV dysfunction, diabetes mellitus, and chronic kidney disease should be prescribed an ACEi. ARBs are a reasonable alternative for ACEi intolerant patients. Renal function should be carefully monitored. |
| 5. | If target BP is not achieved by beta blockers and ACEi then it is reasonable to add on a calcium channel blocker and/or a diuretic to achieve target BP. |

## F. Diabetes Mellitus Management

20-30% of patients undergoing cardiac surgery have pre-existing diabetes mellitus[91]. Diabetes Mellitus (DM) is directly associated with increased morbidity and mortality among CABG patients[91]. In addition to causing general progression of cardiovascular disease and more rapid progression of native vessel atherosclerosis, DM is also associated with decreased vein graft patency[92]. This may relate to the association of DM with both endothelial and platelet dysfunction and its prothrombotic effect. All patients should be screened for DM preoperatively and if labelled with impaired glucose tolerance or diabetes mellitus should have blood glucose levels monitored closely. CABG patients with diabetes should be offered input from an Endocrinologist and a Dietician during the perioperative period. Long term follow up with regular plasma glucose and HbA1c levels must be used as a guide to modification of insulin or oral hypoglycaemic therapies. A HbA1c target of less than 7% has been shown to reduce both microvascular and macrovascular complications of the disease[93].

*Table 6: Diabetes Mellitus Management Recommendations*[51,52]

| | |
|---|---|
| 1. | All CABG patients must be screened for diabetes mellitus preoperatively and those with a new diagnosis of DM should receive input from a diabetic specialist during their inpatient stay. |
| 2. | A target HbA1c of <7% should be aimed for in all diabetic patients with the aim of reducing long term complications of diabetes. |

## G. Smoking Cessation

Patients undergoing CABG are most likely to be in their most vulnerable state and most receptive point for smoking cessation advice. This should be used as an opportunity to practice various smoking cessation strategies. It is estimated from a Scandinavian study that half of patients undergoing cardiac surgery will attempt to cease smoking after surgery, particularly in the first 6 months[94]. The safety of Nicotine replacement therapy has been demonstrated among patients with stable CAD [95] as well as ACS[96]. Drugs such as Bupropion and Varenicline have been shown to be safe and effective adjuncts to Nicotine replacement therapy in reducing smoking rates[97,98].

Electronic cigarettes (e-cigarettes) in comparison have not yet been thoroughly studied and their long term effects are yet to be understood. Although they have recently grown popular in discouraging cigarette smoking they have not been demonstrated to improve smoking cessation rates and there have been some important concerns raised about their potential harmful effects in the long term[99]. The most recent evidence, however, suggests that the long-term health effects of electronic cigarettes use are unknown but compared with cigarettes, they are likely to be much less, if at all, harmful[100]. The risk of vaping is estimated at less than 5% of the risk of smoking[101]. The National Centre for Smoking Cessation and Training (NCSCT) recommends that practitioners be open to electronic cigarette use among smokers trying to quit, particularly if they have tried other methods of quitting and failed[102].

*Table 7: Smoking Cessation Recommendations[52]*

| | |
|---|---|
| 1. | Smoking habit should be addressed in all smoker patients undergoing CABG. Counselling should begin as early as possible in the preoperative period and further focus on this during their hospital stay and follow up upon discharge. |
| 2. | It is reasonable to offer Nicotine Replacement Therapy and adjuncts such as Bupropion and Varenicline to aid smoking cessation. |
| 3. | Practitioners should be open to e-cigarette use among smokers trying to quit, particularly if they have tried other methods of quitting and failed. |

## H. Cardiac Rehabilitation

Cardiac Rehabilitation is a medically supervised interdisciplinary exercise-based program designed for patients with recent cardiovascular events to optimise their overall health status and minimise the risks for future adverse outcomes[103-5]. Its main components include baseline patient assessments, nutritional counselling, risk factor management, psychosocial interventions, and physical activity with counselling and exercise training [106]. Over the years cardiac rehabilitation programmes have evolved from a supervised exercise programme to a complete secondary prevention programme resulting in significant improvements in risk factors management, functional capacity, vascular conditioning, and psychosocial well-being; all of which culminate into a better lifestyle and overall improved clinical outcomes[106]. Cardiac Rehabilitation is now a class IA recommendation in all guidelines[51,52]. The referral process for Cardiac Rehabilitation programmes should begin during the inpatient stay early post CABG with the aim of commencing as early as possible after discharge from hospital.

Clinicians should assume an active role in the referral process as their advocacy remains a strong determinant of whether patients enrol into the programme[107].

*Table 8: Recommendation for Cardiac Rehabilitation*

| | |
|---|---|
| 1. | All patients after CABG should be referred for Cardiac Rehabilitation postoperatively during their hospital stay with the aim of commencing this as soon as possible after discharge. |

## I. Depression Screening and Management

Depression is known to develop in over 30% of post CABG patients at 1 year[110]. It is important to recognise depressive symptoms from the preoperative period and screen for it postoperatively as it is an important predictor of Cardiac Rehabilitation success [111], a risk factor for progression of CAD and correlates with poorer physical, psychosocial functioning

and poorer quality of life after surgery[112]. Appropriate recognition and treatment of perioperative depression reduces the risk of adverse events such as heart failure, myocardial infarction, the need for repeat revascularisation and cardiac arrest[113], [114]. Screening for depression requires a multidisciplinary approach that also involves the primary care physician as well as a mental health specialist.

Cardiac Rehabilitation programmes play a major role in reducing postoperative depression symptoms and improving psychological well-being[115]. Cognitive Behavioural Therapy, supportive stress management and telephone delivered collaborative care have also been shown to improve depressive symptoms.

*Table 9: Recommendations for Depression Screening and management*[52]

| | |
|---|---|
| 1. | It is important to screen depression among all CABG patients, preferably from the preoperative period. |
| 2. | For patients with clinical depression Cognitive Behaviour Therapy or collaborative care can be beneficial to reduce depression. |

## J. Influenza Vaccination

Patients should be encouraged to have their annual influenza vaccination. Evidence suggests that there is a significantly lower risk of major adverse cardiovascular events associated with the use of influenza vaccination. The risk reduction was most prominent in patient who were at the highest risk with more active coronary disease[109].

*Table 10: Recommendations for Influenza Vaccination*

| | |
|---|---|
| 1. | Patients should have annual vaccination against Influenza to reduce the risk of major adverse cardiovascular events, especially if the patient is already at high risk. |

# Summary

Optimal medical therapy for CABG patients is a constellation of interventions, both pharmacological and non-pharmacological that are aimed at optimising secondary prevention with optimisation of risk factors, improving wellbeing and quality of life. Despite the advances in medical care and presence of guidelines the overall care for post CABG patients remains suboptimal[1]. This may partly be due to the misconception of patients that they have been "cured" and that cardiac surgery is the definitive solution to their illness. The majority of clinical trials in patients with stable CAD do not show a mortality benefit in those who receive revascularisation with either PCI or CABG. This highlights the fact that these interventions do not alter the course of CAD. Risk factor modification on the other hand has been shown to alter the course of the disease and reduce mortality[108]. This should therefore be the focus of management once revascularisation is achieved. Physicians must play an active role in highlighting the importance of the various aspects of secondary prevention to patients and proactively involve the multidisciplinary team in addressing them. Departments should devise methods of encouraging employment of guidelines such as daily postoperative checklists as well as a pre discharge checklist to minimise the risk of missing any recommendations. General practitioners should also be actively involved in the process as they take over the care of patients once they have been discharged from cardiac rehabilitation service. They oversee monitoring of blood pressure, diabetes control and renal function for patients on potentially nephrotoxic medications. Depression screening is an important component of post-CABG care[110] that is commonly

understated. Early recognition and treatment of depressive symptoms improves wellbeing and directly impacts outcomes and quality of life.

The above recommendations form what is currently considered to be the optimal medical management for patient's post-CABG surgery.

*Table 10: Summary of our recommendations for the Optimal Medical Management post-CABG.*

| | |
|---|---|
| 1. | Aspirin 75mgs OD +/- clopidogrel 75mgs OD |
| 2. | Atorvastatin 40mgs OD |
| 3. | Bisoprolol 2.5mgs OD (resting HR 60-70bpm) |
| 4. | ACE Inhibitor at 48 hours in LV impairment, DM, CKD, prior MI |
| 5. | Blood pressure control (130/80mmHg) |
| 6. | Diabetes control |
| 7. | Smoking cessation |
| 8. | Cardiac rehabilitation |
| 9. | Depression Screen |
| 10. | Annual Influenza vaccination. |

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Chapter 3

# Bilateral Internal Mammary Arteries as Conduits: Coronary Technical Tips

*Sotirios N. Prapas*

*"Humilitas occidit superbiam"*

## Introduction

Coronary artery bypass surgery still has its unique role in the treatment of coronary artery disease and is considered the gold standard of treatment for 3-vessel and left main coronary artery disease, both in the general population and in patients with diabetes, as confirmed by the SYNTAX and FREEDOM studies[1,2]. The history of coronary surgery is marked by the constant effort to seek the safest method and the most suitable conduits for grafting. The classic coronary artery bypass grafting (CABG) operation with the exclusive use of venous grafts does not provide satisfactory long-term functioning of the grafts[3].

The internal mammary artery (IMA) has been considered globally as the favoured conduit for coronary artery bypass grafting since the benefits were described in 1986[4]. Since then, evidence shows that the use of bilateral IMAs (BIMA) as conduits is superior in terms of major adverse cardiac and cerebrovascular events and survival[5-7] Coronary artery operations with the exclusive use of bilateral internal mammary arteries (BIMA) are associated with better long-term survival than grafting with a single left IMA plus other types of conduits[8]. Efforts to maximise left (LIMA) and right internal mammary artery (RIMA) use have led to sequential grafting and to composite grafts, while the need to increase length has led to the use of the skeletonised IMA.

Whether the CABG procedure should be performed with or without the use of cardiopulmonary bypass (CPB) still remains a matter of large debate. However, a large number of studies have shown that the revascularisation of the myocardium with the heart beating and without CPB support can be superior to classic myocardial revascularisation regarding the reduction of post-operative complications and has favourable results, especially in high risk individuals[9].

One of the drawbacks of CABG compared with percutaneous coronary intervention is the potential high risk of having a cerebrovascular accident (CVA)[10-12]. Off-pump coronary artery bypass (OPCAB) may reduce but does not eliminate the postoperative occurrence of CVAs, because a proximal anastomosis has to be done with the aid of a partial clamp in most cases[13-15]. Partial clamping of the pulsating ascending aorta for a central proximal

anastomoses, however, particularly in the case of an atheromatous aorta raises the risk of neurological complications and increases the possibility of dissection of the ascending aorta[16-17]. Hence, different anaortic strategies were developed to minimise the risk of postoperative strokes, such as aortic no-touch techniques and the use of proximal anastomotic devices (PADs) to perform proximal anastomoses, either automatically or handsewn, on the aorta without partial clamping. Researchers in recent meta analyses compared all these strategies to OPCAB with partial clamping and to on pump CABG, reporting a significant reduction of the possibility of stroke, especially when 'no touch' techniques were used[18-19].

A potential limitation of 'aortic no-touch' techniques is the technical difficulty of applying it to mulitvessel coronary disease. Therefore, we proposed the use of the π-circuit, which involves the use of different conduits, either arterial or venous, grafted together, having one or two mammary arteries as the inflow blood source in order to revascularise two to six peripheral coronary targets[20].

## Definition of the π-circuit

The π-circuit (Figure 1) is an arterial circuit consisting of pre-constructed composite grafts, sequential anastomoses and extensions. Briefly, it constitutes a net that is built using one mammary artery (in general the left IMA) or both IMAs for the inflow. The radial artery, or a saphenous vein (SV), or even short segments of the left or the right IMA can be used as an elongation of, or a side branch of, the main conduit, depending on what is needed.

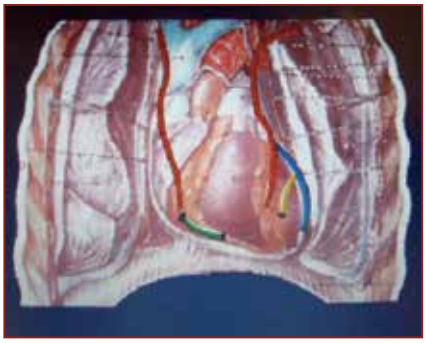

*Figure 1: π-circuit - an arterial circuit consisting of composite grafts, sequential anastamoses and extensions*

The composites are preconstructed before the grafting procedure starts and are used to graft all the stenosed coronary vessels. The π-circuit is completely flexible, and the arrangements of its components can vary according to the needs of the individual patient. The aorta is never touched. The technique is used in cases where all of the peripheral targets have severe and similar stenoses. If a peripheral target has moderate to severe stenoses, a special graft is placed with a top end on the ascending aorta, mainly a venous one, provided that the aorta is healthy.

## The π-circuit graft philosophy – theoretical advantages

The π-Circuit is a philosophy rather than a technique that enables us to revascularise the myocardium by imitating a theoretical secondary natural circuit that could exist in the heart as it does in other organs (Figure 2). Some

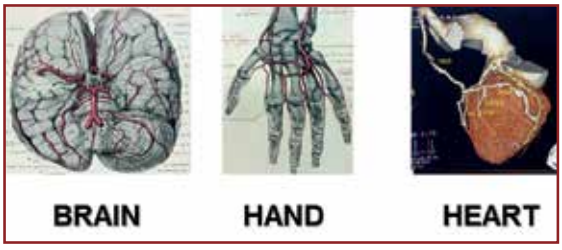


*Figure 2: The Philosophy - natural secondary circuits*

other additional advantages of the method are included in the aforementioned philosophical approach of the myocardial revascularisation.

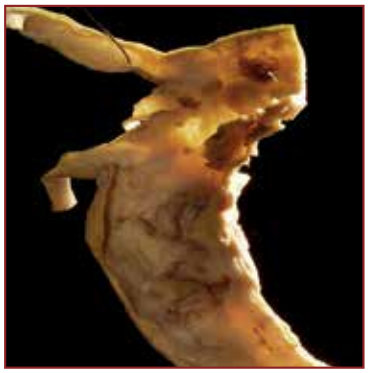

*Figure 3: Excessive atheromatous lesions*

**It follows Nature's way of performing an additional circuit like in all organs and extremities.** The application of the π-circuit without CPB, avoiding any manipulation of the ascending aorta for myocardial revascularisation, is based on the philosophy of an additional self-regulated circuit, as it is directly connected to systemic circulation through the pedicled IMA or IMAs. As a closed circuit, it is subject to the laws of the natural vascular flow regulation. For the same reasons, it irrigates each branch of the coronary system according to distal outflow[20].

**It allows us to perform anaortic surgery, avoiding the risk of CVA and dissection of the aorta, especially in patients with an atheromatous or friable ascending aorta.** Once surgical coronary revascularisation without the use of extracorporeal circulation became feasible, safe and effective, there was strong questioning and concern over the need to implant grafts in the aorta, as no other manipulation of the aorta was necessary. Moderate or excessive atheromatous lesions (Figure 3) of the ascending aorta are observed in approximately 13% of coronary patients[21]. Detachment and embolism of atheromatous matter from surgical manipulations, or shear effects of flow from the aortic cannula constitute the main causes of perioperative stroke[22-23]. This means that the incidence of such episodes is related to the degree of atheroma of the ascending aorta and to the degree of manipulation made during the operation. A no-touch technique for the aorta none-touch helps overcome this issue. Moreover, the fact that the presence of aortic atheromata shows a linear increase as age advances[21] and that one third of patients who undergo coronary bypass today are >70 years of age and rising[24], leads to the conclusion that the problem of an atheromatous or friable ascending aorta will continue to grow.

**It offers Nitric Oxide to the coronary bed, protecting it from new lesions due to its anti-inflammatory effects.** Compared with all other arterial and venous conduits, the internal mammary artery shows increased production of anti-inflammatory and vasoactive molecules, particularly nitric oxide[25]. In our method, the whole coronary bed is potentially protected from new atheroma, benefitting from the anti-inflammatory molecules and nitric oxide that are distributed throughout the π-Circuit which is based on the internal mammary for inflow.

**The circuit functions as a total arterial circuit despite the fact that parts of the saphenous vein are integrated, due to the regulation of the flow of the circuit towards the whole coronary bed as per Bernoulli's principle.** One of the criticisms of the π-circuit could be that it is not fully arterial because of the use of some composite arteriovenous grafts with suboptimal flow in the short term, as a result of runoff and native competitive flow[26]. However, a recent study demonstrated that at 1-year follow-up, SV connected to the left IMA had a reduced luminal diameter but no abnormal internal intima-media thickness[27]. Moreover, a randomised study (SAVE right internal thoracic artery (RITA) Trial) reported a 1-year patency rate of 97.1% for the SV composite grafts, which was not inferior to that of the RIMA composite grafts (97.1%) with a 95% lower confidence limit of -2.6% ($P < 0.001$ for non-inferiority)[28]. Unfortunately, data on the patency rates

of these subsets of conduits are not available in this series. Anecdotally in our practice, after evaluation of the quality of the SV grafts integrated to the circuit angiograpically, or in some redo cases for additional valve surgery some years after the initial operation, we realised that the venous grafts were surprisingly very healthy without atheroma (Figure 7, 8). Trying to theoretically explain the phenomenon, we estimate the Bernoulli's principle plays a role in the function of the π-Circuit.

$$\rho_\epsilon + \frac{\gamma u^2}{2g} = C$$

*Figure 4: Bernoulli's principle*

The simplest form of Bernoulli's principle is shown in Figure 4. In this equation, the "C", "g", "γ" are constant. The constant on the right-hand side of the equation depends only on the circuit chosen, whereas the other parameters depend on the particular point on that circuit. Pressure and velocity in a moving fluid are inversely proportional. High pressure gives low velocity and low pressure gives high velocity.

Applying Bernoulli's principle on the different use of a SV graft with a top end anastomosed to the ascending aorta (Example I, Figure 5), or connected to a pedicled IMA (Example II), we observed crucial differences based on the equation. In Example I, Pε is the systolic pressure of the aorta which is constant. This means that u, which is the velocity inside the aortosaphenous graft, depends on C. Assuming that C is the final run-off of the circuit and ρε is constant (i.e. systolic pressure 120 mm Hg), then the velocity depends on run-off. In cases in which a target vessel is small in diameter the run-off is low and as a result the velocity is low and the pressure becomes high. This might explain the tendency of the SV grafts to failure when these are anastomosed on small diameter coronary vessels. On the opposite side, a large target in diameter results to a higher run-off, higher velocity and lower pressure towards the wall of the SVG.

The theoretical difference in the use of an SVG connected to a pedicled IMA (Example II) is the fact that the pressure at the beginning of the venous segment of the arteriovenous conduit can be influenced by regulations of the muscular wall of the IMA (Figure 6). This means that the proximal part of the artery has the ability to increase or decrease the diameter of the venous segment, which acts to increase the velocity within it and decreases the pressure in the vein graft. This then in turn protects it from additional wall stresses and decreases the lumen diameter according to run-off.

## Surgical technique

The operations are performed through a classic median sternotomy. The technique described is based on the use of both IMAs. In all cases, skeletonised IMAs are harvested. IMAs are carefully separated from the accompanying veins using metal clips[29]. Exposure of the surgical field without disturbing heart function is of chief importance for operative success. The pericardium is suspended by placing deep silk sutures and then drawing them upwards according to Lima's[30] or Zamvar's protocol[31]. Opening the right pleural cavity makes it easier to turn the heart during the anastomoses onto the lateral wall. Better exposure can be achieved by tilting the surgical table to the right and placing the patient in the Trendelenburg position. To stabilise the target vessel, we use all the commercial stabilisers,

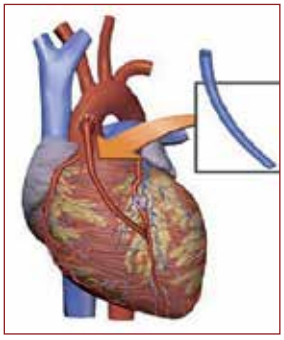

*Figure 5: SVG connected with a top-end on the ascending aorta*

either compression devices, such as the metal re-sterilized Sontec stabiliser or suction devices such as Octopus II plus, III and IV manufactured by Medtronic, as well as with Estech's Synergy. A bloodless surgical field is ensured with the use of intraluminal coronary shunts and with a $CO_2$ blower and irrigation around the arteriorotomy. The active co-operation of surgical and anaesthetic teams is a crucial requirement to provide a stable haemodynamic condition. In all cases the perfusionist and the CPB circuit are on standby during the procedure.

Up to six coronary bypasses can be made with the two IMAs and an additional piece of radial artery or SV, utilising the increased length of the skeletonised IMAs and optional composite grafts and sequential anastomosis. The main preconstructions for left-sided revascularization are bifurcations in a T or Y configuration, or a composite trifurcated graft of our own creation, which we have termed the Pi graft. These are made with the use of segments of right and left distal mammary artery as side branches of the main pedicled conduit, which is generally the LIMA except in rare situations. Also, for specific reasons, side branches could be segments of radial artery or saphenous vein. The main preconstruction for right-sided revascularisation is the elongation of the initial pedicled RIMA by an end-to-end or end-to-side anastomosis using the radial artery (I-radial), or the SVG (I-SVG), or sometimes the entire length of the RIMA with a piece of the distal LIMA (I-dLIMA). The objective is to reach the distally located posterior

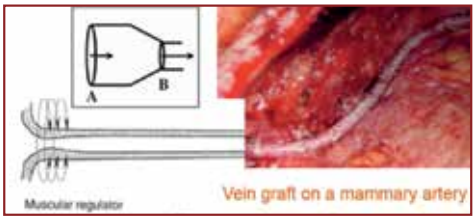


*Figure 6: : pressure regulation in an arterio-venous conduit*

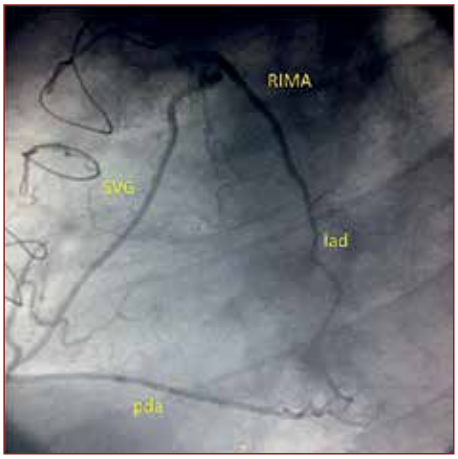


*Figure 7: Vein graft connected to the RIMA as a Y-graft towards the posterior descending coronary artery. Angiography twelve years after the operation.*

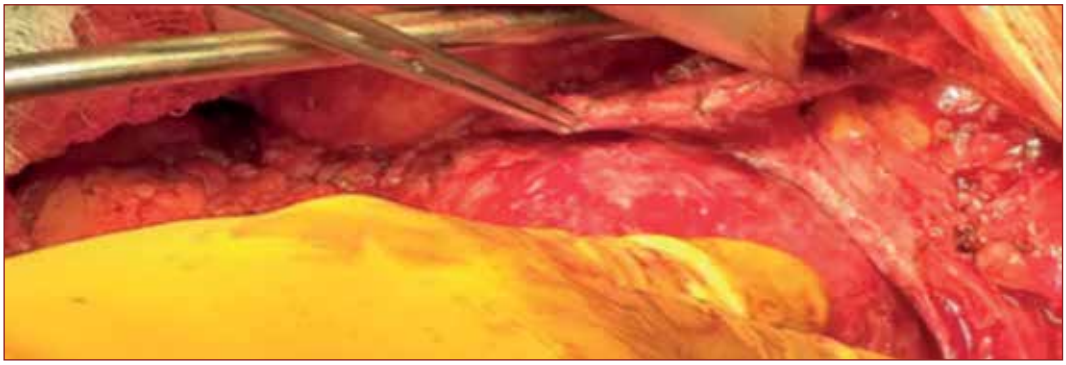

*Figure 8: Vein graft connected to the proximal 1/3 of RIMA without any atheromatosis 13 years after the initial OPCABG x 4.*

descending artery (PDA), which should be preferred for anastomoses on the right coronary system. Sequential anastomoses using the main graft or the side branch of a composite graft are carried out in a very reliable way, as the measurements on a beating heart are made based on the heart's natural size and volume.

## Technical aspects

The cornerstone for achieving full arterial revascularisation without manipulation of the aorta is the creation and use of composite arterial grafts. The following compositions are used:

### *T or Y graft*

The creation of a bifurcation based on the IMA for left-sided revascularisation (T or Y graft) can be done following some specific steps. The IMAs are dissected in a skeletonised fashion, trying to preserve both pleurae. The left pleura is separated from the upper mediastinal tissues and the left side of the opened pericardial sac is divided vertically just opposite the pulmonary trunk 1 to 2 cm above the phrenic nerve. The closed pleura in cases with bulging lungs may be plicated to eliminate tension. Occluding the distal end of the LIMA with a Ligaclip, the pulsatile left IMA is tunneled towards the LAD. The remaining distal part of the LIMA is preserved, in case of the need to use as an additional composite graft. With the lungs inflated, we mark the spot where the T-graft anastomosis is going to be performed, just after the entry of the in-situ LIMA into the pericardial cavity (Figure 9).

The RIMA is then transected distally at the level of its bifurcation and as a free graft at a various level proximally depending on the scheduled plan. In cases with no need for right-sided revascularisation we cut the RIMA at its origin in order to do a long Y or T graft onto the LIMA.

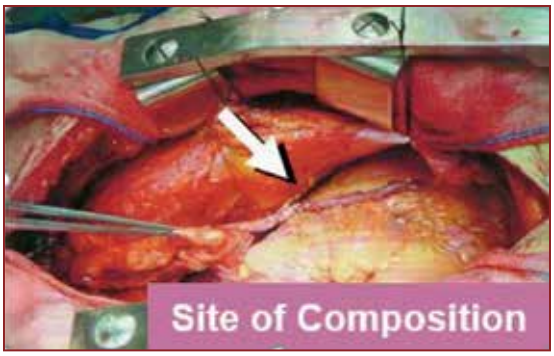


*Figure 9: The correct site for the T graft anastomoses, performed just after the entry of the insitu LIMA into the pericardial cavity*

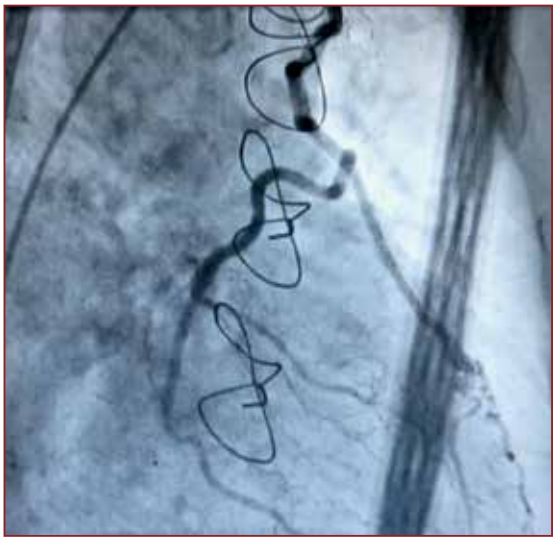

*Figure 10: T- graft towards the LAD and the OM1, OM2 branches. Angiography 18 years after the operation*

Otherwise, we take the distal two thirds as a free graft and use the proximal 4-6 cm from its origin from the subclavian artery as the inflow for an elongated graft. The free RIMA is then anastomosed in a T or Y-fashion (as described by Tector and Calafiore respectively) to the previously marked spot of the attached left IMA.

A very useful trick to avoid any dissection performing the arteriotomy on LIMA for the end-to-side anastomosis is to select a side branch close to the desired part, cut it at its base and open the arteriotomy with a reversed pair of scissors inserted through the hole of the side blanch. The choice of T or Y bifurcation depends on the course that the composite graft has to follow towards the lateral wall and the individual targets.(Figure 10).

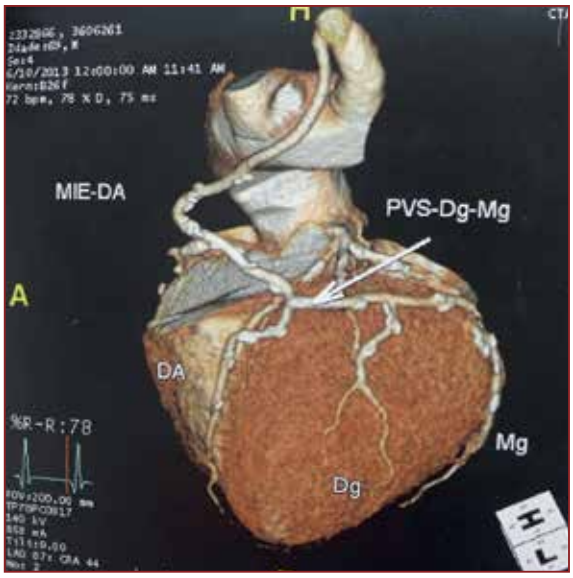


*Figure 11: Pi trifurcation towards the LAD, the INT branch and the OM1, OM2 branches. CT Angiography 13 years after the operation*

### *Pi trifurcation (Π-graft)*

The creation of a trifurcation for left side revascularisation follows the creation of a T-graft in the way which was described above. The remaining distal part of the LIMA after the LAD anastomosis is preserved for use. The next stage of the construction of the Π-graft is the performance of a T-on-T anastomosis. The free, preserved distal piece of the LIMA is connected end-to-side to an appropriate point of the free RIMA depending on the branch that should be anastomosed, by keeping the heart slightly lifted and the free RIMA toward the atrioventricular groove. As a consequence, it is performed at the proximal part of the free RIMA for diagonal grafting, approximately at the middle of the free RIMA's course when the intermediate branch is anastomosed, and at the distal part when any of the two obtuse marginal branches must be grafted (Figure 11).

Practically the Π-graft is used for unstable patients, as the LAD anastomosis can be performed primarily, rather than undertaking a diagonal plus LAD sequential anastomosis which would otherwise need a dangerous extended displacement of the ischemic heart. The LAD anastomosis is perfomed before the diagonal (sequential D+LAD anastomosis). In this way we avoid the extended movement of the heart. Also, we use a trifurcation when INT or OM branches have an intramyocardial course. In this way we avoid the 'Seagull' phenomenon of acute angulation within the conduit.

### *Elongations (I-graft)*

It is not our first option to graft the RIMA directly to the RCA, especially if the stenosis is less than 90%. Another reason is that the pedicle RIMA may not be long enough to overcome the calcified or fibrotic vertical part of the RCA (in most cases) and reach the more distally

located posterior descending artery (PDA), which is invariably a more suitable diameter target. Therefore, an end-to-end anastomosis of the pedicled proximal RIMA with the radial artery (I-radial) or of the whole RIMA towards the distal free section of the LIMA (I-d.LIMA) is performed, always with the objective of elongating the RIMA. (Figure 12).

An important issue is to avoid the use of the I-radial for an anastomosis to a moderately stenosed vessel due to the probability of graft atrophy. Only severely or total occluded coronaries should be considered as targets in these circumstances.

In such cases, an elongation of the RIMA with a piece of SV is preferred. Due to the large lumen of the vein graft in comparison to the RIMAs lumen, an end-to-side anastomosis is performed.

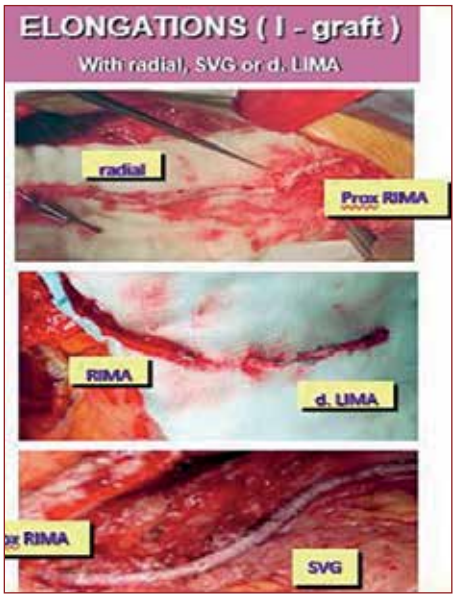


*Figure 12*

### *Sequential grafting*

While performing sequential anastomoses we perform small arteriotomies, taking care to avoid the "Seagull Phenomenon" in intramuscular coronaries or at wide angles from each other and choose the vessel with the greatest stenosis in the final anastomosis.

It is important to ensure optimal orientation of the graft is achieved when making sequential anastomoses to the intermediate and marginal branches or to two marginal branches of the circumflex. This minimises the likelihood of graft torsion or twisting, as its straight course is set among three points (the origin, side-to-side and end-to-side anastomosis) (Figure 13).

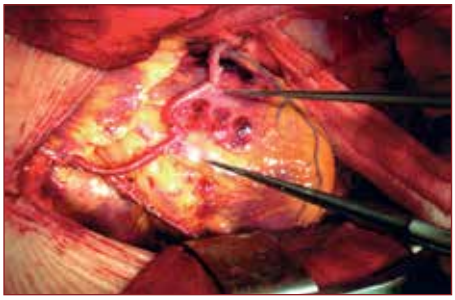

*Figure 13: Triple sequential anastomosis on the lateral wall including the INT, OM1, OM2 branches*

## Arrangements

Combining off-pump CABG with the use of both IMAs seems to be the most favourable method to avoid any manipulation on the ascending aorta. Neither pedicled IMA however, can reach the distal branches of the circumflex (CX) or the right coronary arteries and the difficulty of multiple anastomoses are disadvantages.

By using various arrangements of rerouting IMAs using the π-graft circuit we are able to overcome these limitations. Our approach is considered

an addition to other reported techniques for preconstructed composite conduits or strategies that allow us to perform "anaortic surgery".

## π-circuit in situ arrangement

This is the most classical arrangement for left and right-sided revascularisation. The configurations which are used for the left side of the heart are the bifurcated T or Y grafts or a trifurcation/ Pi graft. On the right side of the heart we use an elongation of the proximal 1/3 of the pedicle RIMA with either the radial artery or SV (Figure 14).

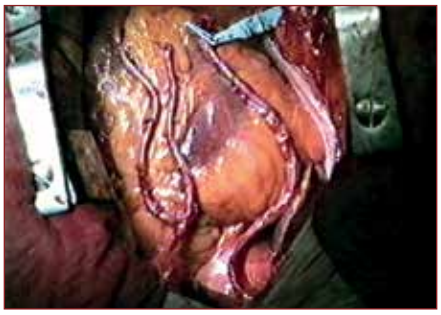

*Figure 14:* π-*circuit in situ arrangement. T-graft on the left, I-radial graft on the right, prior being anastomosed.*

## π-circuit cross arrangement

In cases in which the right coronary artery is normal or the coronary pattern of the heart is left dominant we use the cross arrangement in which the RIMA is connected directly to LAD and LIMA is used to revascularise one or more branches of the anterolateral wall, provided that both IMAs have sufficient length to avoid using the small and muscular distal aspect of the conduit for anastomosis. Younger patients are not candidates for the application of this arrangement because the RIMA crosses the midline of the chest which can increase risk of graft injury in future redo surgery (Figure 15).

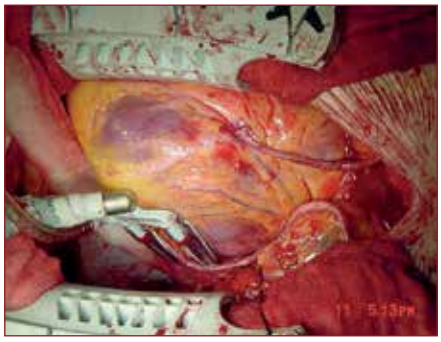

*Figure 15:* π-*circuit cross arrangement. RIMA to LAD, LIMA to OM.*

## Long Y-arrangement

A pattern for complete myocardial revascularization using both IMAs in a T or Y configuration, including sequential grafting. We use this arrangement in cases of severe stenoses in all targets. We can revascularise the anterior wall anastomosing solely the LAD, or diagonal and LAD sequentially, using the limb consisting of the pedicled LIMA. The lateral and inferior wall can be performed with sequential anastomoses to obtuse marginal branches and the posterior descending coronary artery, provided that this is totally occluded or severely stenosed. If a branch of the aforementioned arteries has a moderate stenosis, we prefer to exclude it from the arrangement and to receive an isolated graft with a top end at the aorta (Figure 16).

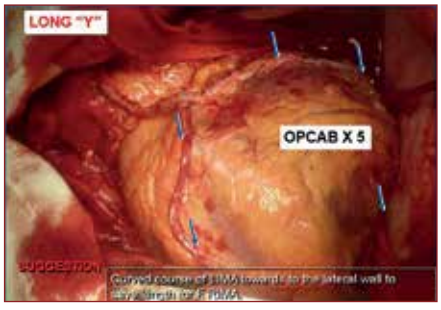


*Figure 16: Long Y graft arrangement. Anastomosed towards the diagonal and the LAD (LIMA limp), INT, OM and PDA (fRIMA limp) branches*

## λ-graft (Lamda) arrangement

This arrangement is used when the long Y graft is unable to reach the inferior wall, since we utilise the whole length of both mammaries. We use the LIMA as an inflow conduit and the free RIMA, divided in two parts, proximal (fRIMAp) for elongation of LIMA, and distal (fRIMAd) as a side branch on it. We start creating the composition by connecting the free RIMA to the LIMA as a long Y graft. Then, we perform a side to side anastomosis of the LIMA to the corresponding point of the LAD, keeping the rest of the LIMA in place. We continue with the anastomosis of the Y graft to a lateral target, cutting the free RIMA limb at the appropriate length. The remaining part is used to elongate the in situ LIMA towards to the inferior wall for PDA vertical end-to-side anastomosis. Care is needed to avoid any tension across the acute margin of the heart, where a shallow tunnel helps to avoid any displacement of the graft (Figure 17-18).

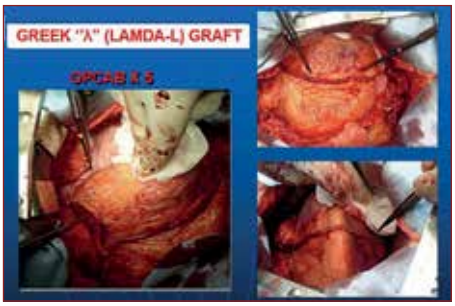


*Figure 17: Lamda arrangement, to succeed an OPCABGx5 revascularization (LAD, diagonal, INT, OM and PDA).*

## Bridging (Ψ – Psi Graft) arrangement

The Ψ-graft arrangement is used for diabetic patients with very small target vessels, in order to increase the total runoff. The free LIMA is anastomosed to all anterolateral targets as a 'bridge' and the RIMA as an inflow conduit is connected to the bridge (Figure 19).

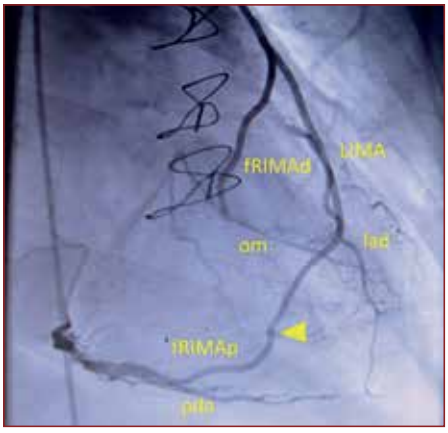


*Figure 18: Lamda arrangement towards the LAD, OM and PDA: Coronary angiogram taken 1 year after surgery. fLIMAd: free left internal mammary artery, distal segment; fRIMA: free right internal mammary artery*

# Discussion

Since I first became involved in OPCAB surgery in 1997, I realised that we were able to offer more advantages to patients by avoiding any procedure on the ascending aorta. Therefore, my cooperatives and I made a great effort to find ways to perform multiple revascularisation of the heart, following rules, methods and using grafts which had been proven to be superior in terms of graft patency.

In 2006, in a retrospective study including 1395 patients who underwent isolated coronary bypass using the π-circuit at the Henry Dunant Hospital Center's Cardiac surgery department, we analysed the mid-term results in 1157 male and 200 female patients, including high-

risk patients, each of whom received a mean 2.75 ± 0.92 distal anastomoses. The overall 30-day mortality rate was 1.5%. In brief, the mid-term cardiac mortality demonstrated the effectiveness and safety of our method in four groups of patients: octogenarians, diabetics, patients with renal disease and patients with chronic obstructive pulmonary disease (COPD) where outcomes were similar to other patient groups[32]. Female gender, emergency surgery for coronary revascularisation, the existence of a left ventricular ejection fraction lower than 35% as well as the pre-operative use of the intra-aortic balloon were highlighted as risk factors for higher mid-term mortality due to a cardiac reason[32-33].

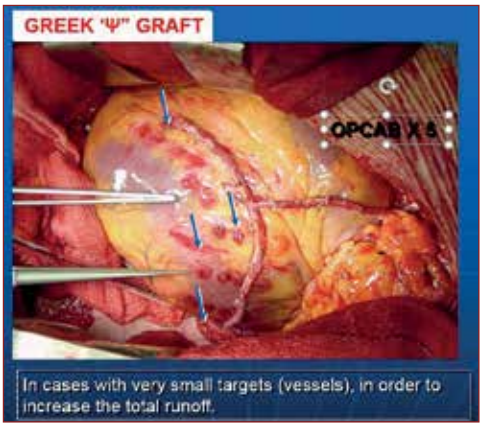


*Figure 19:* Ψ- *graft arrangement : Bridging of the LAD, the diagonal, the INT and the OM branches with the free LIMA. The pedicled RIMA as an inflow graft towards the bridge.*

We extended the review through to 2018. From January 2001 to May 2016 the Pi Circuit was used in 3081 patients with coronary artery disease admitted for CABG at the Henry Durant Hospital Center.

We applied our method in all patients, including high-risk groups once again. Namely, 35% of our patients were over 70 years old, 8% were emergencies, 34% with diabetes, 30% obese, 54% had hypertension, 7% severe chronic pulmonary disease , 9% carotid disease, 4% a previous stroke, 35% a previous cardiac operation, 2% needed preoperative IABP, 2% were on dialysis, 26% had moderate LV impairment and 7% a very low EF. Pre- and peri-operative data were analysed and the observed results were compared to what was expected. Forty patients died within the first postoperative month, 28 from a cardiac cause and 12 due to a non-cardiac cause (observed mortality, 1.3%)[34].

Nowadays, numerous publications have confirmed the accuracy of our choice to use an anaortic method, including OPCABG, aorta non-touch and IMAs use, either isolated or in a composite fashion with radial or SV grafts. Avoidance of aortic manipulation during off-pump coronary artery bypass grafting may decrease neurological complications compared to the classic technique in which the ascending aorta is manipulated[35]. Clamping the aorta during coronary artery bypass grafting may increase the risk of postoperative stroke, regardless of the severity of aortic disease[36]. Zhao et al concluded that avoiding manipulation of the aorta in OPCABG may decrease the risk of post-operative stroke by 90% compared to classical CABG, by 66% compared to OPCABG cases with partial clamping of the ascending aorta, and by 52 % with the use of proximal anastomotic device (PAD)[37]. The postoperative rate of CVAs was 0.5% (14 cases). From the cases examined, 2 (0.1%) were transient ischemic attacks and 12 (0.4%) were strokes. The mean expected stroke rate (1.6%) was significantly higher than the observed rate ($P < 0.001$). None of the patients who experienced a postoperative CVA died[12]. The ϖ-circuit should be considered a safe alternative among other aorta non touch techniques.

Off Pump CABG is associated with a lower incidence of stroke and may therefore improve patient outcomes[10]. Puskas et al, described that the elimination of the CPB reduces the

risk of short-term mortality, stroke, renal failure, atrial fibrillation, bleeding, and length of stay in the ICU and may therefore improve patient outcomes. Based on the observation of 42,471 patients in the STS database, which were analysed according to 32 clinical risk factors, it became evident that OPCABG benefits both genders but females more than male[9]. In a meta-analysis including[38] propensity matched studies of 123,137 patients, Kuss et al., observed superiority of OPCABG in the reduction of the mortality, stroke, renal failure, transfusion and wound infection[38].

The survival benefit of OPCABG appears to be especially apparent in high risk patients with a predicted mortality risk more than 2.5%. The survival benefit of OPCABG increases as predicted mortality increases[39].

Apart from a few cases, we were able to avoid the use of CPB in all patients, including the high risk ones and those with intramuscular targets or huge hearts in terms of size, always using specific protocols and special tricks along the way. The conversion rate, due to the experience of the surgical team and anesthesiology support, was only 0.01%.

Given the IMA's properties and especially the continuous internal laminae, compared with the dashed one in other arteries, long-term results of their use are excellent. Taggart et al., comparing 4693 BIMA to 11269 single IMA grafting from 7 databases matched for age, gender, LV function, demonstrated that BIMA grafting appears to have better survival rates, with up to 10 years follow up in comparison with SIMA grafting. Long-term survival benefit of BIMA seems to continue in the second decade after surgery[6]. Similar results were found by Yi et al., comparing 8270 SIMA and 7313 BIMA at mean 10-year follow up[40]. Takagi et al, based on data from 20 observational studies enrolling 70897 patients, showed that BIMA Grafting is associated with a significant reduction in long-term mortality relative to a single IMA. The BIMA benefits were increased in a higher proportion of male patient studies[41].

Many angiographic studies show that both IMAs have a similar patency rate when used to the same target in left-sided coronaries and that short, medium and long-term results are related with rates ranging from 91% to 100% patency. For example, Dion's follow up of 7 years showed patency rate of 97% for LIMA and 96 for RIMA[42] and Calafiore's follow up of 3 years showed a 100% patency rate[43]. BIMA grafting is underused by cardiac surgeons, and, currently, less than 10% of European and less than 5% of North American patients receive BIMA grafts, which is significantly lower than in our data[48-50]. Alongside the 10 years results of the ART study and many other studies, it is now more than ever clear that the use of BIMA should be more widely spread[5,6,44-51].

The use of BIMA grafts in our practice was one of the highest in the world, as LIMA was used in 98% of patients and RIMA in 71%. Pieces of radial artery or SV as parts of preconstructions were used in 26% and 17 % respectively, trusting the superiority of arterial grafting, as this is also proved by a series of publications[12].

Total arterial revascularisation is the Holy Grail for CABG. An 80% rate of this technique has the potential to prevent more than 10,000 deaths annually and add > 64,000 person-years of life over the course of 10 years[52]. This is the desired goal in all our patients and we schedule the appropriate arrangement for each of them. Use of pre-constructions, sequential grafting, elongations and bridging help us to achieve a total arterial revascularisation strategy. It is important to think that in one third of our patients total arterial revascularisation was possible using just the two mammary arteries[53].

It is our belief that the superiority of the Y graft, which is used in our practice in many patients, is due to the fact that the needed length of the IMAs for the preconstruction

allows us to avoid the distal muscular parts of BIMAs, which are narrower and tend to spasm. Tatoulis et al., in 991 angiograms, found that the patency of RIMA and LIMA were similar when grafted to either LAD or CX[54]. This study, among others, justifies our policy to use a cross-arrangement of the IMAs in convenient situations.

Maintenance of the collateral flow to the sternum in skeletonised IMA reduces the likelihood of complications from the surgical wound and thus makes it possible to use both IMAs in high risk patients such as diabetics, patients with chronic obstructive pulmonary disease (COPD), octogenarians and obese patients[55-57]. When applying our method, we soon observed better outcomes in high risk groups of patients due to the advantages described above.

## Octogenarians

The superiority of BIMA, as well as of OPCAB, on survival in octogenarian patients is proven[58-59]. The pooled estimate of 30-day mortality of classical CABG in other studies was 7.3% (6.3-8.2%) with a 1-year survival rate of 86% (83-88%) and was similar to PCI with a 30-day mortality of 5.4% (4.4-6.4%) and 1 year survival rate of 87% (84-91%). Perioperative stroke occurred in 6% of patients undergoing CABG[60]. Upon evaluating the effects of the Π-circuit technique on octogenarians we compared 62 patients over the age of 80 years to 1297 patients under 80 years of age. We found that apart from a higher incidence of early postoperative morbidity, overall survival was not affected. In our database we observed that the 30-day mortality was 3.2 % (versus 1.5%). The 30-day stroke rate was only 0.45%. During 5 years follow-up, survival seemed to favor the younger group ($P < 0.001$). Nevertheless, further analysis of the data with the Cox regression model to exclude confounding risk factors revealed the survival rates of the 2 groups to be similar[61].

## Diabetes

Whether CABG or PCI is the preferred revascularisation method in patients with multivessel coronary artery disease, particularly in those with diabetes, has been highly debated in the cardiovascular community for more than 20 years. Finally, CABG is still the clear choice for patients with diabetes in current practice, due to the superior endpoint of repeat revascularisation[62,63]. Skeletonisation lowers the risk of sternal infection as has been proven in many studies[64] and the use of skeletonised BIMA is therefore crucial in diabetic patients. In his editorial the central message of C. Locker was that the use of skeletonised BIMA may also be more important to increase longevity in patients with diabetes[65].

As mentioned, 34% of our patients were diabetics who followed the same protocols to the others regarding the skeletonisation and the use of BIMAs. In order to evaluate the frequency, the risk-factors, characteristics and rate of infections applying our method, a prospective cohort study was performed during a period of 3 years, including diabetic patients. Twenty-one of 782 studied patients (2.7%) acquired 26 microbiologically documented nosocomial infections. Eight of 782 studied patients had pneumonia (1.02%), 7 of 782 (0.90%) had bacteremia, 4 of 782 (0.51%) had superficial wound infection at the sternotomy site, 4 of 782 (0.51%) had a urinary tract infection, 2 of 782 (0.26%) had mediastinitis, despite the use of BIMA. There was a statistically significant difference in mortality between patients with and without nosocomial infection (23.8% vs 1.2%, $P < .001$)[66-67]. We attribute the low incidence of wound infection in our patients to the careful regulation of preoperative glucose levels in diabetic patients, to the preparation of skeletonised mammary arteries

and the absence of extracorporeal circulation, which indirectly results in the prevention of intracellular tissue oedema and therefore to a shorter stay in the ICU and less time on mechanical respiratory support. In our series, 84% of the patients spent 24 hours in the ICU, 13% spent 48 hours and only 3% spent more than two days[68].

### Redo surgery, renal failure and COPD

In our practice, redo cases represented approximately 5% of all cases. We were able to perform the operation without CPB support in most of the cases. The use of BIMA was lower than in primary cases (55.1% vs. 89.7%) and the mortality slightly higher (2.6 % vs 1.5%) with p = 0.002. There were also a slightly higher percentage of renal failure and pulmonary complications as well as sternal wound infections[32]. Comparing the results to the STS mortality of 6.25%, our method seems to offer lower mortality and more advantages. In cases with renal failure OPCABG, compared with on pump CABG, is associated with better survival rates and renal prevention[69-72]. In our data, although the 30-day mortality and 5-year mid-term mortality from all causes was higher (3.7% vs 1.3% and 13.8% vs 4.8%), the mid-term mortality from cardiac reasons was similar[32]. Similar mid-term outcomes for the mortality from cardiac reasons existed for COPD patients as well[73].

## Conclusion

In conclusion, π-circuit is an innovative anaortic method for surgical revascularisation, consisting of all the principles described by Puskas et al., as "State of the Art"[74]. The use of BIMAs with special tips and tricks, can achieve a total arterial revascularisation in all patients, regardless of comorbidities and other risk factors. The method has already been applied successfully for more than 20 years, for the population as a whole, and the overall results reflect its effectiveness. Therefore, we believe that it can now be considered the method of choice for the surgical treatment of the coronary artery disease.

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SECTION 1 CARDIAC SURGERY

# Aortic Valve Surgery

*"Aut non rem temptes aut perfice"*

*Publius Ovidius Naso. 43 BC - 17 AD*

Chapter 4

# Do We Deal With Prosthesis-Patient Mismatch Appropriately? Does it Matter?

*Torsten Doenst*

*"Marcet sine adversario virtus"*

## Prosthesis-Patient-Mismatch (PPM)

Aortic stenosis is a disease that inflicts signs of heart failure and significantly reduces life expectancy. It is routinely assessed, using echocardiography, by determining blood flow acceleration over the stenosis and calculating the resulting pressure gradient and effective orifice area (EOA). The determination of the effective orifice area is often considered the most relevant parameter to assess severity and it is often related to body surface area to normalise for patients' dimensions. Postoperatively, the same tools are used to judge the function of a prosthetic valve. In order to address haemodynamic performance of a prosthetic aortic valve, the concept of prosthesis-patient-mismatch (PPM) has been introduced. Although the concept is convincing, there are several issues in daily practice that confuse our ability to optimally assess haemodynamic performance of tissue valves and therefore assess PPM. These issues relate to the projection of the EOA from one patient to another, to confusion about true valve sizes and confusion in the comparability of sizing strategies for different prostheses. We will here systematically address these issues and eventually provide a new perspective that will allow surgeons to better predict the haemodynamic outcomes of their actions and possibly improve it too.

## Introduction

In order to properly assess prosthetic valve haemodynamics and to understand the various areas of confusion in the field, it is required to address the following topics. We will summarise how we currently assess the haemodynamic relevance of an aortic stenosis and which problems arise in the application of this strategy in determining prosthetic valve

stenoses, specifically addressing PPM. We will address the current practice of comparing haemodynamics of different prosthetic valves with each other and finally review the way these different prostheses are selected for each patient. We will finally suggest a (new) strategy for prosthetic valve size selection, implantation and the assessment of postoperative haemodynamics. The understanding of these principles is also key for being able to put results from transcatheter valves into perspective.

## How do we assess the relevance of aortic stenosis and post replacement prosthesis performance?

Aortic valve stenosis is generally diagnosed by echocardiography[1,2]. Pressure gradients and effective orifice areas are determined to assess the severity of the stenosis. Figure 1 shows a schematic illustration of the physical principles of their assessment and the relationship of the two parameters (A-D). Pressure gradients are assessed by measurements of flow velocity and use of the modified Bernoulli's equation (A). The effective orifice area (EOA), representing the smallest cross-sectional area of the transvalvular jet flow, is measured by relating flow velocities and the area of the left ventricular outflow tract according to the continuity equation (B). Pressure gradients and EOA show a logarithmic relationship with a steep rise in pressure gradients once EOA values fall below 1 cm² (C, D). Both

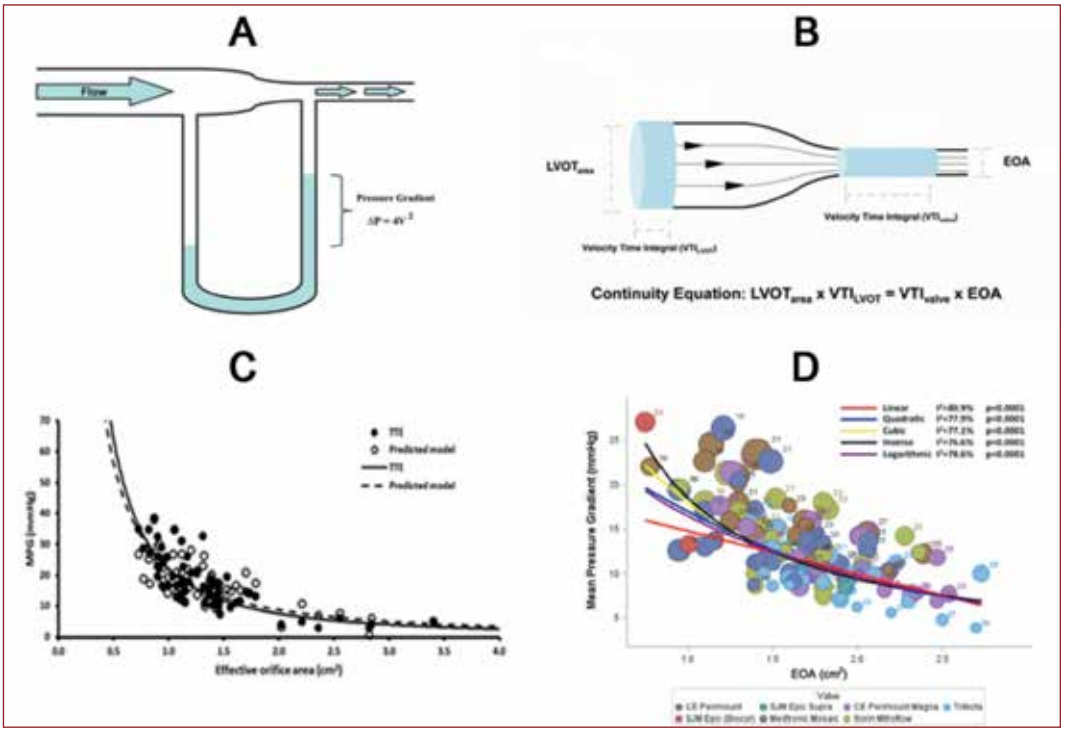


*Figure 1: Schematic illustration of the determination of pressure gradients (ΔP) using the Bernoulli principle (A), determination of the effective orifice area (EOA) by the continuity equation (B), as well as the relationship of ΔP to EOA in patients with aortic stenosis 23 (C) and in patients after surgical aortic valve replacement with biological prostheses 4 (D).*

EOA and pressure gradients have become standards for decision-making in the treatment of aortic valve stenosis and are also used for determining haemodynamic outcome after aortic valve replacement (D). Currently, an effective orifice area below 1 $cm^2$ and a peak pressure gradient above 50 mmHg in conjunction with clinical symptoms are considered an indication for aortic valve replacement[2].

Many years ago, it was suggested to relate effective orifice areas to body surface area (indexed EOA, EOAi) in order to normalise the functional opening of the valve to the patient's physical dimension[3]. This suggestion was based on the rationale that a mouse requires smaller anatomic dimensions than an elephant (personal communication, Eugene Braunwald 2014). While the rationale is convincing, the current obesity epidemic may offset the validity of this relationship. In addition, relating the effective orifice area (which is already a function of a patient specific anatomic dimension, i.e. the left ventricular outflow tract (LVOT) area), to the patient's body surface area, means relating flow velocities to two different patient-specific anatomic parameters at the same time. The precision of this result may be questioned[4].

Postoperatively, the same diagnostic tools are used to assess prosthetic valve performance. With the implantation of a prosthetic valve, usually some residual gradient remains. Since the advent of TAVI, there has been an increased need to standardise the assessment of haemodynamic performance of prosthetic heart valves and several working groups and professional societies have published recommendations[2,5-8]. They all contain the concept that a prosthetic valve may be too small to accommodate physiological flow conditions after valve replacement. This condition has been termed prosthesis patient mismatch (PPM)[9] and is discussed in detail below.

## Definition of PPM and difficulties in its individual assessment

After the initial definition of PPM as a condition where a prosthetic valve after replacement is smaller than the native valve[9], Pibarot and colleagues introduced a quantitative scheme, categorising PPM into three groups based on the indexed effective orifice area[5]. A severe PPM group where the EOAi was equal to or below 0.65 $cm^2/m^2$, a moderate PPM group where EOAi was above 0.65 $cm^2/m^2$ and equal to or below 0.85 $cm^2/m^2$ and a non-relevant PPM group where EOAi was above 0.85 $cm^2/m^2$. Over the following years, a plethora of investigations assessed the impact of PPM on clinical outcomes including mortality using this or slightly modified quantitative schemes.

It is clear from Figure 1B, that EOA and similarly EOAi are influenced by the patient's anatomic features (i.e. the individual size of the LVOT and, for the index calculation, the actual body surface area). Thus, determining a patient's EOA requires the individual assessment of both flow velocities and LVOT area for the desired situation (e.g., haemodynamic assessment after aortic valve replacement). In other words, the EOA is patient-specific. Figure 2 schematically illustrates this principle. If the same valve (with the same maximal opening area of the cusps, red circle) is implanted into two different anatomic conditions, the individually determined EOA (green circle) differs, being smaller in the patient with larger anatomic dimensions (A). From a functional viewpoint, one will conclude that the haemodynamic performance of the valve is worse in the patient with the larger anatomic dimension. That is correct. However, it cannot be concluded that the valve itself is haemodynamically inferior in the larger patient (because the valves are the same and haemodynamic performance of the identical prosthesis in the other case is optimal). Thus, it is clear that haemodynamic performance needs to be assessed individually in every

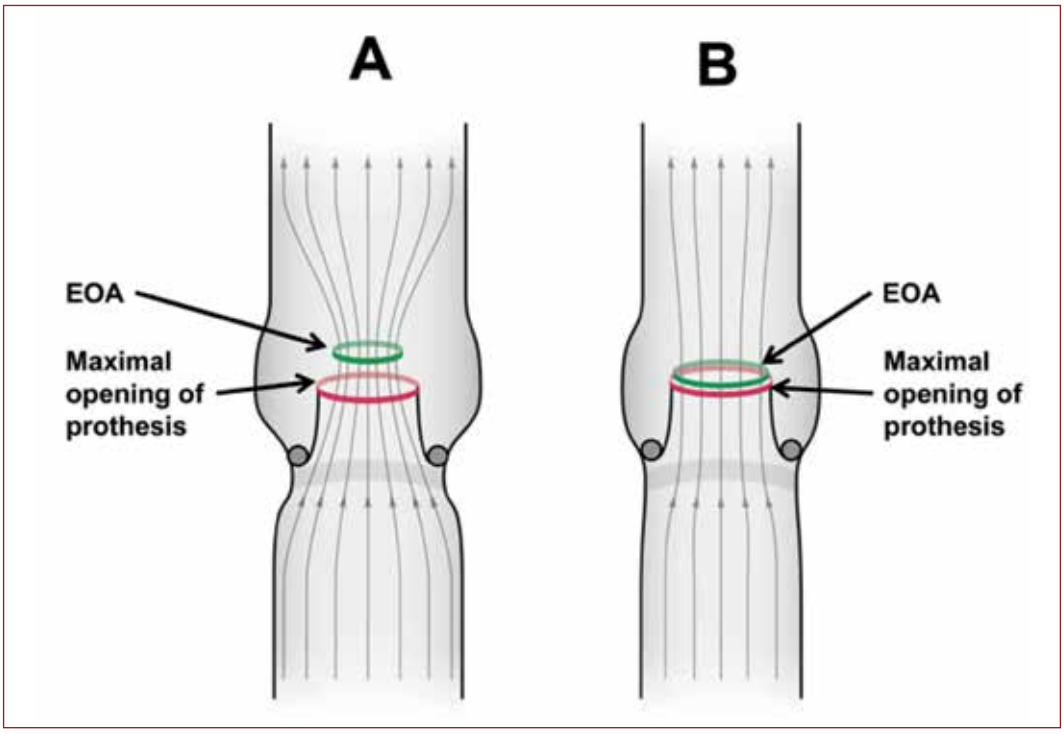


*Figure 2: Schematic illustration of the effect of implanting the same biological prosthesis (with the same maximal valve opening area, red circle) in two anatomically different patients on the effective orifice area (EOA, green circle). Note that the EOA differs while the maximal opening of the prostheses are the same. Thus, EOA is patient-specific.*

single patient. However, the majority of publications addressing the impact of PPM on mortality and other outcome parameters used a projected EOA, where the EOAs were not individually measured, but the EOAs published for a given valve type and size from another patient population was used to relate to clinical outcomes of the own patient population. Thus, the patient-specific EOA from one specific investigation was transferred to become a prosthesis-specific value, introducing a possibly significant systematic error. This error is visible in Figure 2, if you imagine two anatomic dimensions may relate to two patients with the same body surface area (i.e., a tall and slim person versus a short and obese person). It is important to realise that all flow-charts (often with red-yellow-green traffic light markings) showing EOA values associated with a given valve size and type commit this error and are not correct.

These considerations may explain the great heterogeneity and outcomes when PPM is related to mortality in the literature. Table 1 illustrates that just as many publications demonstrate a relationship of PPM (assessed using EOA) with mortality as do not. The vast majority of all these publications have used projected EOAs[4].

*Table 1: Studies assessing the relevance of PPM on mortality using measured or projected EOA*

| PPM relevant | EOA | PPM not relevant | EOA |
|---|---|---|---|
| Rao et al 2000 | *Projected* | Pibarot et al 1996 | *Projected* |
| Pibarot et al 2001 | Measured | Moon et al 2006 * | *Projected* |
| Blais et al 2003 | Measured | Flameng et al 2006 | Measured |
| Ennker et al 2005 | *Projected* | Monin et al 2007 | *Projected* |
| Walther et al 2006 | *Projected* | Ryomoto et al 2008 | *Projected* |
| Tasca et al 2006 | *Projected* | Florath et al 2008 | *Projected* |
| Moon et al 2006* | *Projected* | Mascherbauer et al 2008 | *Projected* |
| Ruel et al 2006 | *Projected* | Moon et al 2009* | *Projected* |
| Kulik et al 2006 | *Projected* | Mohty et al 2009† | *Projected* |
| Yap et al 2007 | *Projected* | Nozohoor et al 2008 | Measured |
| Kato et al 2007 | *Projected* | Vicchio et al 2008 | Measured |
| Fuster et al 2007 | *Projected* | Kato et al 2008 | *Projected* |
| Kohsaka et al 2008 | *Projected* | Urso et al 2009 | *Projected* |
| Moon et al 2009* | *Projected* | Price et al 2009 | *Projected* |
| Mohty et al 2009† | *Projected* | Jamieson et al 2010 | *Projected* |
| Bleiziffer et al 2010 | Measured | Cotoni et al 2011 | *Projected* |
| Head et al 2012‡ | Measured | Jeong et al 2013 | Measured |
| Hong et al 2012 | *Projected* | Concistrè et al 2013 | *Projected* |
| Hernández-Vaquero et al 2012 | *Projected* | Kitamura et al 2013 | *Projected* |
| Hong et al 2013 | Measured | Koene et al 2013 | *Projected* |
| Urso et al 2014 | *Projected* | Dayan et al 2015# | *Projected* |
| Pibarot et al 2014 | Measured | Sportelli et al 2016 | Measured |
| Iosifescu et al 2014 | *Projected* | Joshi et al 2016 | *Projected* |
| Shahzeb et al 2014 | *Projected* | | |
| Une et al 2015 | *Projected* | | |

** Authors reported impact of PPM was age dependent.*
*† Authors reported impact of PPM only on decreased LV-function*
*‡ Largest systematic review and meta-analysis*
*# PPM was not found to be associated with adverse outcome, after adjusting for confounders.*

## Relevance of PPM and a simple way to assess it

The above illustrations are likely to lead to a great amount of confusion. It is important to stress that the criticism of our current assessment of effective orifice areas and their indices for aortic valve prostheses does not question the concept of PPM. It questions our way of assessing it. The indexation and projection of EOA-values introduces a significant degree of "fuzziness" to the picture of PPM in our minds.

This statement is nicely illustrated by examining the results published by Ruel et al. in 2004. The authors assessed long-term outcomes in patients after aortic valve replacement. They identified prosthesis size as an independent predictor of heart failure but not mortality in a follow-up of up to 17 years. EOAi did not qualify as independent predictor of all-cause death, but did predict for NYHA class heart failure symptoms or congestive heart failure (CHF) related symptoms[10]. The most interesting aspect from our perspective is illustrated by reassembling their data as we did it in Table 2. EOA or typical PPM assessment did not predict death. In addition, EOA's ability to predict heart failure (and that of classic PPM assessment) in the statistical analysis was not, or only barely, significant with P values above or just under 0.05. In contrast, the "simple" trans-prosthetic gradients also qualified as independent predictors of heart failure, but with a much higher degrees of significance (P value <0.001). The authors did not present the relation of pressure gradient to mortality. So it remains speculation, whether peak or mean trans-prosthetic gradient may have had an impact on mortality as well. However, the relationship of pressure gradients and heart failure appears much clearer than with EOAs.

*Table 2: Predictors of outcomes after aortic valve replacement – data extracted from a publication by Ruel et al. 10 on 1563 patients.*

| Variable | Adjusted Hazard Ratio | 95% CI | p-Value |
|---|---|---|---|
| **Predictors of all cause death** | | | |
| In vivo EOA | 0.41 | 0.15, 1.14 | 0.09 |
| PPM defined as ≤0.75 cm² | 1.27 | 0.77, 2.07 | 0.34 |
| PPM defined as ≤0.85 cm² | 1.34 | 0.88, 2.02 | 0.17 |
| **Predictors of NYHA III or IV symptoms or CHF-related death** | | | |
| In vivo EOA | 0.41 | 0.17, 0.97 | 0.042 |
| PPM defined as ≤0.75 cm² | 1.64 | 1.01, 2.56 | 0.047 |
| PPM defined as ≤0.85 cm² | 1.20 | 0.79, 1.82 | 0.40 |
| Peak transprothesis Gradient | 1.03 | 1.02, 1.05 | <0.001 |
| Mean transprothesis Gradient | 1.06 | 1.03, 1.09 | <0.001 |

*CHF: Congestive Heart Failure; EOA: Effective Orifice Area; NYHA: New York Heart Association; PPM: Prothesis-Patient-Mismatch*

We assembled all measured EOA values and measured mean pressure gradients from studies assessing haemodynamic performance after aortic valve replacement. Figure 1D shows this relationship from our previous publication[4]. Since the vast majority of EOA values in this post AVR patient population were above 1 cm², this part of the expected logarithmic relationship (see figure 1C for patients with aortic stenosis before surgery) may also be seen as pseudo-linear. The coloured lines illustrate that any type of mathematical function obtains a highly significant correlation coefficient. As a result of this close relationship, the additive value of EOA on top of the assessment of pressure gradients alone may be questioned for this patient population. The image also underscores the above made criticism on the indexation of EOA. We have all accepted to relate the effective orifice area to body surface area for reasons of normalisation. Given the pseudo-linear relationship of EOA and mean pressure gradients after aortic valve replacement, would we

be willing to relate pressure gradients to body surface area as well? Thus, it appears from the available data in the literature that the assessment of haemodynamic performance of bioprosthetic valves is currently performed with the greatest precision using Bernoulli-equation-derived pressure gradients (with all its caveats in their determination)[1]. It is also evident, that leaving high remaining pressure gradients is likely to affect outcome, by causing heart failure and possibly also increased mortality (i.e., the concept of PPM appears valid). However, the impact of "simple" pressure gradients on mortality has been much less intensively investigated when compared to the impact of EOAi[4,11].

## What factor does valve type play and how do we compare different prostheses

If we accept the fact that inferior haemodynamics following an aortic valve replacement (however it is assessed) may negatively affect outcome, the technical question arises of how we end up with a situation where the opening of the new valve is near the physiologic opening of the native valve. This thinking has brought Rahimtoola to suggest the original concept of PPM[9] and has resulted in a plethora of valve designs and replacement strategies[11-14], many of which are part of our current armamentarium for surgical and transcatheter AVR.

We distinguish mechanical from biological valves. They differ in their haemodynamic and durability characteristics, which has been reviewed by us before[15]. Bioprostheses are further categorised into stented, stentless or transcatheter prostheses. The two important parameters for all these prostheses are the actual maximal opening area of the prostheses (that is important for the patient, because his or her blood has to flow through this opening) and the outer diameter of the prosthesis (this is important to the surgeon/interventionalist, because this has to be fitted into the patient's aortic root)[12]. Surprisingly, these two parameters are not part of our decision-making. We currently still assess the EOA in vivo and use projection of EOAs, the practice of which we criticised above[4]. The result of this projection may be the erroneous assumption that the echocardiographically determined EOA is the maximal opening of the new prosthesis. However, as illustrated in Figure 2, the EOA is a result of the interaction of the maximal geometric opening of a prosthesis (green circle) with its anatomic surrounding. Thus, the EOA is a virtual area that reflects the haemodynamic end result after AVR. This conclusion also supports the above mentioned suggestion that pressure gradients equally reflect this outcome and may even be superior in assessing its relevance.

Assessing the valve from this perspective, it is striking to note that information on a maximal opening area for a given prosthesis is practically missing for all valves[12]. In addition, outer diameters are listed in the small print on the valves outer packages and by no means correlate with the actual size of the valve[11,16]. Finally, the size nomenclature of the various valves from different companies also significantly differ, so that mathematically correct comparisons of one valve type to the other are practically impossible (reviewed in detail by us[11] and others[16,17]).

In general, stented tissue valves tend to lose some of the possible opening area determined by the inner area of the stent they are mounted on, so that for a given outer diameter of a prosthesis, the maximal opening areas are smaller than, for instance, that of a modern double leaflet mechanical valve (where the maximal opening area is close to the inner stent area for the almost perpendicular orientation of the two mechanical leaflets during systole). That is the reason for mechanical valves being haemodynamically superior to tissue valves. It is a matter of speculation, whether this haemodynamic superiority is

related to the repeatedly observed survival advantage of mechanical valves[18]. However, since mechanical valves open their leaflets into the outflow area, it is important not to oversize these prostheses to avoid mechanical valve dysfunction. However, bioprostheses open their cusps above the sewing ring, thereby allowing for unrestricted supra-annular placement. Thus, biological prostheses with larger outer diameter may be placed into the aortic root because valve function is not affected by the native annulus or LVOT as in mechanical valves. This principle is illustrated in Figure 3. It shows that the same patient that receives for instance a size 23 mechanical valve may receive a size 25 or 27 biological prosthesis due to different sizing strategies. The figure also illustrates the problem of comparing haemodynamic outcomes based on comparisons of valve sizes, because the outer diameter of the same valve sizes are likely to differ as are the outer diameter of prostheses with different size labels. These differences and the use of size ranges in the transcatheter valve arena (with more or less opening of the valve once implanted) make conventional comparisons of valve types by their labelled size practically obsolete. Finally, new designs for biological valves have generated biological prostheses, where the cusp opening is so large that the maximal opening is getting to close to that of mechanical valves (take for instance the Trifecta or the Mitroflow valves where the biological tissue is wrapped around the stent from the outside). Thus, knowing what to haemodynamically expect from a valve-prosthesis ideally requires the knowledge of the maximal opening area in relation to its outer diameter. The latter size is important for its implantation. We have reviewed this principle previously[12].

Figures. 3A and B show two identical aortic outflow and root anatomies. In Fig. 3A, a size 23 mechanical valve was placed. This valve may have an outer diameter (OD) of 28mm. Figure 3B shows a graphical exaggeration of a supra-annular placement of a biological

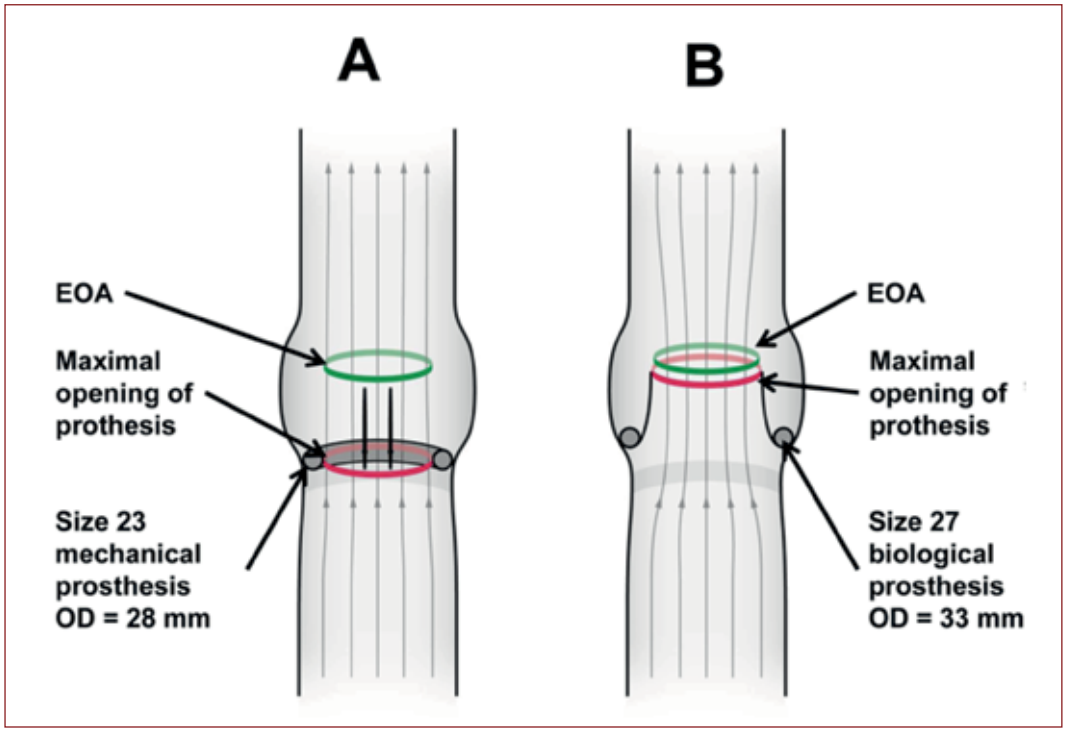


*Figure 3: Schematic illustration of the futility to compare haemodynamic results based on valve size labels.*

prosthesis (optimised by replica sizing). Since this placement allows the selection of a larger outer diameter, the size label for the same patient anatomy may become 27 and the outer diameter may possibly be 5 mm larger. Thus, haemodynamic comparisons by size label (i.e. 23 mechanical vs. 23 biological) may not be appropriate any more.

## Which factor does sizing play for selecting the best prosthesis?

As alluded to above, mechanical valves require space below the sewing ring for proper opening of the mechanical leaflets. Subvalvular tissue may obstruct leaflet motion and may cause valve failure. In order to properly size these valves, the companies provide cylindric sizers to assess the dimension of the outflow tract and annulus. Since biological prostheses do not open into the outflow tract, they may be placed above the annulus (supra-annular placement) and the actual dimension of the outflow tract is of lesser relevance. With the aortic root expanding (to various degrees) above the annulus, supra-annular implantation allows the implantation of a larger outer diameter. This is one reason why the outer diameter of, for instance, a size 23 valve is at times substantially larger than 23mm (see 11 for details). In other words, the manufacturers have accounted for this effect by making their valves larger than the actually measured annulus with their sizers.

Since the anatomic dimension of the aortic root is subject to great variability among patients, we reasoned that individualising supra-annular sizing by assessing the final fit of a given valve size rather than adhering to a manufacturer suggested relationship between annulus and root dimension (i.e. outer diameter of the valve), we may be able to place a larger valve than suggested by the manufacturer[19]. Placing a larger valve, means placing a larger maximal opening area for the patient, which should result in lower pressure gradients. Figure 4 shows the principle of our strategy and the resulting haemodynamic effect. We were able to implant at least 1 larger size valve in more than two thirds of all patients just by assessing the biggest prosthesis fitting into the aortic root using a replica sizer (i.e. a dummy of the implanted valve)[19]. If replica sizing is not appropriate or feasible, there are additional techniques to enlarge the root as described by others[20-22].

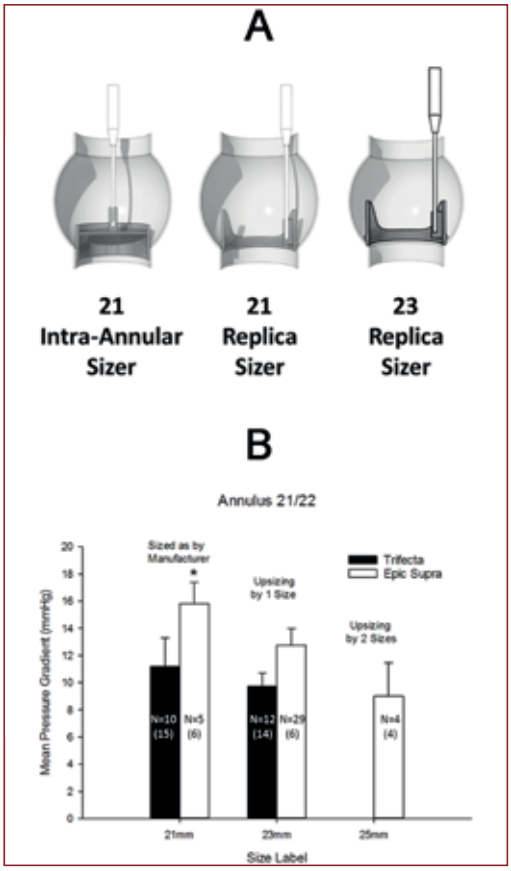


*Figure 4: Principle of Replica sizing (A) and the haemodynamic result of selecting larger than recommended prostheses by replica sizing (upsizing, B) as published by Gonzales et al. 2017[19]. Figure 3B illustrates that placing a 23 or 25 labelled valve in patients with annuli of 21 (as assessed with the intra-annular cylinder) may result in the reduction of postoperative pressure gradients.*

## Putting it all together

The above illustrations and description allow formulation of the following guide and perspective in order to achieve optimal haemodynamics with aortic valve replacement.

1. **Haemodynamics are currently best assessed with pressure gradients.**

   If EOAs are assessed, they must be determined individually. Relating the result to body surface area may actually obscure our ability to predict outcomes and prognosis.

2. **The bigger the prosthesis (opening area) the better.**

   The key dimension of an implanted prosthetic valve is the maximal opening area of that valve. However, this dimension is unknown for most valves. The valve that has a greater maximal opening area at the same outer diameter is haemodynamically superior.

3. **Mechanical valves have the best opening areas but biological prostheses can be "upsized"**

At the same outer diameter, mechanical valves have the largest opening areas. However, by placing biological prostheses supra-annularly (optimised by replica sizing) may allow to compensate for the difference by placing a prosthesis with significantly larger outer diameter.

## Conclusion and Perspective

For aortic valve replacement, it is important to implant the biggest valve opening area possible in every patient, which is generally not reflected by the label size of the implanted prosthesis. The haemodynamic result is currently measured best using the Bernoulli-equation derived pressure gradients. Residual pressure gradients appear to be very much relevant to patients' symptoms and prognosis. Thus, PPM is real, but we are currently using suboptimal tools to assess it. Using individualised replica sizing for each patient may result in the best possible haemodynamic outcome.

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Chapter 5

# Does the Evolving Use of Oral Anticoagulants Help or Hinder Aortic Valve Selection?

*Marc R. Moon and Rita L. Gardner*

*"Semper ad meliora"*

## Introduction

There have been numerous anticoagulation regimens described for the treatment of patients with prosthetic valves including:

- Long-term warfarin, with or without low-dose aspirin
- Warfarin for 6-12 weeks followed by either no treatment or aspirin for 1-2 years or long-term
- Full dose aspirin for 6-12 weeks followed by low-dose aspirin
- Subcutaneous heparin for 1-4 weeks
- Ticlopidine (IIb/IIIa inhibitor) for 3 months
- Dual anti-platelet therapy (DAPT) or Novel Oral anticoagulants (NOAC) for 3 months or long-term

It is generally believed that at 3 months, endothelialization of the sewing ring, sutures and knots, and leaflets of biologic valves has occurred. As a consequence, anticoagulation needs may diminish beyond this time period, but it has been very difficult to obtain consensus. Specific anticoagulation recommendations depend on the type of valve implanted, timing after surgery, and associated patient risk factors. The current report will address how evolving options for oral anticoagulation impact prosthesis selection and postoperative medical therapy following valve replacement.

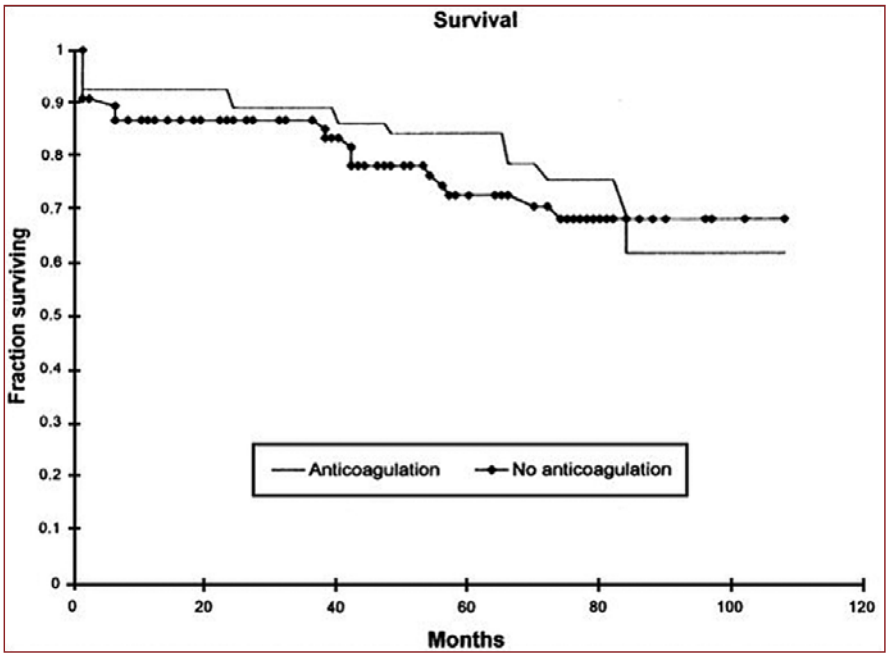
## Mechanism of action for common anticoagulants

The coagulation cascade is initiated with either the contact activation or tissue factor pathway, both of which converge to the common pathway. The contact activation or intrinsic pathway is initiated through damaged surfaces stimulating activation factors XII, XI, IX, and ultimately converting X to Xa. The tissue factor or extrinsic pathway is activated through trauma converting factor VII to VIIa and X to Xa. The common pathway involves prothrombin (factor II) conversion to thrombin (factor IIa), factor V activation, conversion of fibrinogen (factor I) to fibrin (factor Ia), which ultimately becomes a cross-linked fibrin clot following activation of factor XIII. Various anticoagulants inhibit various components of the coagulation cascade. Warfarin inhibits vitamin K-dependent factors (II, VII, IX, X), heparin accelerates antithrombin III activity, and NOACs inhibit thrombin or activated factor X. So, they all have a different mechanism of action which may or may not be more effective to prevent clot formation with prosthetic valves.

### Anticoagulation with warfarin versus aspirin for biologic prosthetic valves

So, why warfarin in the first place with biologic valves? It was Ionescu and coauthors who published a paper back in 1982 suggesting that if you gave oral anticoagulation following biologic valve replacement for the first three postoperative months, you could decrease the risk of stroke from 5.9% (4 of 68 patients without oral anticoagulation) down to 0% (0 of 182 patients with oral anticoagulation)[1]. Of note, however, was that 75% of the 366 patients in their series were in atrial fibrillation, none of whom received anticoagulation after six weeks, and we now know that patients with atrial fibrillation are at an increased risk of stroke without anticoagulation. Despite that limitation, this study changed the way we practice with biologic valves. In 2001, there was an interesting opinion piece where they proclaimed that, "In some important investigations, less than half of the international normalized ratios (INR) were in the target range" and concluded that, "These limitations weaken the basis on which therapeutic recommendations can be made"[2]. I can't disagree with this conclusion more because patients in the real world have widely variable INR levels long-term; that is simply the reality of the situation. If we consider only patients who have a tight INR range, then we are not looking at the majority of the population.

The paper that changed the way many of us treat biologic valves today came from the Yale group and was first presented at the American Heart Association meeting in the late 1990's[3]. Elefteriades group reviewed 195 patients who underwent biologic aortic valve replacement (AVR). This was a retrospective study, not randomized, but the findings were quite interesting. They compared 109 patients who received intravenous heparin then warfarin for 3 months postoperatively (prothrombin times of 20 to 25 seconds, approximately two-times normal) to 76 patients who received no anticoagulation for 3 months. They gave aspirin only to patients who had associated coronary artery disease. The groups were similar in regards to patient demographics, comorbidities, types of concomitant surgery and surgical outcomes. Perioperative (30-day) mortality was similar between groups (4.5% and 5.2% in the anticoagulation versus non-anticoagulation groups, respectively) as was perioperative atrial fibrillation (19.2% and 22.3%), postoperative bleeding (9.2% and 9.2%), and mean hospital stay (11.6 and 11.9 days). Figure 1 from their paper demonstrates that late survival was similar in both groups and there was no difference in the incidence of postoperative strokes. They concluded that early anticoagulation did not confer an advantage in prevention of early strokes or long-term patient survival and



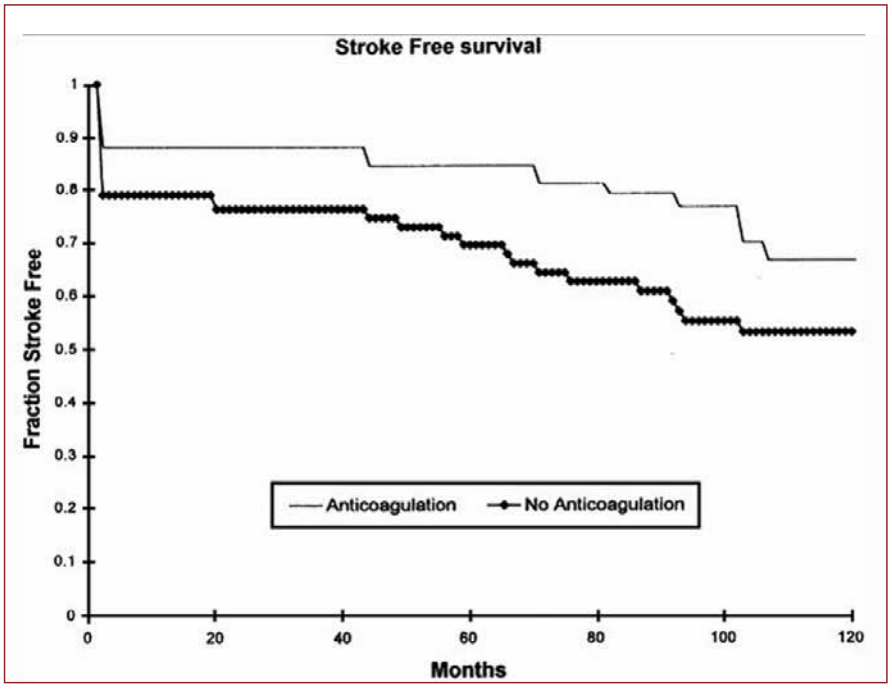




*Figure 1: Long-term survival (A) and Freedom from death and cerebral ischemic events (B) for 109 patients undergoing postoperative anti-coagulation for first 3 months with heparin and warfarin to achieve prothrombin time of 20 to 25 seconds and for 76 patients receiving no postoperative anticoagulation. Reproduced from Circulation Moinuddeen K1, Quin J, Shaw R, et al. 98:II95-8, 1998 by permission of Wolters Kluwer Health, Inc[3].*

valve function. Their statement that "routine early anticoagulation after biologic AVR is unnecessary" was initially controversial but is now accepted by most practitioners. It was bold conclusion, but it was supported by a later prospective study from the University of Parma including 249 patients after biologic AVR[4], but they excluded all patients who had postoperative atrial fibrillation. This study compared 141 patients who received warfarin for 3 months postoperatively (INR 2.0 – 3.0) to 108 patients who received aspirin for 3 months postoperatively. The groups were similar in regards to patient demographics and concomitant surgery. In this series, perioperative mortality was again similar between groups (0.7% and 1.9% in the warfarin versus aspirin groups, respectively) ($p = 0.58$), as was the incidence of stroke at 24 hours to 3 months (2.1% vs 4.6%, $p = 0.30$), stroke beyond 3 months (0.7% vs. 2.8%, $p = 0.32$), and major bleeding (2.1% vs. 3.7%, $p = 0.47$). They concluded, "There is no evidence to support that warfarin is more effective than aspirin," even when correcting for age and EuroSCORE.

## What about dual antiplatelet therapy (DAPT) for prosthetic valves?

Dual antiplatelet therapy has become quite popular for anticoagulation in that serial monitoring of blood levels is generally not necessary. If we look at the transcatheter aortic valve replacement (TAVR) population, a new finding has been identified; hypoattenuated leaflet thickening (HALT) which is subclinical leaflet thrombosis[5]. The incidence of symptomatic thrombosis is rare (1-2%), but the prevalence of HALT, which may be associated with early valve degeneration, can occur in 10-15% of patients. HALT acts as a surrogate for increased transvalvular gradients, decreased valve durability, and ischemic events. Investigation has focused on how we can prevent HALT and other early changes that can occur that may lead to early valve failure. If you examine the source of early cerebral vascular events after surgery, acutely within 24 hours are embolization, hypotension and other types of perioperative insults. Subacute from 24 hours to 3 months could be the consequence of subclinical leaflet thrombosis which we are starting to see now and appreciate more and more, and late (> 3 months) due to atrial fibrillation and other standard causes of ischemic events. Observational studies suggest that oral anticoagulants are associated with a more profound decline in HALT than DAPT. Cavender and Kim concluded, "Given the decrease in HALT with oral anticoagulants and high rates of subclinical AF following both surgical AVR and TAVR, the utility of oral anticoagulants appears promising." There are currently more than 10 randomized studies following more than 6,000 pts, so we should soon have more answers to these types of questions in the next 4 or 5 years.

Since there are so many differences of opinion and lack of Level A evidence, Class I recommendations are not available in societal guidelines, and the guidelines from varying societies are not consistent[6]. The American College of Cardiology / American Heart Association guidelines from 2017 suggest aspirin and say that vitamin K antagonists may be beneficial[7]. The European Society of Cardiology / European Association for Cardio-Thoracic Surgery guidelines from 2018 suggest that aspirin alone is reasonable, essentially suggesting that warfarin is not necessary[8]. The American College of Chest Physicians guidelines from 2012 also suggested that aspirin is satisfactory as long as the patient does not have another indication for vitamin K antagonists[9]. So, all three have varying recommendation levels and strengths to their suggestions.

## Mechanical valves and anticoagulation

Obviously, we cannot have a patient with a mechanical valve, at least historically, that is not anticoagulated since they are prone to thrombosis and embolization. If we look at 2,357 patients with mechanical aortic or mitral valves from the Italian Cooperative study just reported recently, they had a mean follow-up of 9.7 years, totally 24,081 patient-years, with data collected essentially from warfarin clinics[10]. What they examined was the Time in Therapeutic Range (TTR), with a goal TTR of 65-70%, meaning the INR was in the optimal range 65 to 70% of the time (remembering of course that almost no patients have a perfect INR history). When they performed multivariate analysis to see what factors were associated with thromboembolism and bleeding, it was atrial fibrillation, a history of previous thromboembolism, and a mitral more so than aortic prosthesis. For the overall group, the 25th percentile for TTR was ≤ 47%, so far less than ideal, but neither univariate or multivariate analysis identified a low TTR as predictive of thromboembolism. A low TTR was however, associated with an increased incidence of bleeding, with supertherapeutic INR levels. The overall thromboembolism rate was 0.67/100 pt-yrs and bleeding rate was 1.0/100 pt-yrs. The authors concluded that there was a low rate of bleeding and thromboembolism with mechanical valves despite suboptimal anticoagulation control in many patients. The incidence of complications was low despite TTR less than ideal.

## Can we get by with anything other than warfarin with mechanical valves?

If we look at the NOACs, we see that they inhibit thrombin or activated factor X (Xa). Potential advantages of NOACs over warfarin include: 1.) Predictable anticoagulant effects (predictable dose response); 2.) Fixed dosing without monitoring; 3.) No dietary impact (in contrast to vitamin K with warfarin); 4.) diminished drug interactions; and 4.) rapid clinical onset of action. NOACs were first compared to warfarin in patients with atrial fibrillation. A meta-analysis published in Lancet summarized four pivotal phase 3 trials comparing four different NOACs: Re-LY in 2009, ROCKET AF in 2011, ARISTOTLE in 2011, and ENGAGE AF-TIMI 48 in 2013[11]. 42,411 patients receiving NOACs were compared to 29,272 patients receiving warfarin (they were not all 1:1 randomized). Forest plot analysis favored NOACs over warfarin for stroke or systemic embolic event, all-cause mortality, and hemorrhagic stroke or intracranial hemorrhage. Forest plot analysis favored warfarin over NOACs in only one secondary efficacy and safety outcome: gastrointestinal bleeding. The findings were consistent over a wide range of patients that had atrial fibrillation, whether associated with valvular disease or not.

NOACs seem to be fine for patients with atrial fibrillation, so how about in patients with a mechanical valve? Animal studies demonstrated efficacy of NOACs in preventing thrombosis. The Mayo Clinic used a heterotopic, large animal, AVR model and examined thrombin deposition after 30 days[12]. They compared no anticoagulation to enoxaparin (low-molecular weight heparin) and Dabigatran. With no anticoagulation, thrombin deposition was quite extensive at 638 ± 895 mg, improved with enoxaparin to 121 ± 128 mg, but with Dabigatran it was almost non-existent at 19 ± 31 mg ($p = 0.01$). Based on the results of this animal study, the RE-ALIGN study was initiated which was a Randomized, Phase II Study to Evaluate Oral Dabigatran in Patients after Heart Valve Replacement, specifically mechanical valves[13].

In the RE-ALIGN study, there were 252 patients from 32 centers in 10 countries randomized 2:1 to dabigatran to warfarin following mechanical valve replacement[13]. There were 172 (68%) mechanical AVR, 71 (28%) mechanical mitral valve replacement (MVR), and 9 (4%) combined AVR and MVR. There were two study populations: Population A who underwent surgery at the time of enrolment, and Population B who had undergone surgery 3 months or more prior to enrolment. This was a low-risk patient population with a mean Society for Thoracic Surgeons predicted risk of 1.93%. The plan was to follow these patients for 84 months, but the study was terminated after only 12 months because of very poor outcomes in the NOAC group. The study was terminated because there was a substantial increase in death, stroke, systemic embolization, and myocardial infarction in the group receiving dabigatran as well as a higher incidence of valve thrombosis and a much higher incidence of bleeding. The mean duration of treatment was about 5 months, and the study was discontinued because the NOACs were proven not to be safe. The study concluded: 1.) "Dabigatran is not appropriate as an alternative to warfarin after implantation of a prosthetic heart valve," and 2.) "The results may also be relevant to studies of other new oral anticoagulants in pts with mechanical heart valves," which was the kiss of death for all the other NOACs. That warning is out there, probably preventing us from ever trying a study of any other NOAC in patients with mechanical heart valves again.

## Why were NOACs not effective with mechanical valves?

Going back to the coagulation cascade, warfarin inhibits both the contact pathway (factor IX) and the tissue factor-induced pathway (factor VII) as well as the common pathway (factor X and thrombin synthesis). Warfarin affects all aspects of the coagulation cascade, whereas NOACs inhibit thrombin exclusively, which was potentially overwhelmed by the intense contact activation that was occurring in the patients who had a mechanical valve. So there is a theoretical explanation why NOACs may not have worked with mechanical valves. With atrial fibrillation, we know that thrombi form in the left atrial appendage most often due to low-flow, low shear state, triggered by stasis and endothelial dysfunction (tissue factor pathway). With mechanical valves, coagulation activation and thrombin generation are due to release of tissue factor secondary to damaged tissue acutely with exposure to artificial surfaces (contact pathway) such as the sewing ring of the valve.


*Figure 2: Three of the most common mechanical prosthetic valves are the St. Jude bileaflet valve, Medtronic-Hall tilting disc valve, and the On-X bileaflet valve.*

## Options for less aggressive anticoagulation with mechanical valves in the aortic position.

The three most common mechanical valves are the St. Jude bileaflet valve, Medtronic-Hall tilting disc valve, and the On-X bileaflet valve (Figure 2). They all have technical differences including in how they are implanted, but the On-X valve supposedly has a surface that is less thrombogenic. John Puskas from Mount Sinai in New York City led the PROACT trial, which was the Prospective, Randomized On-X Anticoagulation Trial testing lower dose or non-warfarin containing anticoagulation regimens following mechanical On-X aortic valve implantation[14]. It included 576 patients in 41 centers with two arms:
1) Low-risk arm: standard warfarin versus DAPT (after 3 months), and
2) High-risk arm: standard versus low-dose warfarin.

**PROACT – Low-Risk Arm:** The patients in the low-risk had no risk factors for thromboembolism: ejection fraction > 0.30, left atrial diameter ≤ 50 mm, and absence of peripheral vascular disease, history of stroke, hypercoagulable state, hormone replacement therapy and chronic atrial fibrillation. For the first 3 postoperative months, warfarin was given to maintain standard INR of 2.0-3.0 with low dose aspirin (81mg) to allow endothelialization of the sewing ring. After 3 months, patients were randomized to DAPT with clopidogrel and aspiring (n = 99 patients) or standard warfarin (INR 2.0-3.0) with aspirin (n = 102).

**PROACT – High-Risk Arm:** The high-risk arm included patients who had one or more of the risk factors for thromboembolism listed above. They were randomized to standard-dose warfarin (INR 2.0-3.0) with aspirin (n = 190) or low-dose warfarin (INR 1.5-2.0) with aspirin (n = 185). In most cases, INR home monitoring was performed twice per month.

## PROACT Trial – Results:

The low-risk arm, like the NOAC trial with mechanical valves, was discontinued at the mid-term analysis due to the increased incidence of cerebral thromboembolic events in the DAPT group. Again, we are trying a regimen without warfarin, and it just does not work. If we look at the event-free rate of thromboembolism, it is dramatically different between the DAPT group and those who were on warfarin (Figure 3). The hazard rate for the primary endpoint (composite of death, major and minor bleeding, thromboembolic events, and valve thrombosis) was 2.66 favoring standard warfarin (p = 0.003 versus DAPT). The conclusion is simple; we need to give patients with mechanical valves warfarin.

In the high-risk arm of the study, there were some very interesting findings. In regards to the primary endpoint, there was a substantially lower risk in the low-dose warfarin group. The hazard rate for the primary endpoint was 0.59 favoring low-dose warfarn (p = 0.002). If we look at the event-free rate of thromboembolism, the two groups were similar (Figure 4) but there was a decreased risk of bleeding in the low-dose group. The low-dose warfarin group had better outcomes than the standard warfarin group in regards to decreasing the bleed risk while not increasing the thromboembolism risk. Additionally, the INR crossover point where the risk of bleeding crosses the risk of thromboembolism occurred at 1.5-2.0 which supports the recommendation that you can use a diminished warfarin dosing target INR of 1.5-2.0 with a mechanical On-X aortic valve.

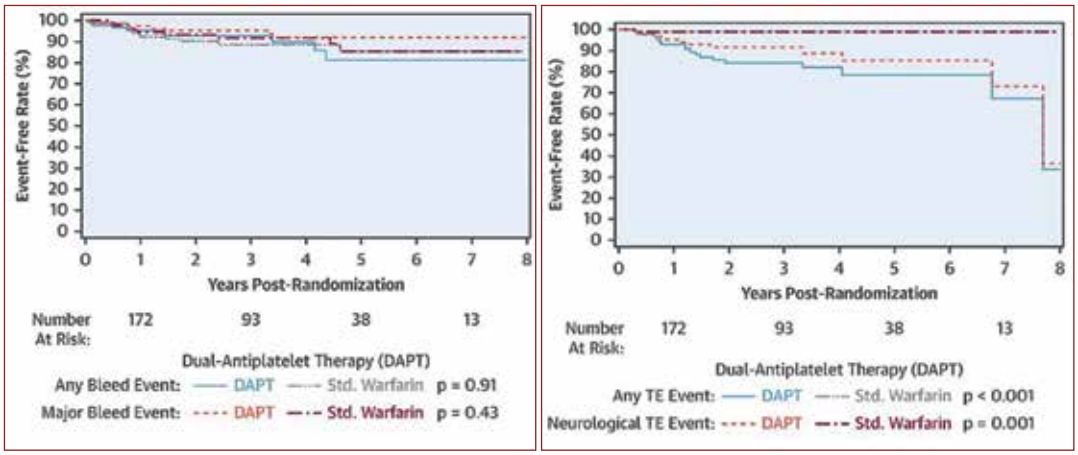



*Figure 3: Event-free rate of bleeding (A) and thromboembolic events (B) following On-X mechanical aortic valve replacement in the low-risk randomized study arm. Reproduced from J Am Coll Cardiol Puskas JD, Gerdisch M, Nichols D,, et al. 71;2717-26, 2018 with permission from Elsevier [14].*

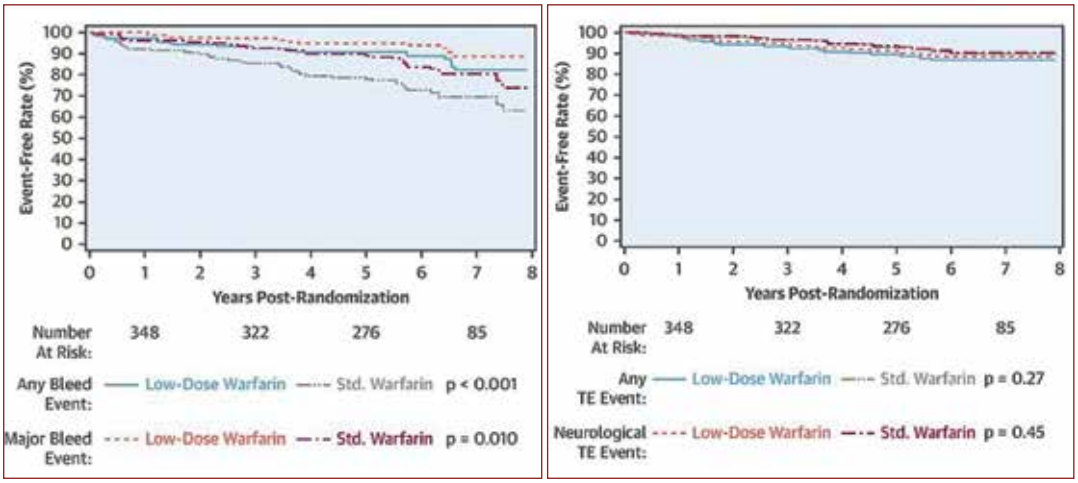



*Figure 4: Event-free rate of bleeding (A) and thromboembolic events (B) following On-X mechanical aortic valve replacement in the high-risk randomized study arm. Reproduced from J Am Coll Cardiol Puskas JD, Gerdisch M, Nichols D,, et al. 71;2717-26, 2018 with permission from Elsevier[14].*

## Valve replacement in dialysis-dependent patients

At Washington University, we recently reviewed our experience in dialysis-dependent patients to determine what role valve prosthesis selection played in postoperative outcomes[15]. This was a retrospective, single center study of 423 patients undergoing either biologic (n = 341, 81%) or mechanical (n = 82, 19%) valve replacement in the aortic or mitral position. In general, long-term survival was poor with either valve. Late 10-year survival was 13% overall, 20% with mechanical and only 5% with biologic prostheses (Figure 5). However,

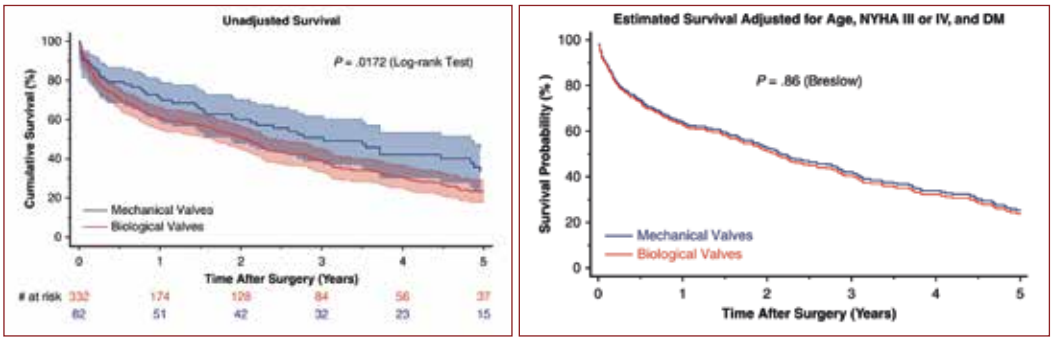



*Figure 5: Survival in dialysis-dependent patients undergoing valve replacement (A) unadjusted and (B) adjusted for age NYHA III or IV, and diabetes. Reproduced from J Thorac Cardiovasc Surg Manghelli JL, Carter DI, Khiabani AJ, et al. 2018 Dec 13 Epub ahead of print with permission from Elsevier[15].*

when you looked at what univariate predictors were associated with poor survival, they included age (hazard ratio 1.09, $p < 0.001$), New York Heart Association (NYHA) Class III or IV (1.36, $p = 0.048$), and diabetes (1.54, $p < 0.001$). When survival was adjusted for these three risk factors, thus matching patients receiving biologic and mechanical valves, there was no longer a difference in survival based on valve choice. Survival was not dependent on valve selection. The only patient group who had a predicted survival greater than 50% at five years was 30-40 year old patients in NYHA Class I-II without diabetes, which may be the one group of dialysis-dependent patients who might warrant a mechanical valve (Table 1).

*Table 1: Estimated 5-year survival based on the basis of 5 age groups (P < .001; HR, 1.09 [95% CI, 1.01-1.11]), diabetes (P < .001; HR, 1.54 [95% CI, 1.21-2.01]), and/or NYHA heart failure symptoms (P = .048; HR, 1.36 [95% CI,1.01-1.82]). Reproduced from J Thorac Cardiovasc Surg [Manghelli JL, Carter DI, Khiabani AJ, et al. 2018 Dec 13 Epub ahead of print] with permission from Elsevier[15].*

| Age group | No diabetes | | Diabetes | |
|---|---|---|---|---|
| | NYHA I-II | NYHA III-IV | NYHA I-II | NYHA III-IV |
| 30 Years | 61 | 50 | 46 | 35 |
| 40 Years | 54 | 43 | 38 | 27 |
| 50 Years | 46 | 34 | 30 | 19 |
| 60 Years | 35 | 27 | 22 | 13 |
| 70 Years | 31 | 19 | 16 | 8 |

*Data are presented as percentages. NYHA, New York Heart Association.*

## Conclusion

In summary, reasonable recommendations for anticoagulation depend on valve location and valve type implanted. 1.) Bioprosthetic AVR: If in sinus rhythm, aspirin only is sufficient. If at high risk for thromboembolism, warfarin for 3 months then aspirin. 2.) Bioprosthetic MVR: Warfarin for 3 months, but aspirin only is probably satisfactory if the patient is a high

bleeding risk. 3.) Mechanical AVR: If standard bileaflet or tilting disc prosthesis, warfarin to maintain INR 2.0-3.0. If On-X prosthesis, warfarin to maintain INR 1.5-2.0 with aspirin (not DAPT). 4.) Mechanical MVR: warfarin to maintain INR 2.5-3.5 with or without aspirin (not NOAC).

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SECTION 1 CARDIAC SURGERY

# Mitral Valve and Atrial Fibrillation Surgery

*"Vitam impendere vero"*

*Decimus Iunius Iuvenalis. 50 AD - ? second century.*

Chapter 6

# Less is More – Minimising Access to the Mitral Valve

*Daniel J. P. Burns, Per Wierup, A. Marc Gillinov*

*"In absentia lucis, tenebrae vincunt"*

## Introduction

Minimally invasive approaches have been developed in multiple surgical specialties, and have become routine or even standard of care in specialties such as urology and general surgery. As a specialty, cardiac surgery has traditionally lagged behind in the adoption of minimally invasive techniques, apart from certain highly specialised centers. Even today, the sternotomy is the default for most cardiac surgical procedures, providing excellent surgical exposure, and a high degree of control during the procedure. A central principle of minimally invasive surgery is that if, at minimum, the same results can be achieved with a less invasive approach, then that approach is, by definition, better. However, it must also be recognised that as invasiveness decreases, complexity increases, and control over the procedure is necessarily diminished. The balance between these factors is of crucial importance, particularly in cardiac surgery, where there are multiple team members interacting during the performance of the procedure.

The benefits of mitral valve repair in patients with degenerative disease are well established. In addition to superior survival, a complete mitral valve repair decreases risks of thromboembolism, endocarditis, anticoagulant related haemorrhage, and re-intervention relative to valve replacement[1–5]. Mitral valve repair is particularly amenable to a minimally invasive approach. Several approaches have been developed in the last 25 years, most of which continue to be used in some capacity today. The spectrum of minimally invasive mitral valve approaches includes partial sternotomy, right mini-thoracotomy, and robotic-assisted. Of these available approaches, robotic-assisted mitral valve repair is the approach favoured by the Cleveland Clinic for patients with isolated degenerative mitral valve disease. In this chapter, we will describe the development of minimally invasive mitral valve approaches, with a focus on current considerations related to patient selection, procedure performance, technical challenges, and clinical outcomes.

## Minimally Invasive Mitral Valve Approaches

Minimally invasive mitral valve operations started being described by highly specialised organisations in the mid 1990s, and continue to evolve to this day. These initially involved partial sternotomy or parasternal access[6–8]. Though the parasternal approach has since been abandoned, the partial sternotomy approach is still in use. Carpentier first described a thoracotomy based approach with video assistance in 1996[9]. This approach evolved to include an endoaortic balloon occlusion device and port-access technology[10]. More recently, this mini-thoracotomy approach has evolved to include a total endoscopic approach with stereoscopic visualisation, rivalling surgical robotics for degrees of visualisation and invasiveness[11,12].

The advent of surgical robotics has been the largest leap forward in minimally invasive mitral valve surgery. Mini-thoracotomy approaches rely on long shafted instruments and video assistance. The major challenges associated with these are the lack of depth perception with 2D video and limited dexterity with long shafted surgical instruments. The evolution of surgical robotics avoids these limitations. Several generations of surgical robotic assistance have passed, beginning with a voice-activated camera arm and proceeding through multiple generations of telemanipulation systems. The newest generation system is the DaVinci Xi (Intuitive Surgical Inc., Sunnyvale, CA), the 4th generation of DaVinci systems. This provides superior visualisation of the mitral valve, with a highly magnified, high definition 3D view. Dexterity is unrivaled with the robotic approach. Using telemanipulation with tremor-reduction, the surgical robot is capable of 7 degrees of freedom. This allows a full, stable, unimpinged range of motion for the surgeon. Though a non-robotic totally endoscopic approach with stereoscopic visualisation may rival the robotic approach, the dexterity advantage in current surgical robotics is undeniable.

Again being intimately involved in the evolution of cardiac surgery, the first robotic-assisted cardiac procedure was described by Carpentier in 1998; this was the repair of an atrial septal defect[13]. Mitral valve repair using the early DaVinci system was pioneered by Chitwood in 2000, using the full range of mitral valve repair techniques and demonstrating excellent results[14]. This experience has been the model from which modern robotic mitral valve surgery has evolved.

## Robotic-Assisted Mitral Valve Surgery

### Patient Selection

Most patients with isolated degenerative disease can have their mitral valve repaired using a robotic approach, though in practice, not all should. Patient selection is essential to the success of robotic assisted mitral valve surgery. Though complications may arise for myriad reasons, they most commonly stem from improper patient selection. The Cleveland Clinic has adopted a screening algorithm for robotic-assisted mitral valve surgery, which has helped decrease incident complications (Figure 1)[15]. If a patient has significant coronary artery disease requiring revascularisation or has had a previous sternotomy, they are precluded from a robotic approach. In the absence of these factors, the decision of whether to offer a robotic approach depends on the results of preoperative imaging studies, with every patient considered undergoing a preoperative transthoracic echocardiogram and contrast enhanced computed tomography (CT) scan (Figure 1)[15].

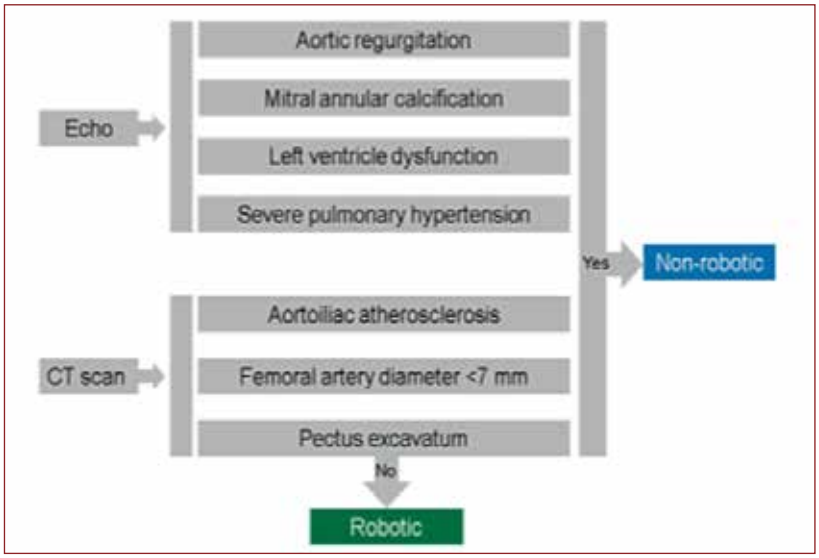


*Figure 1: Patient selection algorithm for robotic mitral valve repair*

Echocardiographic features influencing the decision to offer robotic assisted mitral surgery are mitral annular calcification (MAC), aortic insufficiency (AI), significant left or right ventricular dysfunction, and severe pulmonary hypertension. MAC complicates the performance of an adequate complete repair; if required, MAC debridement can greatly increase the complexity and surgical risk of a mitral valve repair. Patients with severe MAC are best served by a sternotomy-based approach, although those with mild MAC may be candidates for robotic surgery. Greater than mild AI makes cardioplegia problematic, and increases the risk of ventricular distension and inadequate myocardial protection. Though percutaneous retrograde cardioplegia cannulas have been employed, they run the risk of becoming dislodged, a potentially catastrophic event in the patient with AI that is moderate or greater. A sternotomy approach should be employed for patients with severe left or right ventricular dysfunction in order to optimise both myocardial protection and operative time. If there are inadequate or inconclusive results from the transthoracic echocardiogram, a preoperative transoesophageal echocardiogram (TOE) is completed for clarification.

A contrast enhanced CT scan of the chest, abdomen, and pelvis informs cannulation and perfusion strategies as well as the understanding of the patient's thoracic anatomy for incision and port placement. Significant aortoiliac atherosclerosis, particularly if there is soft plaque present, precludes safe retrograde perfusion via the femoral artery, increasing the risk of cerebrovascular events. Small femoral arteries (<7mm diameter) or heavily calcified femoral arteries can preclude safe insertion of an adequately sized femoral arterial cannula. The CT scan will define which side is preferable for femoral access, based on areas of disease or tortuosity. Aberrant vascular anatomy influencing perfusion strategy (discontinuous inferior vena cava (IVC), persistent left superior vena cava (SVC), or retrooesophageal left subclavian artery) will be identified with a preoperative CT.

## Anaesthesia and Perfusion

Single lung ventilation is achieved by intubation with a double lumen endotracheal tube, or a single lumen tube with bronchial blocker. A TOE probe is placed in every case to confirm preoperative findings, better define mitral anatomy, guide peripheral cannulation,

and confirm adequate results postoperatively. Central venous access is obtained via the right internal jugular vein, followed by an inferior "double stick" catheter to facilitate wire placement for bicaval cannulation. Defibrillator pads are placed on the right posterior and left anterolateral hemithorax, avoiding the right anterolateral region used for port placement. The right side of the patient is elevated 30 degrees, and the right arm is supported in internal rotation off the side of the bed. The patient is prepped from the neck to the ankles, and draped to expose the right anterolateral hemithorax, sternum (in case of conversion), and femoral arteries.

The femoral vessels are exposed via an oblique 3-4 cm incision. Once isolated and adequate sizing is confirmed, arterial and venous purse string sutures are placed. After heparinisation, the femoral vessels are cannulated directly using Seldinger technique, with wire placement confirmed by TOE. The femoral venous cannula is placed so that the tip sits 2-3 cm into the SVC. After TOE confirmation of the arterial wire in the aorta, the arterial cannula is placed such that the tip sits in the distal abdominal aorta or iliac artery. Inadequately sized femoral arteries can lead to inadequate systemic flows, as well as to distal limb ischemia. To mitigate this, alternative perfusion strategies must be considered. Perfusion via a femoral artery side graft will prevent distal limb ischemia, though the artery still must be adequately sized to support systemic flow. Though not employed at our institution, antegrade perfusion via direct aortic cannulation or axillary artery cannulation have been described. Our approach however, has been to abandon the robotic assisted approach when faced with inadequately sized femoral arteries.

In patients with a body surface area $\geq 2.0 m^2$, a bicaval venous cannulation approach is used. The inferior right internal jugular catheter is used to pass a guide wire into the right atrium. An additional 15-18F venous cannula is placed percutaneously into the SVC under TOE guidance.

## Port Placement

After confirmation of femoral vessel size, the right lung is deflated and a 3-4 cm working port is created in the right 4th intercostal space, bisecting the anterior axillary line. In women, the right breast is retracted medially and superiorly, so the incision can be placed in the breast crease. Gentle spreading of the ribs allows visualisation of the pericardium and confirmation of position relative to the cardiac structures. If required, a diaphragmatic retraction suture can be placed. The robotic ports are then placed in a triangular configuration around the working port. The atrial retractor port is placed through the 4th intercostal space at the midclavicular line. The right robotic instrument arm is placed through the 6th intercostal space just posterior to the anterior axillary line. The left robotic instrument arm is placed in the 2nd intercostal space roughly in between the anterior axillary and midclavicular lines. The completed setup is shown in Figure 2.

Useful guidelines for port placement include the following:

1. Imagining the ports as the base of a cone, with the apex of the cone located in between the right superior and inferior pulmonary veins.
2. The left robotic instrument port should be roughly equilateral to the retractor port and the right instrument port.
3. Distances between port sites may need to be increased or decreased based on the patient's body habitus in order to optimise robotic arm range of motion and avoid arm conflicts.

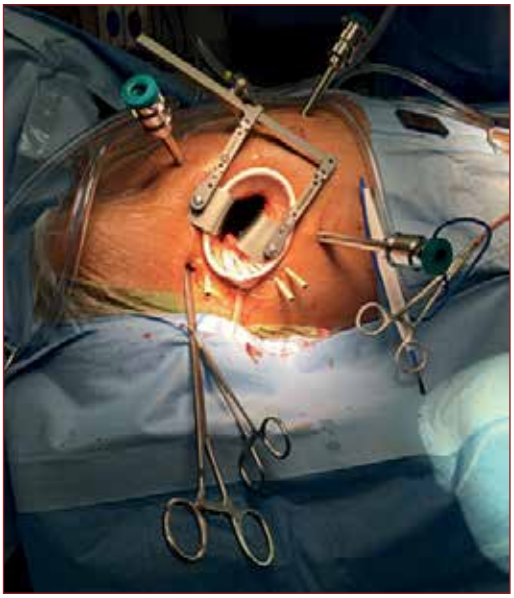

*Figure 2: Final setup prior to docking the robot*

## Clamping and Cardioplegia

Once port placement has been completed, cardiopulmonary bypass is commenced and the heart is decompressed; the patient is cooled to 30°C. Through the working port, pericardial fat is excised, and the pericardium is opened longitudinally starting near the diaphragm and extending cranially to expose the aorta. This incision should be initiated at least 3 cm anterior to the phrenic nerve. It may be useful to mark the phrenic nerve in ink to ensure it is avoided. Autologous pericardium is harvested from the anterior aspect of this incision. Pericardial retraction sutures are placed on the posterior aspect of the pericardial incision in the region of the SVC and IVC, and the sutures are taken out posteriorly through the chest wall.

Two strategies have been described to achieve aortic occlusion and subsequent cardioplegia delivery in minimally invasive mitral valve operations. The first involves placing a separate aortic root cannula for cardioplegia delivery and aortic root venting, along with a transthoracic clamp. The cardioplegia cannula is placed via the working port. The transthoracic clamp is placed through the third interspace in the mid-axillary line. The clamp lies in the transverse sinus, and is oriented so the concavity of the clamp is directed cranially. Care must be taken to avoid the pulmonary trunk, left atrial appendage, and left main coronary artery when clamping the aorta.

The second strategy employs endoaortic balloon occlusion with integrated cardioplegia delivery and venting capability, all facilitated by a catheter introduced via the femoral artery. Balloon positioning is confirmed by TOE and, in some institutions, by fluoroscopy. Bilateral upper extremity arterial lines are required, as the balloon may dislodge, which can be detected by a decrease in right upper extremity blood pressure. Because of the possibility of the balloon becoming malpositioned, placing a retrograde cardioplegia catheter via the internal jugular vein is prudent to ensure adequate myocardial protection. Using the endoaortic balloon allows the working port to be reduced somewhat in size. However, it increases procedural complexity and costs[16]. The endoaortic balloon may also increase the risk of aortic dissection[17].

Our preferred approach is to use a transthoracic clamp and deliver direct antegrade cardioplegia via the aortic root. We employ single dose Del Nido cardioplegia at 20cc/kg. Additional cardioplegia is given at 60 minutes if the cross-clamp time is expected to exceed 90 minutes.

## Mitral Valve Repair

All advanced mitral valve repair techniques used in sternotomy approaches can be used with a robotic-assisted approach[18]. Only minor modifications are required to accommodate the robotic instruments, and several techniques have been developed to improve surgical efficiency[19]. The mitral valve is approached through a left atriotomy, using the robotic atrial retractor to optimise valve exposure. Initial valve inspection takes place, and the repair technique is tailored to the specific valve lesion(s) and morphology.

Posterior leaflet resection and creation of artificial chordae are both routinely performed with robotic assistance. Narrow regions of prolapse can be addressed with a triangular resection using robotic-adapted scissors and Resano forceps. Interrupted figure-of-eight 4-0 polypropylene sutures re-approximate free leaflet edges. Excessively tall and bulky regions of prolapse are managed by quadrangular resection and sliding plasty, again utilising 4-0 polypropylene suture for valve reconstruction. This eliminates the prolapse and decreases the height of the posterior leaflet, reducing the risk of systolic anterior motion (SAM). Remaining cases of posterior prolapse are managed with artificial chordae.

Posterior neochordae are fashioned using CV-4 polytetrafluoroethylene (PTFE) sutures. These are premeasured based on the affected leaflet, knotted at the tail end, and marked at 1.5 cm from the terminal knot (Figure 3). This marking facilitates estimation of chordal length. The PTFE suture is first passed through the valve leaflet (atrial to ventricular). It is then passed through the fibrous region of the corresponding papillary muscle, then back through the valve leaflet (ventricular to atrial), approximately 1 cm from the knotted tail. The suture is then passed twice more (ventricular to atrial) to finish adjacent to the knotted tail on the atrial side. Chord length is then adjusted to eliminate prolapse and ensure a favourable zone of coaptation, and the suture is tied. Care is taken to ensure that the chordae are adequately short to mitigate SAM risk. For a typical P2 prolapse, 2 sets of chordae are used. As required, deep indentations between adjacent P1/2 or P2/3 scallops are closed with interrupted figure-of-eight 4-0 polypropylene suture. Alternatively, these indentations can be spanned by neochordae.

For the repair of isolated anterior leaflet prolapse, artificial chordae are preferred. The technique is identical to that previously described, though the PTFE sutures are longer and marked at 2 cm from the terminal knot (Figure 3). Two sets of chords are fashioned. These are oriented on either side of the leaflet midline, and are anchored posteriorly to the corresponding lateral or medial papillary muscle. Chord length is adjusted such that prolapse is eliminated and the coaptation zone is moved posteriorly. Isolated A1 or A3 prolapse are typically corrected with commissuroplasty.

Bileaflet prolapse can be managed with a combination of techniques. A true Barlow valve with an exceptional amount of redundant tissue can be managed with a posterior resection and 2 sets of anterior chords. Recently, we have adopted a “4 Chords” approach to these complex valves[20]. The anterior leaflet is addressed first to optimise papillary muscle exposure, followed by the posterior leaflet. In all cases, each chord corresponds to the medial or lateral aspect of each leaflet, and does not cross the midline. Neochordae are

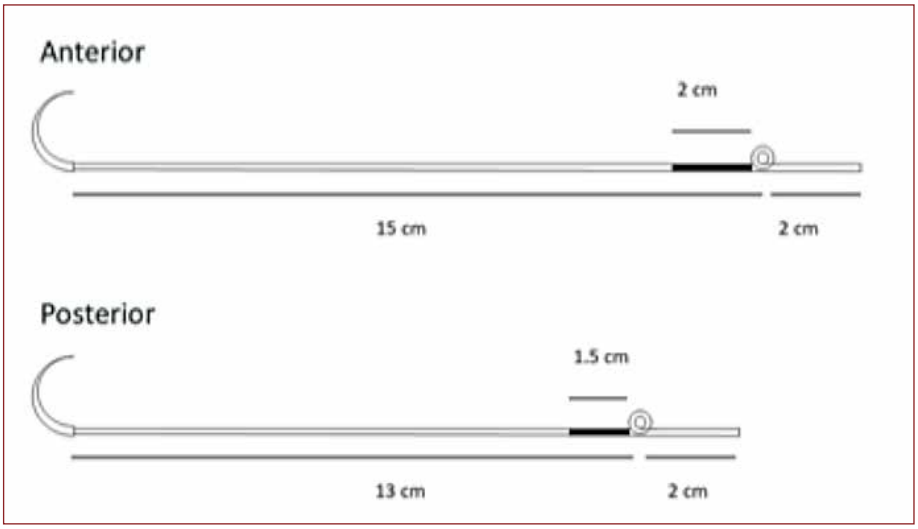


*Figure 3: Parameters for construction of neochordae based on affected leaflet*

anchored to posterior aspects of the corresponding papillary muscles. Indentations in the posterior leaflet are managed as described previously. Great care is taken to optimise leaflet height. Neochordae must both eliminate prolapse, and also move the coaptation zone adequately posterior in order to mitigate against SAM. To this end, posterior leaflet neochordae are left intentionally short (<1 cm).

In line with standard mitral valve repair practices, all repairs should include an annuloplasty. Regardless of the annuloplasty device used, excellent results can be expected[21,22]. We prefer a flexible band annuloplasty due to its ease of manipulation within the left atrium. There are 3 methods of annuloplasty fixation available: interrupted sutures manually tied with a knot pushing device, interrupted sutures fixed with titanium fasteners, and a running suture fixation. The running annuloplasty uses three 2-0 braided polyester sutures measuring 16, 14, and 9 cm. Each has a pre-knotted tail to anchor the suture, decreasing the number of robotically tied knots required. Beginning at the posteromedial trigone, the suture is run clockwise to the mid portion of the annulus, tied to the second suture, and continued until the suture reaches the anterolateral trigone. At this point, the final suture is passed though the annuloplasty band, anchored to the anterolateral trigone, and brought back through the band. This third suture is then tied in close proximity to the second. All knot tying is completed with the robotic instruments. This technique was developed at the Cleveland Clinic to optimise surgical efficiency for robotic cases[19]. On completion of the annuloplasty, the valve repair is then tested using conventional saline insufflation.

Left atrial closure is simplified by using two CV-4 PTFE sutures fashioned with small loops at each tail and 5-8 pre-tied knots[19]. This loop creates a snare at the terminal end of the suture, avoiding additional robotic knot tying. One suture is used at each terminal end of the left atriotomy, and run toward the center. A drop suction is placed across the mitral valve prior to left atrial closure, and removed once the heart begins to eject during weaning from cardiopulmonary bypass, expediting de-airing.

# Pitfalls and Challenges

## Learning Curve

Any mitral valve repair surgeon can transfer to the robotic platform and provide patients with the least invasive complete repair. However, the robotic platform presents several challenges to the surgeon. Lack of tactile feedback requires the surgeon to pay exceptionally close attention to surrounding tissues, which are susceptible to injury. This lack of feedback can also lead to broken sutures while suturing or tying. Though visualisation and dexterity are superior using the robotic platform, the surgeon must necessarily re-learn how to angle / pass needles and manipulate instruments, as the telemanipulation system does not exactly mirror movements used in open surgery. Similarly, knot tying can be quite challenging when beginning to use the robotic platform given the reasons highlighted above.

Equally important is team training. The team requires dedicated members from anaesthesia, nursing, and perfusion who are experienced and comfortable with the procedure. A bedside surgeon is required as well, who must be comfortable with the robotic technology. The entire team must negotiate the requisite learning curve. With experience, comfort with the platform improves, as does operative efficiency, which steadily improves until reaching a plateau at approximately 150-200 cases[15,23]. Simulation, as an evolving adjunct, helps decrease this learning curve[24].

## Intraoperative Injury

Surrounding cardiac structures are uniquely susceptible to injury during a robotic assisted procedure due to placement of the requisite instruments and their interactions during the case. Transthoracic clamping carries the risk of pulmonary artery, left atrial appendage, or left main coronary artery injury. Great care must be taken, with adequate visualisation of the transverse sinus, while placing the clamp in order to avoid these structures. The transthoracic clamp can also be inadvertently manipulated and torqued by the left robotic instrument if the port is placed with inadequate clearance of the cross clamp, increasing the risk of aortic injury. Similarly, the left instrument can interact with the antegrade cardioplegia cannula and cause aortic injury.

Endoaortic occlusion balloon can mitigate the risk of pulmonary artery, left atrial appendage, and left main injury. The lack of a transthoracic clamp eliminates the risk of inadvertent aortic manipulation. However, the endoaortic occlusion balloon appears to increase the risk of aortic dissection and conversion to sternotomy[16,17]. Additionally, aortic occlusion and cardioplegia can be unpredictable, as the balloon is less stable and can inadvertently dislodge[25].

Phrenic nerve injury can be mitigated by incising the pericardium at least 3 cm anterior to the phrenic nerve. We mark the phrenic nerve in ink prior to incising the pericardium. The risk of phrenic injury can further be reduced by ensuring excessive traction is not placed on the posterior pericardial retraction sutures.

## Postoperative Bleeding

Weaning from cardiopulmonary bypass typically requires re-expansion of the right lung. Protamine administration and decannulation should take place in the usual fashion. Subsequently, the right lung is again deflated and the surgical sites are checked for bleeding. Major surgical sites (atriotomy, cardioplegia cannula site, pericardial edge, pericardial

fat) are examined under direct vision, with haemostasis achieved with extra sutures or cautery as appropriate. An endoscope is inserted through the atrial retractor port and the left and right instrument ports are removed. Port sites are examined endoscopically and haemostasis is achieved with cautery as required. The atrial retractor port is then removed and the endoscope is inserted through the working port to examine this port site in the same manner. A chest tube is inserted through the right instrument port site.

As with any cardiac surgical case, meticulous care must be taken with haemostasis. A low threshold to return to the operating room to address post-operative bleeding should be adopted. The best way to address post-operative bleeding, however, is to prevent it, as visualisation, exposure, and repair can be quite challenging in the context of post-operative haemorrhage in the robotic-assisted minimal access patient.

## Clinical Outcomes

Beginning with Chitwood in the early 2000s, robotic assisted mitral valve repair has consistently shown excellent results[14,25]. The entire spectrum of mitral repair techniques are possible[14,15,26]. Cardiopulmonary bypass and cross-clamp times are longer than for sternotomy, especially in the early stages of robotic adoption, but this does not appear to translate into an increase in morbidity or mortality[26]. Intensive care unit and total hospital length of stay are reduced and return to work is improved[26–28]. Incident stroke and operative mortality consistently measure at <1% in major series[26,29,30]. With adoption of the described screening algorithm, the Cleveland Clinic was able to decrease our incidence of stroke by greater than half[15]. Infectious complications are similarly low[15,26,30]. Finally, and very important to the patient, the cosmetic result is excellent.

## Conclusions

Once the requisite learning curve has been negotiated, robotic assisted mitral repair is safe and effective, and produces results of the same quality compared to a sternotomy-based approach. One must be conscious of the inevitable reality that, as one becomes less invasive, complexity is increased, and control is diminished. Using the described approach to robotic-assisted mitral valve repair, we believe we have balanced these factors and can offer a safe, predictable, and durable complete repair.

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Chapter 7

# It is not a lack of evidence: the rationale to treat AF

*Simon Schiettekatte, Filip Rega,and Mark La Meir*

*"Natura non constristatur"*

Atrial fibrillation is the most common cardiac arrhythmia, with an enormous impact on global health. It is characterised by multiple reentrant circuits producing chaotic and uncoordinated myocyte depolarisation. The diagnosis requires an electrocardiogram showing irregular RR intervals; absence of P waves and a variable atrial cycle length of less than 200 ms[1]. AF can be categorised into paroxysmal AF, defined as recurrent AF episodes (two or more) that terminate spontaneously within 7 days; persistent AF, recurrent AF for 7 days or longer; and longstanding persistent AF, defined as continuous AF of more than 1 year duration. Classification is made by defining the most frequent pattern of AF during the prior 6 months[2].

To understand the dangers and possible treatment, it is necessary to understand the mechanisms behind AF. Its main causal mechanism is a remodeling of the atrial structure and ion channel function. External factors such as structural heart disease, hypertension, diabetes, but also AF itself induce a slow but progressive process of structural remodeling in the atria. Activated fibroblasts, enhanced connective tissue deposition, and fibrosis are key mechanisms in this process[3-5]. Furthermore, atrial fatty infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis, and amyloidosis are found in AF patients with concomitant conditions predisposing to AF[6-9]. This remodeling process is already present before the onset of AF, causing electrical dissociation between cardiac muscle cells and local conduction differences, causing re-entry and perpetuation of the arrhythmia. Structural remodeling results in electrical dissociation between muscle bundles and local conduction heterogeneities[10], favouring re-entry and continuing of the arrhythmia[10-11]. In many patients, the structural remodeling process occurs before the onset of AF[5]. Some aspects of the remodeling process will be irreversible, therefore early initiation of treatment may be desirable.

The prevalence of AF has been growing since 1990, and in 2010 approximately 33.5 million patients worldwide received the diagnosis of AF (Figure 1). Not only has the prevalence of

AF risen but so, too, have mortality rates associated with it. A two-fold increase in mortality was observed for men and women in that same time period. Global mortality rates are higher in Western regions such as Europe and the US (Figure 2)[12]. More men than women are affected. Prevalence of AF also rises with age, from 0.9% in patients younger than 50 up to more than 10% in patients from the age of 80 onwards[13]. It is estimated that one in four middle-aged adults in Europe and the U.S. will develop AF by 2030[14].

AF is associated with increased morbidity and mortality because of its relation with stroke and heart failure[15-18]. People suffering from AF have a fivefold increased risk of stroke[19].

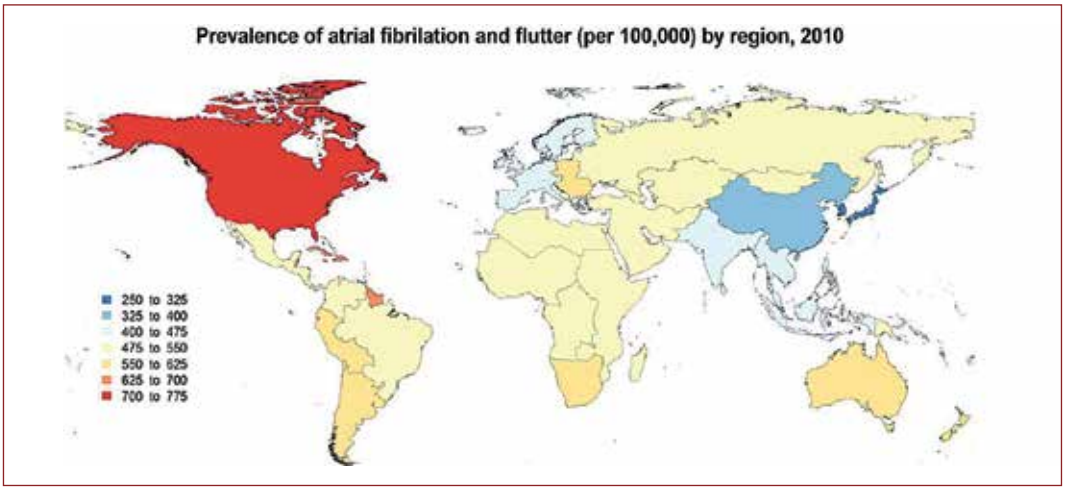


*Figure 1: World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions, 2010. Chug et al Circulation. 2014;129(8):837–847* [12]

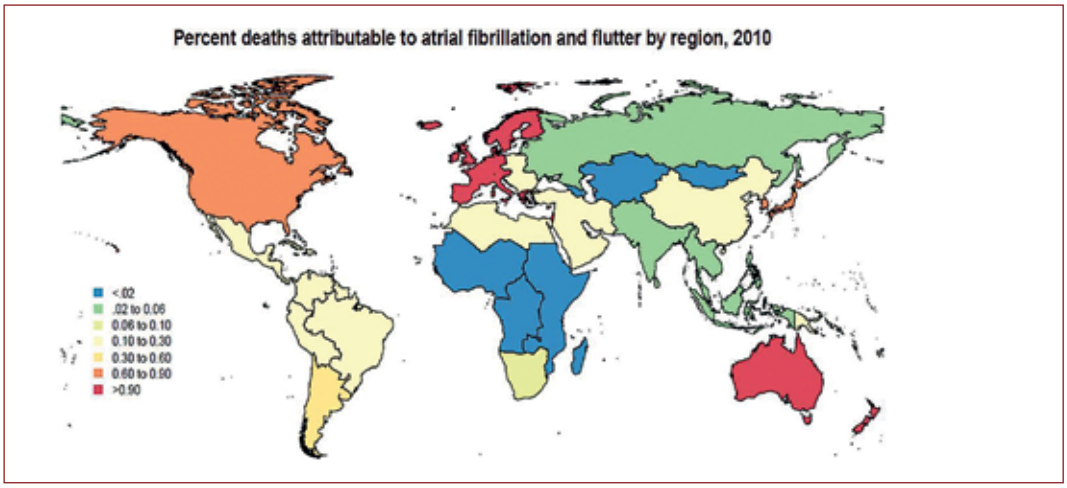


*Figure 2: Proportion of global deaths associated with atrial fibrillation in 2010. The map shows color-coded proportions (in percentages) of global deaths in 2010 associated with atrial fibrillation. Chug et al Circulation. 2014;129(8):837–847* [12]

The Framingham heart study showed that attributable risk of stroke increases from 1.5% age 50-59 years to 23.5% age 80-89 years, with AF accounting for nearly 25% of strokes in those over the age of 80 years compared to 10 to 15% across all age groups[20]. With stroke being the 3rd leading cause of death and the leading cause of serious adult disability in the United States (US) and the United Kingdom (UK), it has a major impact on global health care from a medical and economic point of view[19].

The evolving character of AF has a major impact on heart failure (HF). The prevalence of HF is five times higher in patients with AF. HF leads to AF and AF leads to heart failure [21]. The mechanisms related to AF causing HF are tachycardia, irregular heartbeat, loss of atrial systolic function and genetic disorders. Ventricular tachycardia has a negative impact on left ventricular (LV) function because of the activation of neurohormonal systems, myocardial and exoskeleton remodeling and, if tachycardia continues, cell death and fibrosis. Coincidentally, AF causes loss of atrial function which impacts LV systolic function. It is estimated that normal atrial function contributes up to 20% of the cardiac output, independent of LV function[22]. Regaining sinus rhythm in time may therefore partially restore LV function.

Increased end diastolic ventricular pressures will lead to increased atrial pressures. This will induce neurohormonal activation and structural remodeling of the left atrium. In addition, abnormal calcium handling and adrenergic stimulation in chronic LV dysfunction lead to functional re-entry, pro-arrhythmia and delayed repolarisation. The structural remodeling of the left ventricle will cause functional mitral regurgitation, enhancing atrial remodeling even more[21].

When exploring the surgical treatment of AF there are two groups of patients to consider. Lone AF treatment and AF in concomitant cardiac disease. Lone AF is characterised by the presence of AF and absence of any other structural heart disease or acute trigger in younger adults (<60y)[23]. Until now it remains a diagnosis of exclusion and recently the definition has been the subject of discussion[24]. The largest group of AF patients referred for surgery have a concomitant structural heart disease such as mitral valve disease, aortic valve disease or coronary artery disease. In the remainder of this paper the main focus will be surgical ablation (SA) in concomitant cardiac surgery.

A North American study showed that only one out of three patients with AF was treated in a concomitant setting with CABG, AVR or combined CABG and AVR. Conversely, rates of concomitant surgical ablation (SA) for AF during mitral valve surgery or combined MVR and CABG are up to 60% between 2005 and 2014[25,26]. However the total numbers of treated patients are rising. So why are there still so many patients left untreated?

In 2010, an independent survey was conducted at the annual meeting of the American Association for Thoracic Surgery (AATS) to find out why most U.S. cardiac surgeons simply ignore the opportunity to treat AF in patients who are already going to be in their operating rooms for some other cardiac procedure[27](Figure 3).

The addition of complexity, added pump time and unwillingness to add risk depict a fear of added risk to the procedure. Marie Curie once said “Nothing in life is to be feared, it is only to be understood. Now is the time to understand more so that we may fear less”.

Niv Ad and colleagues addressed this concern in a study adding Cox Maze III to AVR and CABG procedures in patients with AF. Their conclusions were that adding a Maze procedure to the primary procedure did not increase the risk of surgery and that in fact, those patients who had the additional Maze procedures actually seemed to do better than

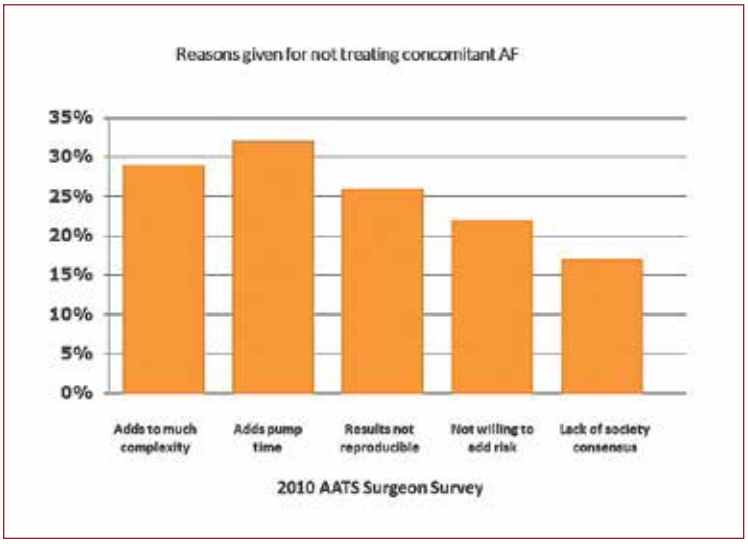


*Figure 3: Reasons given for not treating concomitant AF in a survey conducted at the annual meeting of the American Association for Thoracic Surgery (AATS) 2010*

those patients in whom AF was simply ignored[28]. A more recent study that was published in 2018 compared patients without AF to patients with AF receiving concomitant ablation and patients with AF who didn't receive SA. Operative mortality, reoperation for bleeding, sternal infection, prolonged ventilation, permanent stroke and new renal failure were examined. They concluded that for patients with AF at the time of mitral surgery, the performance of concomitant ablation is associated with a lower risk-adjusted operative mortality compared to patients who do not undergo surgical ablation and significantly lower risk of permanent stroke[29].

A review examining the effect of SA on postoperative freedom of AF and patient-important outcomes showed improved freedom of AF (n = 1407). Twenty studies had a follow-up of 12 months and reported freedom of AF in 70% in ablated patients, as opposed to 30% in the control group. However, the tools used to assess AF in follow-up were quite heterogenous across studies, ranging from single ECG, Holter assessment, implantable loop recorder, or combinations of these. Furthermore, no significant differences in peri-operative mortality (n= 1869) or stroke (n= 1326) were reported. When comparing bi-atrial and left atrial lesion sets, no significant difference was seen in peri-operative mortality, stroke or hospital length of stay. Both lesion sets reported an improved freedom of AF after 12 months[30]. A Belgian registry conducted between 2011-2016 and published in 2019, confirms the previous findings for concomitant SA for AF and reports a freedom of AF after 3 months of 69.9%[31].

Rankin et al reported that 17% of patients with AF undergoing CABG also received SA. In this group, risk adjusted long term survival after 90 days was significantly better than in the group where AF treatment was ignored (HR 0.58 (p= 0.03))[32]. In 2012, a paper published by Lee et al reported that patients undergoing surgical treatment of atrial fibrillation had survival similar to that of patients without a history of atrial fibrillation. More interestingly patients with successful sinus restoration were reported to have improved survival 1 year after surgery, compared with those who were treated but remained in atrial fibrillation[33].

There are many papers supporting SA of AF in concomitant cardiac surgery. However, underreporting of long-term outcome after surgical ablation is frequently observed. EHRA guidelines suggest at least a 12-lead ECG at each follow-up visit and a 24h Holter

monitoring after 12 months for paroxysmal AF. For persistent and long-standing AF, a Holter monitoring of at least 24h is recommended. Symptom driven monitoring is advised for all AF types. Pacemaker readouts may replace Holter monitoring[34]. Henn et al published long-term results of surgical ablation (SA) for AF, including 534 patients. Average follow up time was 3.3 ± 4.7 years. At 1, 2, 3, 4, and 5 years following surgery, follow up was 84% (446/534), 67% (304/457), 58% (223/383), 55% (166/300), and 58% (139/241), respectively. After two years there were only 201 patients in whom prolonged continuous monitoring was obtained (Holter monitoring of 24h or more). The reason why so many patients were lost in follow-up or had incomplete data was not reported. This may cause a bias in reported outcome. Nevertheless, the available results were good with a freedom of atrial tachyarrhythmias up to around 80% after 5 years[35]. Another example is the milestone paper by Gillinov and associates, that reported on SA of AF during mitral valve surgery. 260 patients were randomly assigned to a SA group or no SA group. Primary endpoints were freedom from AF at 6 and 12 months. Follow-up was performed with a 3 day Holter monitoring and pacemaker readout when available. Freedom of AF was achieved in 63,2% of patients after 6 and 12 months[36]. 20% of patients, however, had no primary endpoint data on Holter monitoring, vital status or subsequent ablations.

Most recently the PRAGUE-12 trial published 5-year follow-up results comparing patients with AF receiving SA in concomitant cardiac surgery vs cardiac surgery alone. The primary endpoint was a composite of cardiovascular death, stroke, hospitalisation for heart failure, or severe bleeding. Secondary endpoint was a recurrence of AF. 224 patients were initially enrolled in the study, 11 in-hospital deaths occurred, 2 patients were refused for surgery and 4 were lost to follow-up. A total of 207 patients were analysed. Follow-up was complete in all reported patients and was undertaken by peripheral cardiologists according to current guidelines. It was done by means of at least yearly 24h Holter monitoring and a 7-day Holter after 5 years in the investigating center when the patient remained in sinus rhythm. In case of recurrence of AF, further follow-up and treatment was left to the treating physician. A higher incidence of adverse outcome was seen in the non-SA group (61.6%) vs SA (42.6%). Incidence of death, stroke, heart failure and severe bleeding were higher in the control group. However, the only statistically significant difference was in incidence of stroke (p=0.02). AF-free survival after 2 years was 50% in SA group and 25% in the control group[37]. Although freedom of AF is slightly lower than in other reports, a large benefit of SA is still observed compared with no SA in terms of AF-free survival, death, stroke and heart failure. This paper is an example of a high level and long-term follow-up favoring SA during cardiac surgery over ignoring AF.

In the last 10 years numerous papers have been published supporting SA as a treatment for AF in concomitant setting. Therefore, the latest guidelines of different societies have included SA of AF. Evidence has been growing stronger over the years and most recent 2017 guidelines state a IA or IB class of recommendation and level of evidence for concomitant SA in mitral valve surgery, level IB for concomitant AVR, CABG or AVR and CABG, level IIB for stand-alone SA and IIC for lone atrial appendage management[35,38,39,40].

## Conclusion

As can be seen in the number of studies included in the review discussed previously, lack of reproducible data and evidence is not an issue. The evidence of the problem of AF is clear. The prevalence of AF in patients is rising together with the numbers of elderly patients creating a large economic and health care burden. Its relationship with heart failure and stroke is undeniable, causing significant mortality and morbidity among patients with AF.

As surgeons we are often exposed to AF and should take responsibility and play our role in managing these patients in heart teams. Nevertheless, there is still a big gap between the need and reality. For a variety of different reasons, many patients remain untreated, even though the evidence shows that a solution exists. Surgical ablation restores sinus rhythm, is safe and improves long term outcome. However, long-term results and follow-up data may be underreported, as in most papers the number of patients at follow-up is not the number of patients initially included in the study. Furthermore, the tools used in follow-up are heterogenous and should be used in a more standardised fashion, according to recent guidelines, to produce high quality data. Most recent reports have proven that this is possible and that the benefit of SA remains strongly present, even after 5 years. Following the current evidence, different societies are including SA in their guidelines with increasing levels of evidence and recommendation. Stronger and more complete follow-up data will support these guidelines.

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SECTION 1 CARDIAC SURGERY

# Aortovascular Surgery

*"Si parva licet componere magnis"*

*Publius Vergilius Maro. 70 - 19 BC*

Chapter 8

# Annuloplasty Techniques in Aortic Root Repair

*Pouya Youssefi and Emmanuel Lansac*

*"Factum fieri infectum non potest"*

## Introduction

The most common aetiology of aortic insufficiency (AI) in the western world is dystrophic AI, according to the Euro Heart Survey on Valvular Heart Disease[1]. Dystrophic AI is characterised by dilatation of the aortic annulus, sinuses and/or sinotubular junction diameters preventing coaptation of pliable leaflets which may also be subjected to prolapse. Three phenotypes of AI exist, depending on whether the sinuses of Valsalva and/or the tubular ascending aorta are dilated: 1) normal root and ascending aorta (all diameters <40-45mm) – termed isolated AI; 2) dilatation of the aortic root (sinus of Valsalva ≥ 45 mm); 3) dilatation of the ascending aorta (≥45 mm). In all 3 phenotypes, dilatation of the annulus and sino-tubular junction (STJ) are almost constantly present. All 3 phenotypes of AI are good candidates for aortic valve repair.

Aortic valve (AV) repair is an emerging field in cardiac surgery and is following in the footsteps of mitral valve repair. The recommendation from the 2017 European Association for Cardio-Thoracic Surgeons/European Society of Cardiology guidelines for valvular heart disease for management of aortic root aneurysm (originally called annulo-aortic ectasia) is to use "reimplantation or remodelling with aortic annuloplasty" for valve sparing root replacement[2]. This refers to the need of addressing the annulus. Numerous studies have now shown that if left untreated, a dilated aortic annulus greater than 25–28 mm is a major risk factor for failure of aortic valve repair in both bicuspid and tricuspid valves[3,4].

Aortic annuloplasty reduces the dilated aortic annulus and in doing so increases the surface of coaptation. When used in conjunction with annuloplasty of the sinotubular junction (STJ), it also restores the physiological ratio of annulus/STJ. This is now considered to be

an essential component of both aortic valve repair and valve-sparing root surgery. In this chapter, we describe the history of aortic annuloplasty, the surgical considerations in terms of anatomy and technique, as well as our standardised approach to aortic valve repair with external ring annuloplasty.

## The 3 phenotypes of dystrophic aortic insufficiency

According to the Euro Heart Survey on Valvular Heart Disease, dystrophic AI represents approximately two-thirds of all cases of AI in the western world. In all 3 phenotypes described above, the annulus and STJ are invariably dilated, and form part of the combined mechanism of AI. Other factors commonly involved in the mechanism of AI include cusp prolapse, elongated or ruptured fenestrations and commissural diastasis. It is therefore important for aortic valve repair techniques to address each component of the aortic root: the annulus, cusps and STJ.

The 2017 European Association for Cardio-Thoracic Surgeons (EACTS) / European Society of Cardiology (ESC) guidelines for heart valve disease recommend a 'heart team discussion' for selected patients 'with pliable, non-calcified' aortic valve insufficiency 'in whom aortic valve repair may be a feasible alternative to valve replacement' (class I C indication)[2]. The vast majority of patients with dystrophic AI are good candidates for aortic valve repair. The Society of Thoracic Surgeons' database reported 14% of patients who underwent aortic root surgery received a valve sparing procedure (20% of low risk and 6% of high risk patients). This still leaves 80% of root procedures for AI and/or root aneurysm as composite valve and graft replacement (Bentall procedure)[5,6]. There has been a recent push in the uptake of aortic valve repair techniques, with a number of high volume centres of expertise conducting international courses for emerging surgeons. The key to disseminating these techniques and improving uptake is the standardisation of aortic valve repair techniques.

## The aortic annulus

Due to different descriptions and terminology, there is some degree of confusion regarding the anatomy of the aortic annulus. Terms such as virtual ring, basal ring, or ventriculo-aortic junction have been used to describe the annulus[7-12]. The general consensus for defining the annulus is the inflow of the aortic root as the plane passing through the nadir of the aortic cusps that can be measured either on echocardiographic long axis view or by direct intubation intra operatively. By avoiding the term "ring", it helps to avoid confusion with repair techniques which involve prosthetic rings.

A study by Kunzelman et al. in 1994 led many to believe that the aortic annulus was larger than the STJ[13]. However, this study was based on a small number of root homografts which were measured ex-vivo in non-pressurised flaccid conditions. We now know from large pooled echocardiographic studies that the annulus is in fact smaller than the STJ. These studies have measured in-vivo live echocardiographic measurements of hundreds of pressurised roots, showing that the mean STJ diameter (27.2 mm [range 24.7–29.5]) is larger than the aortic annulus (22.3 mm [range 20.5–24.5]) diameter with a STJ/aortic annular base ratio of 1.2[14,15]. We can therefore now classify an aortic annulus diameter larger than 25 mm and a STJ diameter larger than 30 mm as functionally dilated.

Reduction of the annulus or the STJ has important effects on geometry of the aortic root. This in turn affects competence of the aortic valve. Reducing the annulus has the benefit of increasing coaptation height (cH) of the valve, much like in mitral valve repair[16]. STJ

reduction also increases coaptation height but, can induce a reduction of effective height (eH) with a resultant symmetrical cusp prolapse. This influences the order of steps when repairing the aortic valve/root (see below) – i.e. it is important to measure cusp effective height and to deal with cusp prolapse after the STJ annuloplasty. Another important characteristic of the annulus is its dynamic expansibility. The systolic enlargement of the aortic root lowers leaflet stress during the opening and closure of the aortic valve. The annulus expands 6.2% with the STJ expanding 5.7% during systole[14,17].

When repairing the aortic valve or root, an important component of the operation is externally dissecting down to the subvalvular plane. This dissection allows for an annuloplasty to be carried either using an external ring or by way of the proximal suture line of the reimplantation technique. External dissection of the annulus can be achieved down to the subvalvular level below the nadir of the left and the non-coronary cusps, and below or within 3mm of the nadir of the right cusp in 80% of cases of tricuspid aortic valves[7,18-22]. In the region of the right-non commissure, dissection can be more difficult due to the presence of the membranous septum. The membranous septum limits the dissection plane, and the base of the right-non interleaflet triangle corresponds externally to the insertion of the membranous septum, right atrium wall, infundibulum and septal leaflet of the tricuspid valve[19]. Therefore, by carrying out this dissection, the external annuloplasty ring or the proximal suture line of the reimplantation tube graft would reach the subvalvular plane below the left and non-coronary cusps, and remain below or within 3mm of the nadir of the right coronary cusp 80% of the time (Figure 1). It is important to note that whatever the size of the external ring used, or the diameter of the tube graft in the case of the reimplantation technique, the final internal diameter of the annulus will be 5mm smaller. This is because the muscular part of the annulus is the thickest portion (with a mean thickness of 2.5mm). This would give a total reduction of 5mm (2.5mm on both sides of the annulus) by an external annuloplasty[8,23].

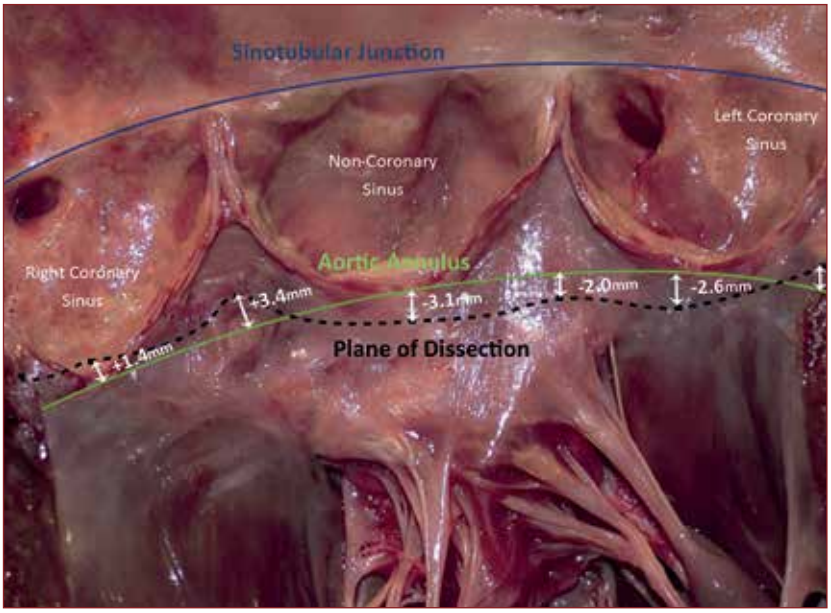


*Figure 1: Anatomy of the aortic root opened up. The blue line indicates the sinotubular junction. The green line indicates the aortic annulus. The dotted line shows the subvalvular dissection plane.*

## The role of annuloplasty in valve-sparing aortic root replacement

The remodelling technique and the reimplantation technique have been used for many years to replace the aortic root whilst preserving the native aortic valve. The remodelling technique was described by Yacoub and involves a tube graft modified to create 3 scallops or neo-sinuses which are sutured to the aortic wall directly adjacent to the cusp insertion points[24]. This physiological root reconstruction allows the root to expand during systole through expansion of the interleaflet triangles. The reimplantation technique was described by David, where the aortic valve is placed within a tube graft (David I technique)[25]. Both techniques bring the commissures to the diameter of the tube, and therefore treat dilation of the sinotubular junction. The remodelling technique represents the more physiological reconstruction by preserving the geometry of the 3 sinuses of Valsalva and its resultant vortical flow[26], as well as maintaining a dynamic expansile root. It also pulls the commissures cephalad and corrects interleaflet triangle dilatation. However, it does not on its own address the annulus, especially in patients with severely dilated annuli or connective tissue disorders. A dilated annulus (>25-28mm) has been shown to be a risk factor for reoperation and recurrent AI after the remodelling procedure alone for both bicuspid and tricuspid valves[3,4,27,28]. The reimplantation technique, on the other hand includes an annuloplasty through the proximal suture line of the tube[29]. However, it elicits less than physiological haemodynamic effects showing loss of vortical flow, with potential cusp impaction on the tube graft and rapid valve closure[26].

A number of modifications have been made to both techniques to address some of these limitations. An external expansile annuloplasty ring has been combined with the remodelling technique in order to restore the annulus back to its normal diameter in patients with a dilated annulus as well as preventing late dilatation[27,28,30-33]. In doing so, it also helps to restore the physiological annulus/STJ ratio. A spherical bulb-shaped graft has been used in the reimplantation technique in order to improve vortical flow patterns and cusp motion within a more physiological root shape[34,35].

The above changes, along with new techniques in addressing and repairing the valve cusps has led to improvement and increased uptake of valve-sparing root procedures. The long-term results of these operations have also improved over this time. One of the most important developments in cusp management has been the systematic measurement of cusp effective height (eH), which allows for the assessment of cusp prolapse. Cusp prolapse is one of the most important cusp mechanisms of AI and can be pre-existing, or induced, as a result of the valve-sparing root procedure[3,36]. By achieving an intra-operative eH of at least 9mm, with good alignment of cusp free margin length, the long-term outcomes of valve-sparing root procedures have been significantly improved[3].

An annuloplasty can be provided by the reimplantation technique as long as a deep subvalvular dissection is carried out for the proximal suture line. However, we prefer to use remodelling in combination with a subvalvular annuloplasty ring for a number of reasons. Firstly the remodelling technique has demonstrated superior haemodynamics with vortical flow formation, preserved root expansibilty and more physiological valve movements[26]. From a surgical aspect, there are advantages to remodelling + ring with regards to the standardisation and reproducibility of the technique; in the reimplantation technique the surgeon has to make an eye-balling judgment on how high to place the commissures inside the graft; in the remodelling technique the commissures follow the graft and are placed at the same level. Furthermore, in the reimplantation technique, the annuloplasty is the first step carried out through the proximal suture line, meaning that subsequent effective

height measurement is made more difficult by measuring within a small reduced annulus; in remodelling + ring the annuloplasty ring is the last step of the technique, meaning cusp effective height measurement is carried out in an untouched (often large) annulus. This makes accurate measurement easier. Thirdly, in the event of a poor outcome from the repair when there is persistent AI after cross-clamp removal, the aortic valve will need to be replaced. Given that the graft performs an annuloplasty in the reimplantation technique, the annulus will be reduced and small in size for the placement of a prosthetic valve. This may potentiate problems with patient-prosthetic mismatch, which would not be an issue with remodelling + ring as the external ring could be cut and removed thereby making the annulus enlarge again. Thus, a large prosthetic valve could be placed.

## The importance of the annulus / STJ ratio in isolated aortic valve repair

Isolated AI is defined as AI in the presence of both the sinuses of Valsalva and the ascending aorta measuring ≤ 45mm. As these cases form part of the spectrum of dystrophic AI, the annulus and/or STJ are commonly dilated despite the absence of significant aneurysmal disease (annulus ≥ 25mm, STJ ≥ 30mm).

"Aortic circumclusion" was the first attempt at aortic annuloplasty by Taylor and colleagues in 1958. It was used to treated isolated AI and involved silk sutures being placed as a circumferential annuloplasty running underneath the coronary arteries on a beating heart[37] (Figure 2, next page). The first prosthetic aortic valve replacement was carried out 2 years later, and thus this operation soon fell out of favour. Over the past 60 years, a number of different annuloplasty techniques have been used. Cabrol described the first internal annuloplasty technique in 1966, addressing both annulus and STJ using sub- and supra-commissural plication sutures. The Cabrol subcommissural annuloplasty technique was adopted by many surgeons. Initially good results were reported by the Duran and Cosgrove groups [38,39]. However, this technique has since fallen out of favour due to high published rates of recurrent AI in cases where the annulus is dilated[35,40]. Furthermore, this technique was shown to have poor results in bicuspid aortic valves, where its use was shown by Aicher et al. to be a predictor of re-operation when combined with remodelling root repair[41]. De Kerchove et al. compared subcommissural annuloplasty against the reimplantation technique in a bicuspid cohort and found 77% freedom from AI ≥ 3 at 4 years for subcommissural annuloplasty, compared to 100% for the reimplantation technique[35]. The subcommissural annuloplasty was found to be an independent predictor for aortic valve re-operation due to redilatation of the aortic annulus in both bicuspid and tricuspid aortic valves[42].

Carpentier proposed a continuous U-shaped internal suture along the cusp insertion line [43], subsequently also described by Haydar[44], and Scholhorn[45]. To aid in sizing the annuloplasty, the suture can be tied internally or externally with a Hegar dilator placed inside the annulus. The results from these techniques remain unclear due to lack of available outcomes or very small patient numbers.

Lansac et al. developed double sub- and supravalvular annuloplasty techniques using 2 external rings placed at the annulus and STJ for isolated AV repair in 2003. For the subvalvular ring, the annuloplasty is performed with an open ring passed below the coronaries. This increases the surface of coaptation to protect the repair. Furthermore, a supravalvular annuoplasty is also performed at the level of the STJ. It must be noted that the supravalvular STJ annuloplasty is carried out automatically by the tube graft in valve-sparing root procedures. The tube graft performs a supravalvular STJ annuloplasty

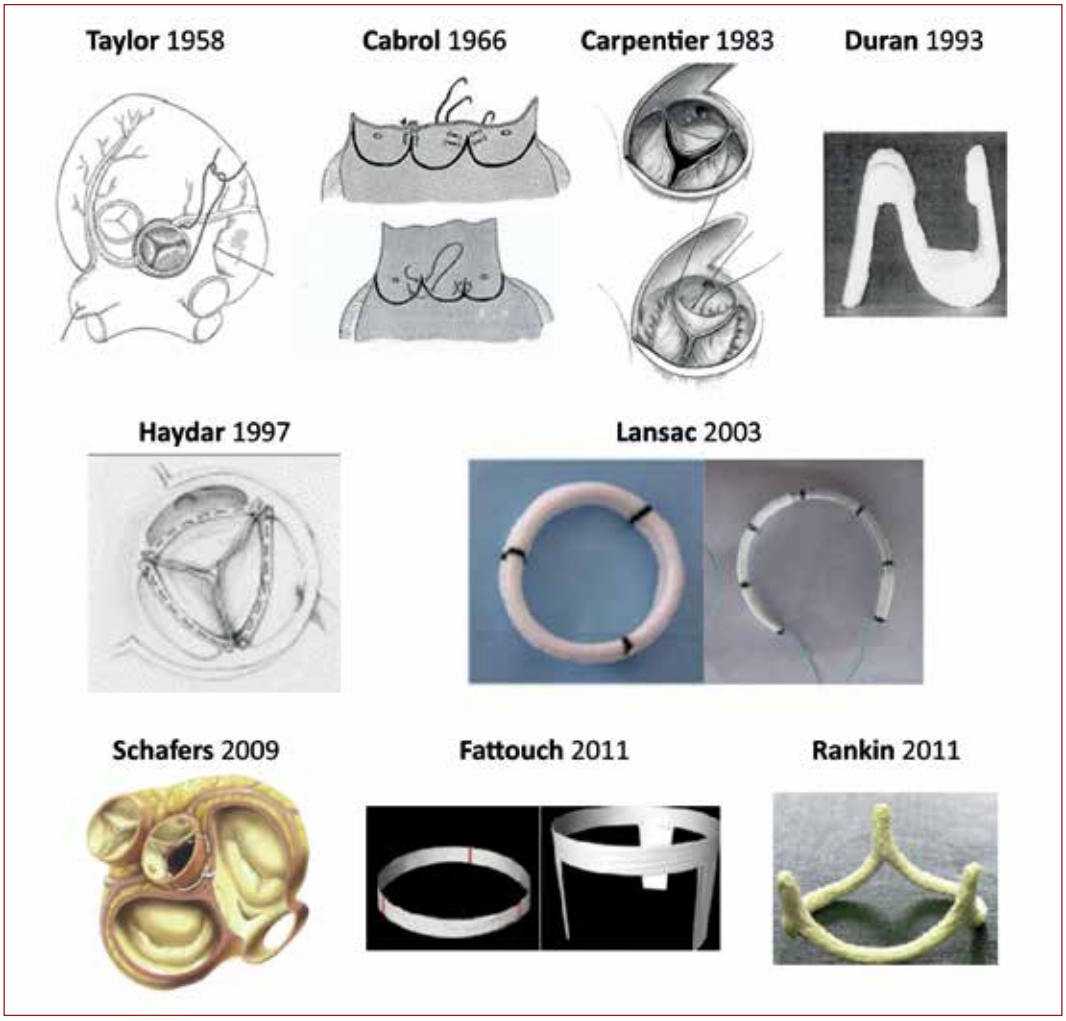


*Figure 2: Different external annuloplasty techniques. Reprinted by permission from Springer Nature, Gen Thorac Cardiovasc Surg. Annular management during aortic valve repair: a systematic review. Kunihara T (2015)*[57].

by bringing the commissure to the diameter of the tube. In isolated AV repair, the STJ must be separately addressed. As part of the repair process, the ratio of annulus/STJ must be addressed. By restoring this ratio to the physiological value of 1:1.2, a better coaptation height and long-term competency of the valve is achieved. By using a standardised sizing system, the combination of using an expansible annuloplasty at the supravalvular STJ level in addition to a subvalvular annuloplasty at the annular level would provide a reduction in respective diameters as well as maintaining this geometric ratio of annulus/STJ and systolic expansibility.

When the aorta phenotype is that of a dilated ascending aorta with preserved root, the supravalvular annuloplasty at STJ level will be performed by the supracoronary tube graft. This is similar to the case of valve-sparing root replacement in dilated roots, where again

the STJ annuloplasty is carried out by the tube graft. When the patient falls in the grey zone, such as in cases of borderline root diameters (close to 45 mm), a decision must be made as to whether to perform a valve-sparing root replacement, or an isolated valve repair. In this situation, the height of the coronary ostia in relation to the STJ is an important factor. When the coronary ostia are higher than the STJ, a valve-sparing root replacement is indicated, as the STJ ring in an isolated aortic valve repair would cause coronary ischaemia (and is therefore contra-indicated).

A similar concept of double annuloplasty was described by Fattouch et al in 2011 with a home-made double annuloplasty. This was an internal/external annuloplasty in combination with a crown shaped STJ ring[46]. Their mid-term results showed better freedom from AI grade ≥ 2 compared to subcommissural annuloplasty[47]. Further evaluation is needed regarding interaction of valve cusps with the internal ring and potential left ventricular obstruction at the subvalvular level.

Schäfers et al. described circumferential suture annuloplasty using Ethibond and subsequently polytetrafluoroethylene Gore-Tex 0 suture in 2009. This showed improved outcomes compared to no annuloplasty, especially in bicuspid valve repair[4,48]. Satisfactory mid-term outcomes for this technique have been published, and we await longer term outcomes to evaluate the stability of this approach. This technique may have particular advantages in redo operations.

Duran first described an internal aortic ring in 1993. This was implanted on a small number of patients, with no clinical outcomes published, and subsequently abandoned. In 2011, a rigid internal ring HAART (Hemispherical Aortic Annuloplasty Ring Technology) was introduced by Schomburg and Rankin[49,50]. Outcome data for this ring has only been shown in a small number of patients with short follow-up[51]. Further evaluation will be needed, especially with regards to the effect of the internal ring on the valve cusps, as well as incomplete STJ stabilisation.

## Aortic annuloplasty: a standardised approach to aortic valve repair

In order for uptake of aortic valve and root repair techniques to increase internationally, one of the most important tasks for the schools of aortic valve repair is to teach these techniques in a standardised manner. This will allow the techniques to be learned more easily and will ultimately provide the benefits of repair to more patients. We have developed a standardised approach to aortic valve repair which has the following aims: 1) reduce the annulus < 25mm; 2) restore the annulus/STJ ratio of 1:1.2; 3) restore symmetrical free margin length; 4) restore the effective height of all cusps to > 9mm. Dystrophic AI is almost always associated with dilatation of the annulus (>25mm) and STJ (>30 mm).

The procedure performed for treatment of AI depends on the phenotype of the aorta (Figure 3). In cases where the sinuses of Valsalva are dilated ≥ 45mm, a valve-sparing root replacement using the remodelling technique with subvalvular annuloplasty is performed. When only the ascending aorta is dilated ≥ 45mm, a tubular aorta replacement with subvalvular annuloplasty is performed. In cases of isolated AI where all aorta diameters are <45mm, an isolated aortic valve repair with double supra- and subvalvular annuloplasty is performed. All 3 procedures follow the same steps: 1) alignment of cusp free margin; then 2) supravalvular STJ annuloplasty; followed by 3) cusp effective height assessment; and finally 4) external ring subvalvular annuloplasty (if the annulus is ≥ 25 mm). In the case

of root aneurysms, the supravalvular STJ annuloplasty is performed by the remodelling root repair bringing the commissures to the diameter of the tube; with ascending aorta aneurysms, it is similarly performed by the supra coronary tube; and in isolated AI, the supravalvular STJ annuloplasty is performed using an expansible aortic ring (Figure 3).

Between 2003-2017, we have performed 482 aortic valve/root repair procedures using this standardised approach. The results show a 92% freedom for reoperation at 8 years for this whole time period. However, since 2007 we have used systematic effective height assessment along with an expansible calibrated annuloplasty ring (Extra-Aortic; CORONEO, Inc, Montreal, QC, Canada), which has improved freedom from AI grade ≥ 3 (100%), re-operation (99.1%) and major adverse valve-related events (96.3%) at 7 years follow-up with similar results for bicuspid and tricuspid valve repair[52]. This expansible ring has been shown to preserve systolo-diastolic expansibility of the annulus following the annuloplasty (5.1 ± 9.5%)[53].

The impact of STJ stabilisation on long-term durability of isolated AI repair has been shown to be highly protective. We have shown that use of double ring annuloplasty (annulus and STJ) was associated with 100% freedom from recurrence of AI ≥ Grade 3 compared to

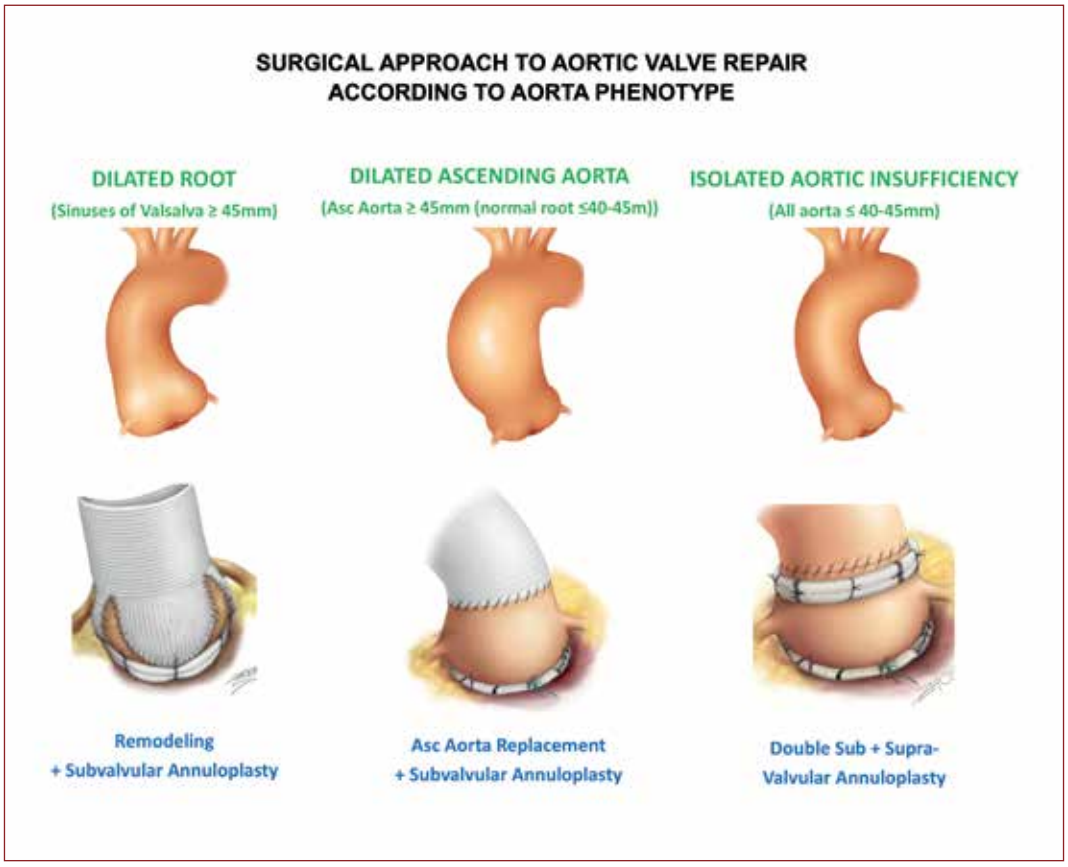


*Figure 3: Surgical approach to the management of aortic insufficiency according to aorta phenotype. Drawing by Pavel Zacek (used with kind permission).*

67% in the single annuloplasty group (annulus only) at 6 years (p=0.008). Moreover, use of double annuloplasty was correlated with 97% freedom from AV-related reintervention compared to 73% in the single annuloplasty group at 6 years (p=0.02)[54]. Long-term survival after AV repair is excellent and similar to sex- and age-matched populations.

The CAVIAAR trial assessed the safety of valve-sparing root surgery using the remodelling technique and expansible subvalvular annuloplasty[55]. This trial demonstrated similar 30-day mortality compared to a mechanical Bentall procedure, with a trend towards more major adverse events in the Bentall group (OR 2.52, p=0.09). Mid-term results at 4 years using crude and propensity matched analyses confirm that freedom from valve-related death and freedom from haemorrhagic events are significantly higher after valve repair than replacement; respectively 99% vs 94% ($p < 0.001$) and 89% vs 78% (p=0.02), whereas freedom from valve related reoperation was similar (p=0.22).

## Conclusions

As we have seen in mitral valve repair, dissemination of AV repair techniques will improve with standardisation of techniques thereby increasing the rate of aortic valve repair for both tricuspid and bicuspid valves, even in patients with severe AI. The significance of the annulus/STJ ratio has been established, hence the importance of a calibrated annuloplasty at sub- and supravalular levels in order to restore the annulus/STJ ratio. Furthermore, the surgical treatment of AI should be adapted according to the phenotype of the root and ascending aorta. Current medical evidence shows that AV repair is safe, reduces valve-related mortality compared to prosthetic valve replacement, produces better quality of life and provides similar life expectancy as that of the general population. Uniform clinical reporting of all available AV repair techniques such as in the AVIATOR registry will be key to evaluating long term patient outcomes[56].

## Acknowledgements

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# Section 2

## Thoracic Surgery

*Michael Shackcloth, Liverpool, UK.*

*"Causa latet, vis est notissima"*

*Publius Ovidius Naso. 43 BC - 17 AD.*

SECTION 2 THORACIC SURGERY

# Emphysema

*"Victrix causa diis placuit, sed victa Catoni"*

*Lucian of Samosata. 120 - 192 AD.*

Chapter 9

# When is Lung Volume Reduction Surgery indicated in an era of Endobronchial Treatment?

*Claudio Caviezel, Bo L. Holbek, Tamim A. Haidari, Laurens J. Ceulemans*

*"De omnibus dubitandum"*

## Introduction

More than 15 years ago, the multi-centre randomised National Emphysema Treatment Trial (NETT) revealed that lung volume reduction surgery (LVRS) improves dyspnoea, lung function, exercise tolerance, quality of life, and even survival in selected patients with emphysema compared to medical treatment[1,2]. However, two years before publication of full NETT results, the results of a high-risk patient group was published, showing increased mortality[3]. The paper, entitled "Patients at high risk of death after lung volume reduction surgery" caused a widespread misinterpretation of the beneficial effects of LVRS which led to a reduction in the surgical treatment of emphysema[3].

Over the last 15 years, several bronchoscopic treatments have been developed. Among these, consensus has shifted towards the use of endoscopic valves and coils.

Regarding the procentual gain in forced expiratory volume in one second ($FEV^1$) from baseline, the bronchoscopic results for treating heterogeneous emphysema with valves range from 4.3%[4] up to 29.3%[5]. The same studies reported an improved 6-minute walking distance between 19 and 79 metres. In patients with mostly homogeneous emphysema, coils led to a gain of 10.3 metres[6]. These endoscopic trials, among other similar studies, are all randomised and of high quality. Some results should be interpreted with caution in favour of the intervention due to collateral ventilation in valve treatment, and mixing and/or misinterpretation of emphysema morphology in the intervention groups.

On the other hand, the surgical community still refers to single-center trials from a time before and during the NETT. Nevertheless, improvement in $FEV^1$ are reported between

52% and 73% in patients with heterogeneous emphysema[7,8,9]. Comparison of surgical with endoscopic treatment by citing completely different trials is keen and almost impertinent. But LVRS does seem superior when the emphysema is heterogeneous and located in the upper-lobe, where similar results in this selected group have so far not been reproduced by endoscopic procedures. Homogeneous emphysema, however, may need a completely different approach, where evidence for surgical treatment is limited[10,11].

While the medical community in charge of emphysema patients agrees more and more about the importance of a multidisciplinary treatment board[12], each medical speciality still seems to defend its own treatment. A randomised controlled trial comparing LVRS with endoscopic (valve) treatment seems to be mandatory to guide future treatment. The content of this chapter aims to highlight the evidence and selection criteria in favour of LVRS, and when to avoid it.

## When is lung volume reduction indicated?

The typical patient with chronic obstructive pulmonary disease (COPD) and emphysema presents clinically with shortness of breath. They can only walk a limited distance, and other daily activities are impaired. They use their accessory respiratory muscles and rest on their arms. Many patients show the typical barrel-shaped thorax. The most important respiratory muscle is the diaphragm, which is flattened because of the emphysematous and hyperinflated lung (Figures 1&2).

The more flattened the diaphragmatic muscle fibres are, the less they adequately function [13,14]. The goal of volume reduction is to restore this emphysematous, hyperinflated lung to its "normal volume". A more dome-shaped diaphragm works better and results in improved lung function after volume reduction[15].

Quantitative measurements of hyperinflation are determined by body plethysmography, with residual volume (RV), total lung capacity (TLC) and their ratio (RV/TLC) the

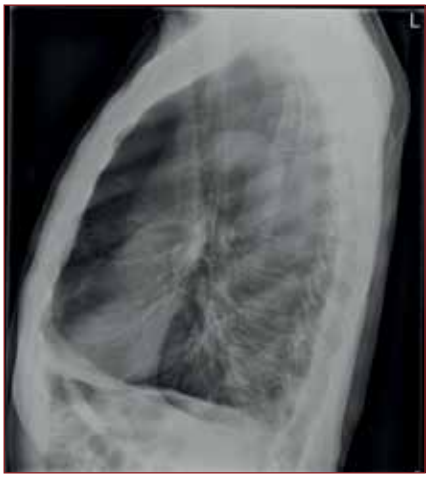

*Figure 1: Lateral chest X-ray of a patient with emphysema showing the typical flattened diaphragm together with the widened space in the anterior mediastinum.*

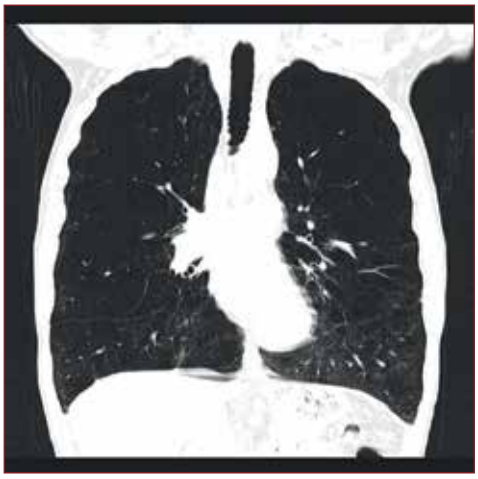

*Figure 2: Coronal CT scan in a patient with heterogeneous, upper-lobe predominant emphysema and flattened diaphragm.*

measurements used. The NETT defined as a result of their study possible responders as patients with a TLC higher than 100% predicted and RV higher than 150% predicted as inclusion criteria[1,16].

Sciurba and colleagues showed that RV higher than 225% predicted results with a far better benefit than lower preoperative values[6]. Patients with COPD, emphysema and dyspnoea with relatively low RV values might primarily suffer from heart diseases, pulmonary hypertension or other diseases and should not be selected for lung volume reduction.

Although several studies indicate possible widening of the classic NETT defined inclusion criteria for lung volume reduction (surgery), they might still be used as standard, especially for centres starting a new program[17]. Lung volume reduction surgery (LVRS) seems to work as well in different types of emphysema morphology[11], patients with alpha 1-antitrypsin deficiency[18], diffusion capacity values lower than 20% predicted[19], mild pulmonary hypertension[20] or as repeated procedure after successful previous surgical treatment[21]. The limited single-centre based experience in these borderline indications might reflect once more the key issue of lung volume reduction surgery: hyperinflation and preferably heterogeneous emphysema morphology.

## Heterogeneous or homogeneous - the importance of morphology

The best results following LVRS are obtained in patients with heterogeneous, upper-lobe predominant emphysema[2,7,8,9]. Lower-lobe predominant emphysema and segmentally distributed emphysema show good results as well, but do not have that much evidence[11,22]. One classification of emphysema distribution describes an "intermediately heterogeneous emphysema"[23]. This is a distinct regional difference in the severity of emphysema, with a maximum in the area of one or more, but not in adjacent lung segments of either lung. The markedly heterogeneous group (n=17) showed a mean increase in $FEV^1$ of 81%, compared with a mean increase of 44% for intermediately heterogeneous emphysema (n = 16)[23]. It is therefore justified to accept all types of heterogeneous morphology for LVRS - agreeing with our concept, of well planned and reserved resection of a destroyed area.

There is not much evidence available regarding LVRS in true homogeneous morphology, where emphysematous changes are evenly distributed throughout the entire lungs.

However, one study from Zurich showed good results[11]. While the 112 patients with heterogeneous emphysema showed a $FEV^1$ % predicted improvement of 61%, the homogeneous group (n=138) improved by 38%. However, the homogeneous group also included patients with the above mentioned intermediately heterogeneous emphysema. Nevertheless, well selected patients with homogeneous emphysema and severe hyperinflation might benefit from a bilateral upper-lobe "over the top" LVRS similar to a hockey-stick resection, like in upper-lobe predominant heterogeneity.

Marchetti and colleagues recently compared patients with homogeneous emphysema and LVRS from the NETT with patients from three recent randomised endoscopic coil treatment and medical therapy trials[10]. They found a slightly better result for coil patients regarding increase in $FEV^1$, benefit durability and survival. Despite their careful matching of patients, the authors point out the difficulties of this comparison between surgical cases from 1998 to 2003 and the endoscopic treatment in these newer studies. However, while careful patient selection may lead to a benefit after LVRS in patients with homogeneous emphysema, the endoscopic treatment has greater evidence so far and might be a valuable, or even better option in these patients.

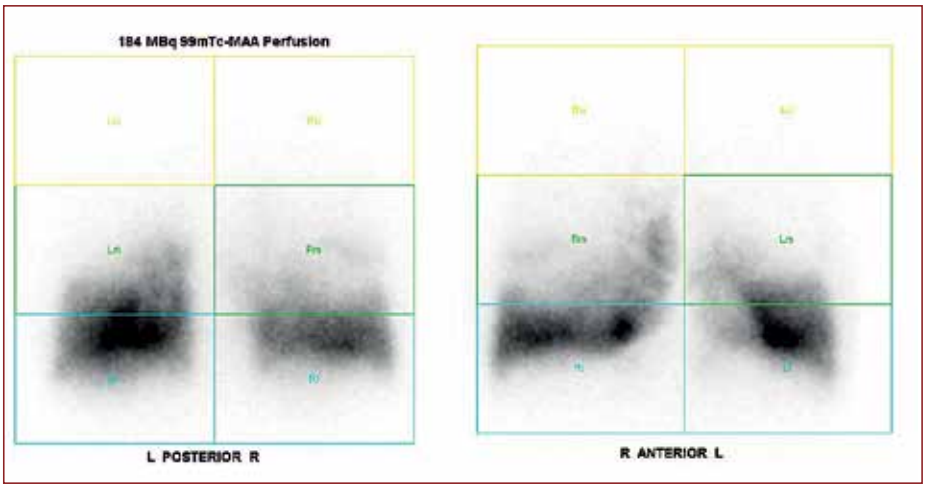


*Figure 3: Perfusion scintigraphy in a patient with heterogeneous, upper-lobe predominant emphysema (L & R Anterior)*

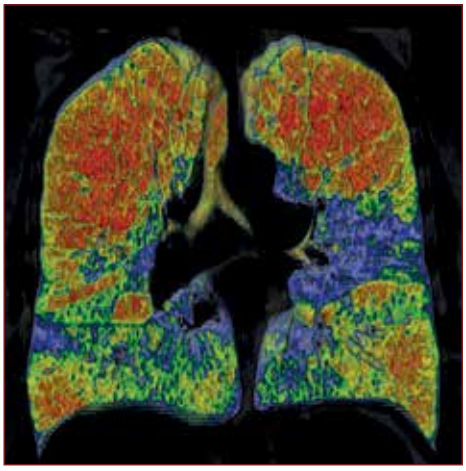

*Figure 4: Coronal CT scan with densitometry in a patient with heterogeneous, upper-lobe predominant emphysema. The red color indicates areas with less ventilation.*

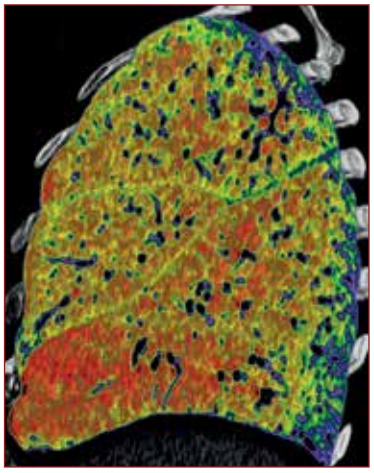

*Figure 5: Sagittal CT scan with densitometry in a patient with heterogeneous emphysema. The anterior basal part of the right lower lobe is identified as target area.*

Preoperative assessment of emphysema morphology is therefore a key issue in LVRS. This is mainly done be evaluating computer tomography (CT) scans using specifically developed software to delineate air from tissue.

One study found that functional improvement after LVRS was more closely correlated with preoperative hyperinflation and the degree of emphysema heterogeneity estimated by chest CT compared with the degree of perfusion heterogeneity assessed by scintigraphy [24]. Nevertheless, the perfusion scintigraphy may help to identify the correct target areas for resection. Recently introduced colour-coded so called densitometry CT images may also help in preoperative planning[25] (Figures 3, 4 & 5).

## Mortality and morbidity after lung volume reduction

Discussion about mortality following LVRS always lead to the results from the NETT[10]. In this trial the high-risk group with FEV1 lower than 20% combined with homogeneous emphysema or diffusion capacity lower than 20% had a postoperative 30 day mortality of 16%[3]. The surgical group of all other patients had a 90 day mortality of 5.2%[1]. Ciccone and colleagues showed a mortality of 4.8% in their patients with heterogeneous emphysema[8]. Weder and colleagues published a 90 day mortality of 3.6% in all types of morphology (n=250)[11]. The same authors showed a 90 day mortality of 2.4% in another 212 patients [9]. Waller and colleagues in a series of 265 patients with heterogeneous emphysema had a 30 day mortality of 3%[12]. Ginsburg published the New York LVRS programme since the NETT and showed no mortality 6 months after LVRS in 91 patients[26]. Mortality doesn't seem to be a good argument against LVRS any more - as long as patient selection is strict and multi-disciplinary.

Nevertheless, postoperative morbidity is still an important issue and involves mainly prolonged air leak. Ciccone reported a 45.2% rate of prolonged air leak (> 7 days) with a revision rate of 3%[8] and Ginsburg 57% with the same revision rate[26]. The Zurich patients showed a rate of 35%[9,11,27], but got revision surgery in 10%. Other postoperative complications are relatively low, pneumonia for example can be expected in about 4%[26].

Due to the desired atelectasis of the target lobe after endoscopic valve therapy, postinterventional pneumothorax is relatively common and has an incidence between 20 and 30%[28]. It is worth mentioning that about 70% of these pneumothorax patients show a prolonged air leak as well[29].

Again, narrative comparison of completely different retrospective data is overzealous. But mortality rates after LVRS have become lower and lower and more or less high morbidity rates constitute mostly of air leaks which are also seen after endoscopic treatment. Therefore, LVRS should still be a main treatment option for emphysema patients, despite lacking multi-centre randomised evidence since the NETT.

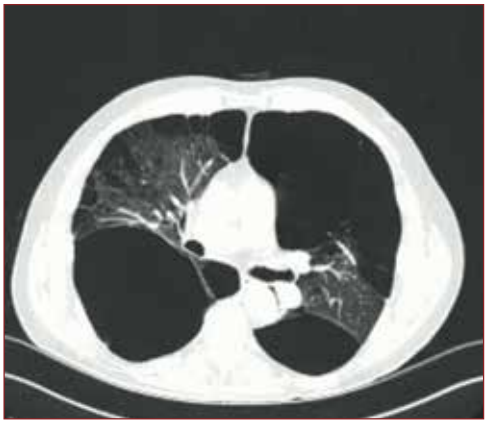

*Figure 6: Axial CT scan in a 43 year old patient with bilateral bullous emphysema.*

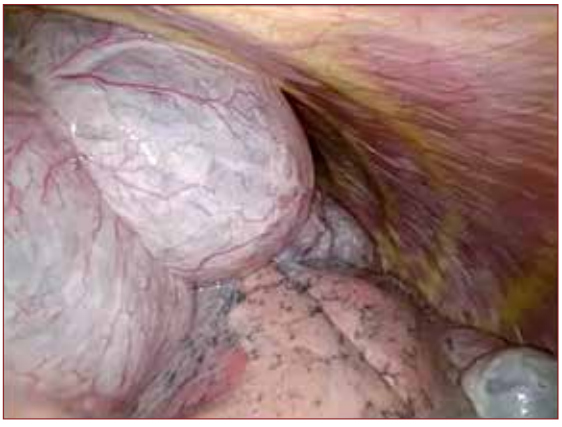

*Figure 7: Intraoperative view on the left side of the same patient as in Figure 6.*

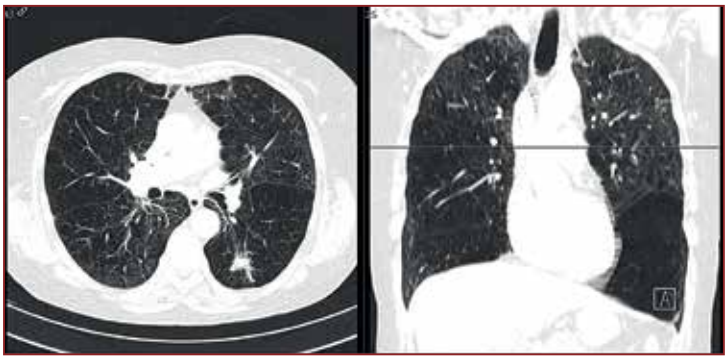

*Figure 8: 78 years old female patient with proven non-small cell lung cancer in the left 6th segment (left figure), heterogeneous lower lobe predominant emphysema and severe hyperinflation. Preoperative FEV¹ was 40% predicted, diffusion capacity 14 % predicted and RV/TLC ratio 63.*

## Surgery and only surgery

Emphysema appearing as giant bullae is probably at no multi-disciplinary board worth the discussion about surgical versus endoscopic treatment (Figures 6 & 7). This type of emphysema is a clear indication for surgery and the target areas are more than obvious.

Patients with concomitant lung cancer or a suspicious nodule might also be considered for LVRS. Most guidelines recommend radiotherapy as primary local therapy for inoperable patients with non-small cell lung cancer due to high mortality and morbidity rates after anatomical resection in patients with severely impaired lung function[30,31,32,33]. Nevertheless, a small proportion of patients with T1-T2 lung cancer (or suspected lung cancer), present with heterogeneous emphysema with hyperinflation (Figure 8). They can profit from (wedge-) resection with its histological advantage and from the lung volume reduction effect[34]. Endoscopic treatment is usually not recommended in case of (suspicion of) concomitant cancer[35]. The surgical evidence so far concerns only a few studies and patients are highly selected. In times of increasing importance of (molecular) histology and the possibility of improved lung function after surgery, the thoracic surgeon participating at a multidisciplinary tumour board might consider a few tumour patients with emphysema as potential surgical candidates.

A left sided thoracosopic segment 6 resection with concomitant lower lobe LVRS was performed. Three months after surgery the FEV1 was 48% predicted and diffusion capacity improved to 18% predicted.

## Heterogeneous emphysema: the clash of the titans

In the largest study of endobronchial valves in 331 patients with heterogeneous emphysema, a subgroup analysis of the potentially ideal valve candidates was performed: 60 patients had complete interlobar fissures and with CT confirmed successful lobar collapse 6 months after procedure was confirmed. They showed the best results and had a 20.6% mean improvement in FEV1%[4]. Eberhardt and colleagues compared the results of patients with upper-lobe predominant and lower-lobe predominant emphysema and found equal benefit[36].

The above mentioned LVRS studies concerning heterogeneous upper-lobe predominant emphysema patients show mean improvements up to 80%. While endobronchial valve therapy only can exclude whole lobes, LVRS can be tailored. Most upper-lobe emphysema

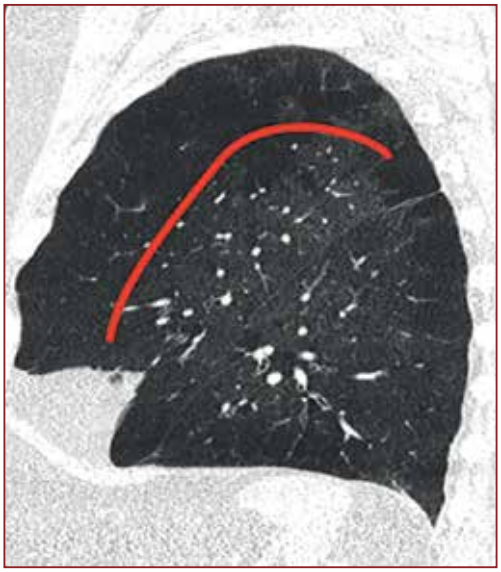

*Figure 9: Sagital CT scan in a patient with heterogeneous, upper-lobe predominant emphysema. The red line shows the potential resection line on the left side, preserving the central lung tissue with better quality.*

patients show parts of better quality lung tissue in their target lobes, which can be spared by careful surgical resection (Figure 9).

The same is true for most other, non-upper-lobe predominant emphysema morphologies. This could - until proven otherwise - be considered an important advantage. Simultaneously, LVRS can be offered bilaterally, although there is no good evidence to support the argument for either staged over bilateral LVRS[37,38]. There are multiple, recent and well-designed randomised trials comparing endobronchial valve treatment with medical treatment. They show a clear benefit of endobronchial valve therapy in heteregeneous emphysema over medical management alone. The functional results of LVRS are older, rarely randomised and therefore about to be called old-fashioned. Nevertheless, they seem to be better.

## Conclusion

Industry-, hospital-, country- as well as specialist-driven decisions at a multidisciplinary treatment board regarding the management of the emphysema patient are current practice. Patients with heterogeneous emphysema, bullous disease and concomitant nodules will benefit from surgery. So long as there is no randomised trial directly comparing LVRS versus endoscopic treatment, the board may decide to the best of their knowledge and belief and act based on the local experience.

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SECTION 2 THORACIC SURGERY

# Neuroendocrine Tumours

*"Sic itur ad astra"*

*Publius Vergilius Maro. 70 - 19 BC.*

Chapter 10

# Need for Specific Strategy for Management of Thoracic Neuroendocrine Tumours

*Hema Venkataraman, Stacey Smith, Maninder Kalkat, Tahir Shah*

*"Semper ad meliora"*

## Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of malignancies that originate from neuroendocrine cells throughout the body, most commonly from the lungs and gastrointestinal tract[1]. Their behaviour is complex, and their management is significantly different to other cancers as medical therapy and surgery requires careful consideration to maximise benefit and minimise harm, given their slow growth and significantly higher survival rates[2]. Additionally, chemotherapy is only effective in limited scenarios.

Recent data from the from Public Health England (PHE) National Cancer Registration and Analysis Service database reports the age-standardised incidence rate for NETs was 8.6/100,000 in 2015, increasing from 3.1/100,000 in 2001. The most common primary tumour sites for NETs were 20.2% colorectal, 19.5% lung, 14.1% small intestinal, 9.6% pancreatic, 6.9% skin, and 5.3% stomach, with overall 1 year survival probability of 74%[2].

Since the first European Neuroendocrine Tumour Society (ENETS) consensus conference in 2007[3], the landscape for management of NETs and process of standardisation has evolved significantly, with special focus on the NETs of gastrointestinal and pancreatic origin (GEP NETs). This has been driven by enthusiastic experts in Europe working through UK and European Neuroendocrine Tumour Societies to develop a robust auditing and licensing system for designating Centres of Excellence (CoE). The collaborative nature of NHS services has facilitated the centralisation of GEP NETs patients at ENETS certified CoE, of which there are presently 13 in UK. This is the largest number of ENETS certified centres of any nation globally and a tremendous base for delivering co-ordinated care for whole of UK, providing quality services, trials and research.

Lung NETs represent approximately 25% of all primary pulmonary neoplasms[4] and about 20-25% of all NETs[1,5]. The 2015 World Health Organization (WHO) classification divided lung NETs into four different groups based on biological behavior. These are low-grade typical carcinoid (TC), intermediate grade atypical carcinoid (AC), high-grade large-cell neuroendocrine carcinoma (LCNC) and small-cell lung cancer (SCLC)[6]. The term bronchial carcinoids (BCs) encompasses TC and AC, which are well differentiated NETs with unique clinico-pathological traits that differentiate them from the poorly differentiated NETs (LCNEC and SCLC) and account for only 1-2% of all lung neoplasms[4].

About 85% of BC are located centrally in the major or lobar bronchi and rest are peripheral, in the lung parenchyma[7]. The majority of centrally located tumours present with cough, haemoptysis, shortness of breath and other obstructive symptoms, while the peripheral BC mostly present as incidentally discovered lung masses[7,8]. The carcinoid syndrome is rare in patients with BC and seen in 10% of patients even in the absence of liver metastases[9]. Their medical management is similar to, though more challenging than, GEP NETs.

The centrally located tumours are amenable to bronchoscopy assisted examination and biopsy sampling in order to establish a histological diagnosis. Since, these patients are at high risk of bleeding rigid bronchoscopy is often recommended. A CT-guided biopsy for the peripheral placed lesion can be attempted, but tissue yield may not be enough to differentiate between TC and AC. The histological diagnosis for the patients referred for surgery is often not present in about a half of the patients.

## Challenges in management of BCs

### Key role of NET CoE and their relationship with thoracic surgeons in UK

Most BCs that are discovered early, have ‘essentially’ curative surgery. In particular, patients treated in the later part of adult life can be expected to have near normal life expectancy, given the very slow growing nature of BC and therefore very low lifetime risk of recurrence and/or clinically significant progression.

Historically, this left only a limited number of BC patients with unresectable and/or metastatic disease who would then have been referred to a NET team for medical management. The surgically ‘cured’ patients are either followed up in Thoracic Centres or referred back to the base hospitals.

Unless the regional NET CoE has built strong links with the Thoracic Centres patients with BC do not get access to specialist care in the NET CoE. Thereby these patients are denied access to the multi-disciplinary team delivered NET service, advanced imaging and advanced therapies, dedicated NET education, clinical trials and research. The general lack of engagement between the Thoracic and NET CoE means that patients with BC are at a significant disadvantage in comparison to those with GEP NETs.

Clinical trial evidence for the management of BC is limited and still evolving when compared to GEP NETs, where there are established therapies backed by large clinical trials. For instance, in the UK, National Institute of Clinical Excellence (NICE) approved peptide receptor-targeted radionuclide therapy (PRRT), a highly effective therapy in somatostatin receptor positive metastatic GEP NETs. However, NICE did not approve PRRT for BC as current evidence only exists for GEP NETs[10,11]. We are therefore limited to older treatments that have been historically available for GEP NETs. These treatments include, somatostatin analogues (SSA) (octreotide and lanreotide), interferon and chemotherapy.

Again, the largest trials in SSA did not include BC[12,13]. Everolimus is the only agent that has shown efficacy in BCs and GEP NETs in phase III clinical trials[14] and has been approved by NICE for treatment of BC.

NET Centres of Excellence have expertise gained from managing large groups of GEP NET patients. Although, the behaviour of BCs is not always similar to that of GEP NETs, on the whole the same principles can be applied in terms of investigations and treatment choices. For instance, somatostatin analogues used in GEP NETs have been backed by large clinical trials e.g. PROMID and CLARINET trials[12,13].

Although BC patients were not included in the clinical trials of somatostatin analogues, they have been frequently used in BC with somatostatin receptor expression as determined by octreotide scan or 68Ga-DOTATATE PET scan. Interferon is used only occasionally now in GEP NETs but has also been used in BC.

Clinicians are able to prescribe SSA and Interferon therapies in BCs due to historical use of these agents predating the demand for strong evidence base for prescribing anti-cancer treatments.

Although there are no clinical trials to back liver resection or trans-arterial embolisation in BC, these treatments can be useful for debulking the tumour and help with symptom control, applying the same principles as in GEP NETs[15,16].

All clinical trials in NETs have taken place through NET Centres of Excellence. The lack of centralisation of BCs has meant that only a limited number of these patients have been recruited in to NET clinical trials, usually together with GEP NETs. When there have been attempts at recruiting patients for pure BC trials these have usually failed, discouraging further research and limiting treatment options for BCs, the SPINET study being the latest example[17]. There is in fact now reluctance for drug companies to consider new trials in BC patients. There is, therefore, an urgent need for better collaboration between the Thoracic and NET Centres to make way for better treatments for BCs as the lack of a unified service platform impedes research and therefore patient care in this area.

## Challenges in Surgery

There is expected variation in practice within and between thoracic centres but more importantly the Thoracic Teams are less aware of innovations in staging and management of NETs. Although the NET Teams are abreast of the latest modes of managing these cancers, only a few of the NET CoE in the UK have strong affiliations with their neighbouring Thoracic Centres. This can mean that BC patients miss useful staging investigations such as 68Ga-DOTATATE PET scans and tumour markers that can be crucial in deciding future treatment pathways.

Preoperative histological diagnosis of the lesion in the lung is available in about half of the patients across the country[8], although again variation exists. Even in patients with confirmation of BC, the work-up is aligned with routine primary lung cancer, including FDG PET, rather than NET-specific staging. There is therefore a need to enhance pre-operative histological diagnosis and standardise staging for BCs.

All GEP NET patients with potential for surgery have a computed tomography (CT) scan of thorax, abdomen and pelvis (TAP) together with magnetic resonance imaging (MRI) of the liver and 68Ga-DOTATATE PET scans to accurately stage the cancer. Similar staging protocols are required in confirmed or suspected cases of bronchial carcinoids.

## The need for accurate information giving

Patients with BC are usually referred by respiratory physicians or a General Practitioner to the thoracic surgeons following incidental discovery of a lung nodule, often bypassing the NET team. Patients can have a limited understanding of diagnosis and prognosis. Often, they are wrongly informed that they do not have a cancer or that they have been cured of cancer after surgery. This can be particularly problematic in very young patients who may get recurrence or develop a new NET 10 or 20 years down the line.

The NET Centres can address unmet needs of NET patients by providing access to a team of NET experts and support staff. The NET CoE have active links to patient support charities such as the NET Patient Foundation (NPF) that can help offer patient information, patient education events, patient support groups and key information that aids patient confidence and well-being. Patient education regarding prognosis, management and signposting plays a significant role in patient satisfaction and well-being.

## Development of specialist BC services through ENETS CoE

The ENETS certified CoE have the expertise and infrastructure for management of NET patients. The existence of an already established MDT setting in the NET CoE can help support and oversee patient pathway from diagnosis, risk stratification, to treatment and life-long surveillance. Multidisciplinary care in cancer is known to be associated with improvements in diagnosis, treatment planning, survival, patient satisfaction, clinician satisfaction, and financial efficiency[18].

The ENETS Centres of Excellence have excellent links with the surgical, gastroenterology and oncology teams in their catchment domains that allow for early and efficient referrals. The Centres manage the patients either directly or may provide advice and assistance for local care. Examples would include confirming diagnosis and extent of disease by review of histology and imaging, performing baseline investigations and full staging before handing patients back to the referring team for surgery. The CoE can also provide specialist surgery, such as on the liver, and specialist therapies such as PRRT.

Most ENETS Centres of Excellence do not have strong links with Centres performing Thoracic surgery. A link up between the two specialisms should lead to a comprehensive service for these patients and development of new patient management pathways. For instance, when the diagnosis of BC is confirmed, or strongly suspected, the ENET Centres could arrange baseline investigations including specialist staging scans, biobank blood and tissue for research, educate patients early about the diagnosis and be involved in making decisions on management, including surgery, given their understanding of prognosis with medical therapies. An example would be a 75-year-old female with limited but node positive disease having extensive surgery with removal of 2 lung lobes and being left severely breathless with reduced quality of life. Such a person could be counselled about prognosis with medical treatment as well as surgery and be allowed to make an informed choice.

ENETS began with developing standards and guidelines for management of GEP NETs only[19]. There is now a growing desire for ENETS to encourage the NET CoE to take on BCs also. This is likely to be formalised in the near future such that management guidelines will be written, and standards set for auditing the ENETS certified Centres of Excellence. Such moves will likely drive better collaboration between Thoracic Centres and ENETS certified NET Centres.

In the United Kingdom, members of the NET community have been working with Thoracic Surgeons through the Society of Cardiothoracic Surgeons (SCTS) to achieve consensus for evolving specialist services for BC patients. This is raising awareness of the issue amongst the relevant experts and the two responsible societies in UK; SCTS and UKINETS (UK and Ireland Neuroendocrine Tumour Society). UKINETS is working with the relevant experts to issue guidance on essential management of BCs. It will soon publish 'Bite-size Guidance' on its website. Additionally, the West Midlands Cancer Alliance has agreed to the setting up of a NET Expert Advisory Group in order to draw up guidance on referrals and management of NETs, including BCs. It is the only stand-alone NET EAG in England and its advice is likely to be adopted by other regions in the UK.

In summary, there has been rapid evolution of expert services for NET patients in UK and Europe driven by expert teams and strongly encouraged by the audit and licensing process of ENETS. The certified centres of excellence have to meet very high minimum standards. With the UK having 13 such Centres of Excellence and other smaller centres affiliated with them we are at the forefront of high-quality service delivery, especially for GEP NET patients. It is now time for the UK to lead the way in setting high standards and developing quality services for BCs also.

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Chapter 11

# Neuroendocrine Neoplasms (NENS): Incidence, Diagnosis and Follow-up

*Nicholas Reed*

*"Memento audere semper"*

## Introduction

Traditionally bronchial neuroendocrine neoplasms (NEN) consist of 3 principal subtypes[1-4] namely typical bronchial carcinoids (TC), atypical bronchial carcinoids (AC) and large cell neuroendocrine carcinomas (NLCEC). A variety of terms are used in the literature including lung, bronchial, broncho-pulmonary or pulmonary NENs, furthermore the term NEN is increasingly adopted to embrace the NETs and NECs as discussed later in this paragraph[4,5]. Small cell lung cancers (SCLC) are normally considered as part of the lung cancer family and are usually treated oncologically. There are areas of overlap such as mixed large cell and small cell tumours and more recently there are patients with extra-pulmonary NENS who have tumours grade 3 histologically but where the Ki-67 is less than 55%; these other neuroendocrine tumours are now referred to as G3 neuroendocrine tumour (NET) whereas those with higher Ki-67 are called G3 neuroendocrine carcinomas (G3NEC). It is anticipated that this terminology will change with the next edition of the WHO Blue book to bring broncho-pulmonary NENs in line with extra-pulmonary tumours[4]. Their clinical behaviour is different and more favourable and they are more likely to express somatostatin receptor scintigraphy. A recent review article has addressed the unmet needs in broncho-pulmonary NETs[5].

## Incidence

Bronchial neuroendocrine tumours account for approximately 20-30% of all NEN. However, when focusing on lung neoplasms they account for about 5% of all lung neoplasms (if we exclude small cell lung carcinomas from the NEN family of neoplasms). Around 3% are large cell neuroendocrine carcinomas (LCNEC) and 2% typical carcinoids and less than 1% atypical carcinoids[6-7]. Their survival is determined by histological subtype, nodal status,

grade of tumour and increasingly including ki-67 index. Although until recently it has not been the standard of care to count Ki-67, but scoring is now strongly recommended in all NENs. Survival data on follow up nicely demonstrate the importance of distinguishing between TC and AC[1-3,8] and demonstrates a clear separation of survival between typical and atypical tumours and a further gap survival between these and LCNEC and SCLC which behave equally.

The incidence of broncho-pulmonary NENs is slowly rising, as applies to all NEN[9,10]. Some of this is attributed to better recognition and registration, but also due to incidental pick-up on imaging for other indications. A significant proportion of patients discussed at the tumour board/MDT will be as a result of chance findings on imaging or screening. The improved training and sub-specialisation by histopathologists has also had a significant impact with better identification and recognition of NEN using appropriate immunocytochemistry techniques. The next big breakthrough will be wider application of next generation sequence in molecular profiling. This is still very much in early stages in bronchial NEN.

## Pathology

The traditional pathology subdivided tumours into low-grade tumours such as typical and atypical carcinoids, and high-grade tumour such as large cell neuroendocrine and small cell carcinoma. There are well-established authoritative papers describing classical histology subtyping[1-4]. This is at variance from the formal histo-typing of extra-pulmonary NEN. The WHO is expected to modify this for the next edition and exclude small cell lung cancer. Large cell neuroendocrine carcinoma, (G3 NEC) will also be subdivided depending upon the Ki-67. When less than 55% it is anticipated that these will be called G3 NET because of their different clinical and biological behaviour and more favourable outcome. This will be covered by a separate chapter but different chemotherapy regimens may be used and G3 NET may have clinical benefit from radionuclide therapy. A separate subgroup has been identified and called diffuse interstitial pulmonary neuroendocrine cell hyperplasia (DIPNECH). By definition these are usually tumourlets, i.e. less than 1 cm and may be multiple[11]. It is now suggested these may account for up to 10% of bronchial NEN.

## Causation

For the majority of patients at present the causation is unknown, although smoking may play a role. Between 5 and 15% may be associated with MEN 1 syndrome[12,13]. Rarely tumours may also produce Cushing's syndrome[14,15]. Molecular markers have been identified in large cell neuroendocrine carcinoma and may give clues to help in treatment selection as there appears to be some differential response to chemotherapy[16-18]. Similarly there has been recent work from the Manchester and Dutch groups who have identified three different clusters of disease patterns[19-20]. These are very rapidly changing areas and this article will almost certainly be out of date in this respect by the time it gets to the printers!

## Presentation

At least 10-30% of bronchial NENs are asymptomatic and an incidental finding on imaging. These tend to be peripheral lesions. These issues are well reviewed in consensus papers [5,21]. The more recent widespread use of FDG PET has also led to picking up asymptomatic solitary lung nodules. The most common presentation is persistent cough and repeated chest infections. Some tumours will cause haemoptysis, chest pain, or shortness of breath.

Systemic symptoms are uncommon and carcinoid syndrome occurs in less than 10% of patients and is rare at presentation. Up to 5% may present with features of Cushing syndrome due to ectopic ACTH secretion, or even rarer, acromegaly due to ectopic growth hormone secretion[14,15]. It has been suggested that thymic carcinoids may be more likely to have a syndromic presentations.

There is a difference between central and peripheral tumours in their mode of presentation. Around 10% will arise centrally or in main bronchi, around 75% in lobar bronchi and 15% peripherally. Some series have reported that up to 10% may have multiple tumour nodules associated with DIPNECH[11].

Central tumours are more commonly typical carcinoids that present with obstructive symptoms due to tumour mass such as cough, haemoptysis, wheezing, dyspnoea, chest pain and pneumoni. Peripheral tumours are more commonly asymptomatic. Hoersch in the German consensus paper in 2011 nicely summarises difference in presentation[22]. The Manchester and Amsterdam groups have investigated ortheobox homeoprotein and demonstrated different clusters of behaviour[19,20]. This may have potential to assist with treatment planning.

The tumour sample size may be very crucial to making the diagnosis. Quite commonly a small fragment is obtained at bronchoscopy and the pathologist is expected to make a definitive diagnosis working on very small material. It is now recognised that the addition of reporting the Ki-67 may be helpful in discriminating between high-grade (G3 NEC) and intermediate grade tumours. For example the patient may have been diagnosed with a small cell lung cancer based on morphology but when the Ki-67 score is incorporated and comes back at less than 55%, this will indicate a differently behaving tumour with a different outlook. Retrospective review of "longer surviving" cases may show that they have lower Ki-67 and thus fall into lower risk categories, where Ki-67 was not done routinely at time of diagnosis.

## Investigation and tumour markers

Apart from the standard haematological and routine biochemical investigation there are some tumour markers that should be measured. Specialist markers include chromogranin A and B, and neurone specific enolase (NSE) especially for G3 NEC. Urine 5 HIAA collection is of limited value as carcinoid syndrome is unusual. Other markers that may be measured include alpha-fetoprotein, beta-hCG, CEA and a "full gut hormone profile" which will include a range of neuropeptides. These may not be useful at time of diagnosis but may be of value for serial monitoring on follow-up[5,18,21,22].

## Imaging

A chest radiograph may still have a role to play as the initial test, but increasingly patients will go straight to CT. It has already been mentioned that a significant proportion will be picked up incidentally on imaging for other purposes. The dilemma is whether to arrange a biopsy before proceeding to other imaging to save inappropriate investigation and keep within waiting time targets. The assumption will be commonly made that this is a bronchogenic carcinoma and so an FDG PET scan will be carried out. Ironically quite a high proportion of bronchial NEN will be positive but arguably somatostatin receptor scintigraphy with gallium dotatate PET, or Octreoscan 111In or technetium labelled Tektrotyd will give better quality information particularly in lower grade tumours. Gallium PET scanning is still not

universally available but is the preferred choice. Given that bronchial NENs are uncommon it is likely that the former process will be followed and patients may finish up getting both FDG PET and somatostatin receptor imaging. The purpose of these investigations is multiple, not only to provide staging investigations prior to surgical decision making, but also to look for functionality with somatostatin receptors which informs decision making on treatment with somatostatin analogues or radionuclide therapy and prognosis[5,18,22,23,24].

## Guidelines

There are now many guidelines that have been published from recognised National and International groups including ENETs and NCCN, together with some review articles, from specialists working in recognised centres. Whilst the UKINTS produced the first authoritative NETs guideline, it has been superseded by the ENETS guidelines which are now used throughout Europe[5,18,21,25].

## Molecular profiling and Genomics

The most exciting development for the future will be genomics. Not only will this help to differentiate the clinical behaviour of different tumour types but it may also help the identification of the optimal treatment. Furthermore, with the rapid expansion of targeted treatments, new drugs will be developed specifically for clusters of patient who share similar molecular characteristics. There are many examples in other tumour types, and it has been slow to come about in NENs[16-20]. Everolimus is a mTOR (mammalian Target of rapamycin) pathway inhibitor which has been approved for use in bronchial NET based on the evidence from the RADIANT-4 clinical trial[25,26]. There is now emerging evidence that some tumours do show loss of pTEN and changes in the mTOR pathway but this does not affect all, which may explain why selected patients will benefit from drugs like everolimus. Future testing will identify those most likely to benefit, and thus avoid wasteful ineffective prescribing. We are still very much at the beginning of the journey of understanding targeted agents and "precision or stratified" medicine and their molecular pathways. The next 5-10 years will see dramatic change in management with personalised therapy becoming the standard. Costs for Next Generation Sequencing (NGS) are plummeting and will soon be affordable. It is beyond the scope of this chapter to go into further detail.

## Patterns of Relapse

The clinical behaviour for typical, atypical and large cell neuroendocrine carcinoma is very different. This had been shown by many studies in Europe, North America and the Far East. Typical bronchial carcinoids with low risk features carry an excellent prognosis with fewer than 5% relapsing, whereas the opposite pattern is seen in LCNEC where survival beyond 18 months is unusual, especially in patients presenting with stage IV disease. Early development of brain metastasis is commonly seen in LCNEC and may even be seen at time of diagnosis. Even when patients have a good response to initial chemotherapy, relapse occurring 3-6 months after recent treatment is common, and responses to second line treatment are infrequent. In the minority where there is a longer treatment free interval a better response may be seen. In those who remain alive 3 years after treatment without relapse, it would be useful to review the initial pathology as many of these will turn out to have less aggressive tumours such as AC with a higher Ki-67, and would have been labelled as G3 NET at other sites, ie a G3 tumour but with a Ki-67 between 20 and 55%.

Atypical bronchial carcinoids fall in between, with around a 70% survival at 10 years. The usual risk factors such as resection margin, lymph node status and lymphovascular space invasion will influence outcome. For both typical and atypical carcinoid there may be a pattern of delayed or late relapse occurring more commonly between 5 and 10 years after diagnosis, hence the need for prolonged follow-up. Some guidelines suggest lifelong follow-up, but a reasonable compromise is to discharge patients at 10 years if there has been no evidence of recurrence[5,18,22,27].

## Follow up

There are no precise follow-up guidelines. It should obviously be a combination of clinical assessment, radiological imaging, tumour markers and, more controversially, bronchoscopic assessment. The author's personal view is to recommend annual assessment for typical bronchial carcinoids with low risk factors for up to 10 years. Some form of annual imaging is recommended, currently most usually CT scan of chest, abdomen and pelvis. There may be a place for somatostatin receptor scintigraphy and this may become more frequent as gallium PET becomes more widely available. In addition to clinical examination, measurement of chromogranin A (and B) is advised, with NSE in higher grade tumours. If patients have more worrying symptoms specialist investigations including Octreoscan or gallium PET are advised. When there is a significant interval between primary diagnosis and relapse, strong consideration be given to re-biopsy so that the grade and Ki-67 can be reassessed[5,18,19,22,27] as tumours may evolve to higher grade over time.

For node positive bronchial typical carcinoid and all atypical, a more frequent policy of review is instigated in the first 5 years with 6 monthly visits to check tumour markers and annual scanning, or more frequent if clinically indicated. After 5 years conversion to annual review can be recommended for up to 10 years. The author does not recommend routine use of urine 5 HIAA testing but this can be done if there is suspected recurrence. The introduction of plasma 5 HIAA may change the guidance in time. Carcinoid syndrome is relatively rare with bronchial carcinoids.

The rare patients with Cushing syndrome or acromegaly will require specific monitoring of cortisol, ACTH and growth hormone. This is often best done in conjunction with endocrinology.

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Chapter 12

# Surgical management of pulmonary neuroendocrine tumours

*Helen Weaver, Florentina Popescu, Metesh N Acharya, Sridhar Rathinam*

*"At astra per aspera"*

## Introduction

Pulmonary neuroendocrine tumours (NETs) are a rare group of pulmonary neoplasms that are often characterised by indolent clinical behaviour[1]. They encompass a spectrum of disease from typical carcinoid (TC) tumours to atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNC) and small cell lung cancer (SCLC)[2,3]. Lung NETs are believed to originate from peptide and amine-producing neuroendocrine cells. NETs can arise at a number of sites throughout the body, including the thymus, lung, gastrointestinal (GI) tract, and ovary. The lung is the second most common involved site for NETs after the GI tract[4].

The behaviour, management and prognosis of SCLC is very different from other neuroendocrine tumours and so these malignancies are often discussed separately and will not be included in the 'pulmonary NETs' discussed in this article.

As with other primary lung cancers, surgical resection is advocated for the majority of pulmonary NETs, provided the patient is fit enough to undergo anatomical lung resection and there is no evidence of disseminated malignancy[5,6]. There is little consensus between key international groups on the duration and modality of post-operative follow up for these patients[1,7,8]. This is largely because NETs are generally slow-growing, and whilst any recurrences tend to occur within a couple of years, there is evidence that delayed recurrence may occur even after several years[9,10].

This article discusses the current opinions on peri-operative care, techniques for surgical resection and ongoing follow up of patients with pulmonary neuroendocrine tumours.

## Neuroendocrine tumours (NET)

Pulmonary NETs are characterised by strikingly heterogeneous pathological features and clinical behaviour[11]. The typical carcinoids, which are well-differentiated, low-grade, slowly growing, neoplasms that seldom metastasise to extra thoracic structures, are at one end of the spectrum. At the other end are the poorly differentiated and high-grade neuroendocrine carcinomas, as typified by small cell lung cancer, which behaves aggressively, with rapid tumour growth and early distant dissemination. The biological behaviour of 'atypical' NETs, which are of intermediate grade and differentiation, is on a spectrum between that of low-grade NETs and small cell lung cancer[12]. Approximately 6% of primary lung cancers diagnosed each year in the UK are NETs (~2% TC, ~1% AC and ~3% LCNC)[13].

Multifocal disease is relatively common in patients with low-grade lung NETs. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), is a condition characterised by diffuse hyperplasia of pulmonary neuroendocrine cells and formation of multiple tumourlets and invasive NETs[14].

## Classification

In 2015, the World Health Organization (WHO) classified pulmonary NETs into four histologically distinct variants: typical carcinoids (TC), atypical carcinoids (AC), large cell neuroendocrine carcinoma (LCNC) and small cell lung carcinoma (SCLC)[2]. This classification is based on histopathological features, including cell size, morphological features, mitotic index, architectural growth patterns and the presence of necrosis. Prior to this, the 2004 WHO classification grouped carcinoid tumours separately from LCNC and SCLC[15].

The two key characteristics used to differentiate between pulmonary NET subtypes are the number of mitoses per 2 $mm^2$ of viable tumour, and the presence or absence of necrosis. Expression of Ki-67 antigen, a cellular marker for proliferation, is an additional important immunohistochemical feature included in the recent WHO classification, allowing pulmonary carcinoid tumours to be discriminated from SCLCs. The various characteristic differences are summarised in Table 1.

*Table 1: Classification of pulmonary NETs according to histological features.*

| | Typical Carcinoid (TC) | Atypical Carcinoid (AC) | Large Cell Neuroendocrine Carcinoma (LCNC) | Small Cell Lung Carcinoma (SCLC) |
|---|---|---|---|---|
| Cell Size | Large | Large | Large | Small |
| Cytoplasm | Abundant | Abundant | Abundant | Q |
| Organoid Pattern | Characteristic | Characteristic | Less extensive | Absent |
| Prominent Nucleoli | No | No | Yes | No |
| Mitotic Count per 2 $mm^2$ | <2 | 2-10 | >10 | >10 |
| Necrosis | Absent | Absent or punctate | Extensive | Extensive |
| Ki-67 Proliferation Index | ≤5% | ≤5% | 50-100% | 25-50% |

Microscopically, carcinoid tumours may be mistaken for SCLCs, however the lower Ki-67 proliferation compared to higher-grade NETs enables confirmation of the carcinoid diagnosis[16,17]. The overlap in the distribution of the Ki-67 labelling index between TCs and ACs does not permit reliable differentiation between these tumour subtypes[1,2,15,18]. LCNC patterns may be identified by immunohistochemistry using chromogranin, CD56 or synaptophysin antibodies, although this is difficult with small biopsies or cytology[2]. Surgical lung biopsy is therefore necessary to achieve a diagnosis of LCNC.

## Grading

Pulmonary NETs are stratified as low-grade (TCs), intermediate-grade (ACs) or high-grade (LCNCs, SCLCs) for prognostic stratification and to determine the optimal choice of therapeutic modality. Proliferative index with Ki-67 labelling is currently not used as part of tumour grading, owing to variably reported cut-off values and difficulties with measurement and reproducibility, despite its being demonstrated as a significant prognostic factor[1,2].

## Staging

Accurate staging of lung cancer is fundamental to determining optimal treatment strategies There is no specific staging system for pulmonary NETs; hence the current Tumour-Node-Metastasis (TNM) classification for non-NET lung cancers devised by the American Joint Committee on Cancer/International Association for the Study of Lung Cancer is used[19]. By placing more emphasis on tumour size and nodal status in the staging classification, the TNM 8th edition is superior in predicting outcome compared with the TNM 7th edition 20.

However, the transferability of the TNM staging system to pulmonary NETs has been cautiously advocated due to the predefined 3, 5 and 7 cm size criteria stipulated for maximal tumour dimension. Lung carcinoid tumours are usually <3 cm in diameter, which may erroneously imply a better prognosis in a small, yet aggressive, high-grade tumour assigned to a lower T stage. Furthermore, survival in TNM stage I and II pulmonary NETs may overlap, and significant differences in prognosis only emerge in stages III and IV[21,22]

The prognostic utility of TNM staging for survival has nevertheless been demonstrated in carcinoid tumours, although histological subtype of pulmonary NET serves as the major prognostic indicator[23,24].

Haematological spread and lymphovascular invasion, invasion of lung parenchyma or invasion of cartilage have been evaluated as predictors of biological and clinical behaviour in pulmonary NETs. They carry a poorer prognosis in the AC subtype, but have not been extensively studied in other pulmonary NETs[25,26].

## Tumour behaviour: Functional versus non-functional

Lung NETs are also classified into functional (secretory) and non-functional (90%) based on tumour cell secretion of hormones and peptides, such as serotonin, adenocorticotropic hormone (ACTH), melanocyte-stimulating hormone, vasoactive intestinal peptide (VIP) and antidiuretic hormone (ADH)[27,28]. They can produce bronchopulmonary carcinoid syndrome (wheezing, cutaneous flushing, and diarrhoea), gastrinoma, insulinoma, VIPoma, glucagonoma and somatostatinoma.

Pulmonary carcinoid can occur in 5-8% of patients with multiple neuroendocrine (MEN -1) syndrome. Paraneoplastic syndromes may occur, and testing for 24h urine 5-hydroxy-

indole-acetic acid, ACTH, ectopic growth hormone releasing hormone (GHRH) syndrome is recommended.

Lung carcinoid-related Cushing syndrome is seen in 1-6% of lung NETs which is diagnosed by measuring serum cortisol, 24h urine free cortisol, ACTH and performing a CT head (pituitary), chest (carcinoid nodule) and abdomen (adrenals). ACTH-producing carcinoid tumours are associated with a good prognosis, even in the presence of metastases[28].

## Carcinoid syndrome

Carcinoid syndrome consists of a combination of symptoms, physical manifestations, and abnormal laboratory findings in patients with NET. Carcinoid syndrome is found in 2-5% of pulmonary carcinoids, mainly when liver metastases have occurred. It is the most frequent functioning syndrome in lung NETs[1].

Major symptoms of carcinoid syndrome include facial flushing, wheezing due to bronchoconstriction, diarrhoea, hypotension, and weight gain. They occur due to excessive production of serotonin, bradykinins, tachykinins, and prostaglandins by the tumour cells, in patients with liver metastases. Serotonin is usually inactivated by hepatocytes, therefore, if these substances are no longer inactivated, and they are released into the systemic circulation, the signs and symptoms of carcinoid syndrome develop[2].In later stages, carcinoid syndrome may produce congestive heart failure through damage to the cardiac valvular system.

Diagnostic tests for carcinoid syndrome include 24 hour urinary 5-Hydroxyindolecetic acid (5-HIAA), chromogranin A serum levels and CT scan of the thorax, abdomen and pelvis.

Carcinoid crisis is extremely rare, but can be life-threatening when there is acute carcinoid syndrome plus cardiovascular instability, manifesting as hypotension, tachycardia, weakness and syncope[29]. Octreotide (a somatostatin analogue) injections are the mainstay treatment of symptomatic carcinoid syndrome; This may be combined with low dose alpha interferon to increase effectiveness.

## Tumour markers

Neuroendocrine tumours are known to produce a variety of peptide hormones and amines, and they can cause several syndromes such as carcinoid, Zollinger – Ellison, hyperglycaemic, glucagonoma and the 'WDHA syndrome' (watery diarrhoea, hypokalaemia and achlorhydria syndrome). Specific markers for these syndromes are urinary 5-HIAA, serum plasma gastrin, insulin, glucagon, and VIP.

The non-functioning tumours, that do not produce any symptoms or syndromes, can potentially be monitored by measuring levels of chromogranin A, pancreatic polypeptide, serum neuron-specific enolase and subunit of glycoprotein hormones. Chromogranin A is very sensitive and specific serum marker for various types of neuroendocrine tumours. It is found to be increased in 50-100% of patients with different types of neuroendocrine tumours as well as a prognostic marker in carcinoids[30].

## Considerations for Surgical Resection

Pulmonary NETs should be surgically resected when possible as this offers the best therapeutic outcome[5,6,8,22,31,32]. The key considerations when assessing a patient's suitability for surgery and the planned surgical approach include patient and tumour characteristics.

In broad terms, as with other lung cancers, the location, size and stage of the tumour determines whether surgery is technically possible, and potentially curative, as well as affecting the planned surgical approach (Video-assisted thoracoscopic surgery (VATS) or thoracotomy). Patient characteristics such as other significant co-morbidities, lung function and performance status affect suitability for surgery as well as giving an indication of the risks of undertaking any surgical resection.

## Role of the MDT

Given the relative rarity of pulmonary NETs it is advised that all cases are discussed in a specialist neuroendocrine multidisciplinary team meeting (MDT) to better co-ordinate patient investigation, management and longer-term follow up. It is important to recognise potential carcinoids in imaging MDTs and lung cancer MDTs as these may be dismissed as benign lesions due to the indolent growth.

## Pre-operative assessment

As with other lung cancers, the pre-operative assessment can be broadly divided into two parts. Firstly, the assessment of 'resectability', that is whether the tumour is technically resectable and whether this resection is potentially curative. Secondly, the factor of 'operability' which is patient-dependent and determined by factors such as their other co-morbidities and underlying lung function.

Patient selection and work up broadly follows the same principle as the British Thoracic Society & Society for Cardiothoracic Surgery in Great Britain and Ireland (BTS-SCTS) and NICE guidelines for selection for lung resection[33].

Assessment includes tumour related factors like tumour size, location, nodal distribution and histology as this determines resectability, stage, surgical approach and extent of resection based on bronchoscopy and imaging [Figure 1].

Patient related factors are assessed by evaluating comorbidities, cardiopulmonary reserve, performance status and patient wishes.

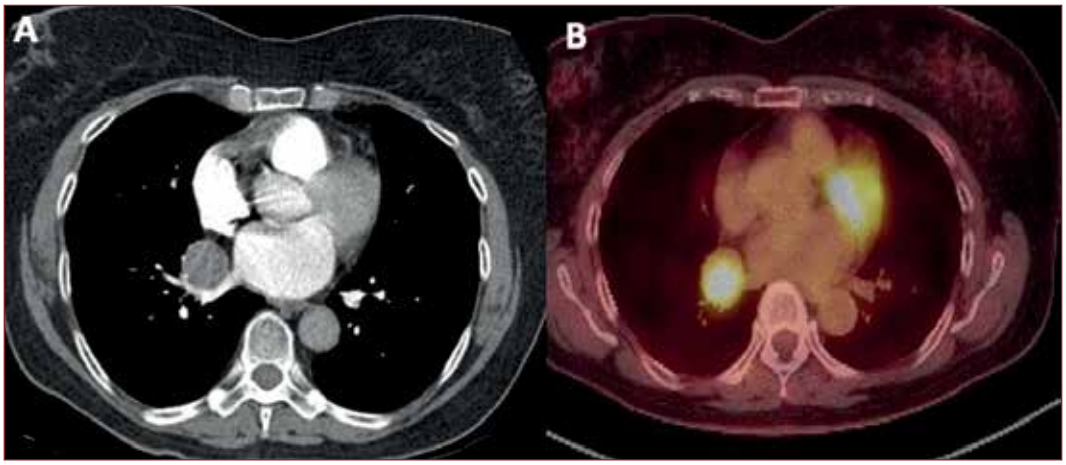


*Figure 1: A CT scan and B PET scan demonstrating right lower lobe carcinoid tumour.*

## Pre-operative investigations

All patients potentially appropriate for surgical resection should have:

- Contrast CT chest, abdomen and pelvis (High Resolution CT (HRCT) without contrast if poor renal function)
- Imaging-guided/Flexible bronchoscopic biopsy to confirm neuroendocrine tumour histology
- Octreotide scan
- Baseline Chromogranin A levels
- Full pulmonary function testing
- Most patients will have an FDG-PET as they will have been investigated along the 'lung cancer pathway'. It is acknowledged that an FDG-PET is less sensitive than Gallium-DOTA-PET in NETs and if possible, Gallium-DOTA-PET should be performed[1].
- EBUS / Cervical mediastinoscopy considered for mediastinal staging
- MRI for liver/spinal imaging if concern over metastases
- General investigations if concern over fitness for surgery (e.g. echocardiogram, Cardiopulmonary Exercise Testing)[33]

# Role of Surgery

Surgery is the mainstay of treatment in patients with resectable disease. The extent of resection depends on the nature of the tumour; extent of the disease and the fitness of the patient (Figure 2). As with other lung tumours, surgery for NETs offers diagnosis, staging, cure and palliation.

Surgical resection is the preferred treatment approach for patients with localised lung neuroendocrine tumours, provided there is adequate pulmonary reserve. For patients where fitness does not permit complete resection and for exceptional low-grade cases where the lesion is entirely luminal, endobronchial approaches may be an alternative[34].


*Figure 2: A CT Chest demonstrating a peripheral nodule on the left lower lobe amenable to sublobar resection. B Endoluminal central tumour of the left lower lobe which may require a lobectomy or sleeve lobectomy.*

## Surgical resection

Surgical resection is advocated with surgical principles of cancer surgery underpinning the strategy. As in other lung cancers, surgery for pulmonary NETs should be an anatomical resection with mediastinal lymph node sampling or dissection. In patients who have compromised lung function or have significant comorbidities, a limited resection may be considered.

Surgery is the therapeutic option offering the best chance of cure. Anatomic resections, such as lobectomy and segmentectomy, are superior to wedge resections. These have better prognosis and reduced tumour recurrence, even for low-grade tumours.

## Key principles

- Always aim for curative resection.
- Complete resection with lymphadenectomy should be performed in the same way as for other primary lung cancers.
- Mediastinal N2 positive disease should not prevent resection given generally slow disease progression.
- Anatomical resection (lobectomy/segmentectomy) should be performed. Sleeve resection is preferred to pneumonectomy.
- Non-anatomical resection (e.g. wedge resection) may be considered in individual cases (e.g. poor baseline lung function).

### Lobectomy & Pneumonectomy

Standard oncological resection is performed in a similar way as for non-small cell lung cancer (e.g., lobectomy, or even pneumonectomy when necessary, with appropriate lymphadenectomy). More extensive resections may be required for tumours with extensive central parenchymal involvement or those that are associated with severe distal parenchymal disease (i.e., non-functioning lung parenchyma). Intermediate-grade (atypical) lung NETs should always have anatomical resection where possible. The surgeon should attempt to preserve lung parenchyma by using lung-sparing techniques (e.g., sleeve resection)[35,36] particularly for smaller, central tumours. Pneumonectomy should be avoided where possible, however, it is still an appropriate option for more extensive low-grade lung NETs, especially those located proximally and those which present with distal parenchymal destruction.

Surgical approach should be determined by the expertise of the surgeon and the location of the lesion. Resections can be performed using thoracotomy, VATS or robotic assisted thoracic surgery (RATS). The use of ligatures or staplers for vasculature is also as per surgeon choice.

Unlike bronchogenic carcinomas, lung NETs which are low-grade (typical) tend not to spread submucosally, hence a narrow 5 mm surgical margin on the bronchial aspect is considered adequate, but a >2 cm histologically negative lung parenchymal margin is preferred. Intra-operative frozen section analysis is crucial in some situations to ensure adequate margins. Although long-term survival has been reported in patients with positive margins, re-resection is preferred in this setting.

During anatomical resection, it is worth considering ligating the vein first, particularly in patients with functioning carcinoid tumours, to avoid the increased release of vasoactive substances (eg serotonin) into the systemic circulation which may occur on manipulation of the NET and result in haemodynamic instability.

## Sleeve resection

Proximal endobronchial tumours which are polypoid low-grade (typical) will lend themselves to parenchyma-sparing procedures. Tumours of the main bronchus or bronchus intermedius can be treated with a wedge or sleeve resection of the bronchial wall thus preserving the distal lung parenchyma[35,36]. However, caution must be taken whilst attempting such parenchyma-sparing procedures due to possible "iceberg" lesions, where the tumour appears entirely intraluminal bronchoscopically but also has a significant extra luminal component. These will be evident with pre-operative high-resolution computed tomography (CT) scanning. In such cases, a sleeve lobectomy may still be feasible with appropriate planning where in a section of the airway is resected with the lobe or in isolation sparing the parenchyma completely. The edges of the airway are then anastomosed end to end (Figures 3 & 4). Sometimes it may be necessary to perform a double sleeve where a section of airway as well as the pulmonary artery are removed and reconstructed. Care should be taken to have a buttress between the two anastomoses to prevent fistula formation.

As with any resection, it is important to ensure adequate margins and this can be checked by intraoperative frozen section analysis. The bronchial anastomosis is completed with either interrupted absorbable sutures or continuous sutures and it is important to have the knots outside the lumen to avoid granuloma formation. As with pneumonectomy bronchial stumps, it is advisable to cover the bronchial sleeve anastomosis with an intercostal flap, pericardial fat or diaphragm flap[37].

## Sub lobar resections

The ideal approach for peripheral lesions in the outer one-third of the lung is still controversial. Anatomical sub-lobar resection, segmentectomy, are preferred, although wedge resections may be considered in patients where there is concern about baseline lung function or other co-morbidities. Lobectomy is generally advised in the case of a more central tumour involving the orifice of a segmental bronchus. However, a more limited resection (i.e. segmentectomy) is acceptable for a low-grade (typical) lung NET because of the low likelihood of a local recurrence[38]. The feasibility of segmentectomy in these more central tumours depends upon the segment involved and individual surgeon experience.

A wedge resection of small, <2 cm diameter, low-grade lung NETs may be acceptable as long as adequate tumour-free margin can be obtained in patients with poor respiratory and physiological reserve. However, there is evidence that patients undergoing wedge resection have significantly worse survival compared to those having a lobectomy for early stage typical carcinoids[39].

## Lymph node dissection

Lymph node metastasis is observed in between 5 and 20 percent of low-grade (typical) lung NETs and 30 to 70 percent of intermediate-grade (atypical) tumours[22,40]. Complete mediastinal lymph node sampling or dissection should be performed as per the ESTS

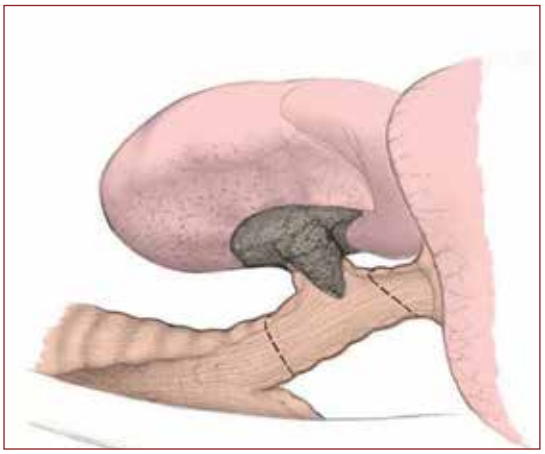

*Figure 3: Sleeve lobectomy where a sleeve of main airway is removed with the lung*

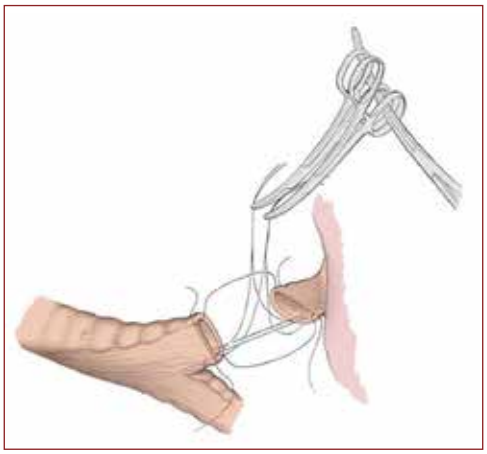

*Figure 4: The end to end anastomosis of the airway.*

guidelines for nodal assessment[41]. Complete resection of nodal metastasis (our preferred approach) should always be performed where possible as that is better than sampling[42]. Nodal status is a predictor in long term outcomes[43]. Metastatic involvement of mediastinal lymph nodes does not preclude a complete (R0) surgical resection or long-term cure due to the indolent course of the disease. The use of diathermy and energy devices in mediastinal and hilar nodal dissection should be used with caution, particularly when performing bronchoplastic procedures or pneumonectomy. Care should be taken to preserve bronchial vascularity to prevent anastomotic dehiscence and later fistula development.

## Endobronchial Management of NETS

Bronchoscopy is used for diagnosis, staging assessment, curative endobronchial ablation and palliation of obstruction in advanced diseases (Figure 5). This can be accomplished by fiberoptic bronchoscopy under sedation of with the aid of a rigid bronchoscopy under a general anaesthesia[44].

### Key considerations for bronchoscopies in NETs

- It is essential to ensure the lesion is sampled from the centre after clearing the covering debris.
- Carcinoid tumours are vascular and vasoactive hence the propensity for bleeding is high. Bleeding can be controlled with pressure with a pledget with or without adrenaline or cold saline lavage.
- If bleeding is significant, that can be controlled by various adjuncts like cautery, laser or argon beam.

### Ablation of Endobronchial Tumours

Bronchoscopy is an essential technique in obliteration of the endobronchial NETS for diagnostic, therapeutic and palliative purposes[34,45]. Bronchoscopy can also be used as a bridge to definite treatment[46].

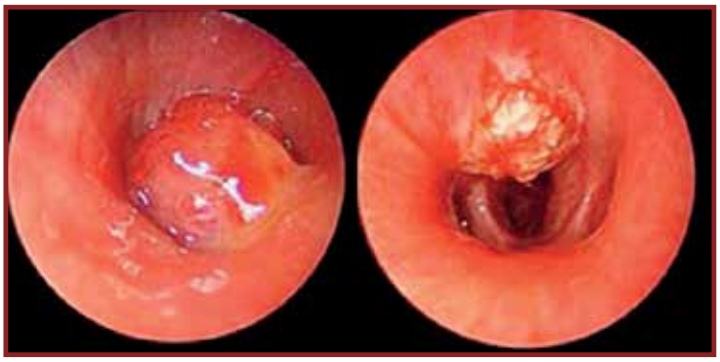

*Figure 5: Endobronchial carcinoid completely occluding the lumen with the second image highlighting partial recanalization after laser.*

Laser therapy uses the heat energy from laser light to coagulate and vaporise endobronchial tissue. Most current work is performed using Neodymium Yttrium Argon (Nd: YAG) laser[47].

Cryotherapy is a technique used to deep freeze the lesions, arrest bleeding or ablate tumours. Cryotherapy uses extreme cold to cause delayed local destruction of tissue[48]. Standard cryotherapy is performed when the cryoprobe is inserted through the instrument channel of a bronchoscope and applied directly to the target tissue.

Freezing and thawing in repeated cycles leading to tissue necrosis ablate the target tissue. A further bronchoscopy is performed to extract and to remove necrotic material.

Electrocautery and laser must be used cautiously with suspension of jet ventilation when deploying to reduce the risk of fire. The laser is directed on to the tumour, ensuring it is parallel to the bronchial tree to avoid perforation of the bronchial wall. Depending on the size of the endobronchial lesion, sometimes it may be useful to core or debulk the volume and laser the base. Patients undergoing endobronchial ablation may go into respiratory failure following the procedure due to carbon dioxide retention, smoke injury, or reperfusion injury to the lobe, which may cause an obstructive hypoxic vasoconstriction[44].

## Peri-operative considerations in patients with Carcinoid syndrome

It is important to evaluate and identify patients with carcinoid syndrome and plan a peri-operative strategy to avoid a carcinoid crisis[1,4]. Somatostatin analogues (eg Octreotide) should be used peri and intra-operatively to prevent excessive hormonal secretions and avoid a carcinoid crisis.

### Cardiac assessment

Cardiological evaluation plays an important role in the pre-operative assessment with echocardiography and NT-proBNP (N-terminal prohormone B-type natriuretic peptide) measurements to identify significant cardiac dysfunction and valve disease, presence of congestive heart disease and raised 5–HIAA levels are predictive factors for potential carcinoid crisis.

### Nutrition

Diarrhoea secondary to carcinoid syndrome will cause electrolyte abnormalities, hypoproteinaemia, and niacin deficiency which need to be identified pre-operatively.

Parenteral nutrition should be considered prior to any surgical intervention in patients with chronic or severe diarrhoea, weight loss and hypoproteinaemia.

### Intra-operative monitoring

Any factors which increase stress, physiological or psychological can increase the risk of carcinoid crisis. Benzodiazepines and antihistamines may be considered to reduce anxiety and stress pre-operatively. Continuous temperature monitoring and airway pressure monitoring should be used. Warming devices, which are often standard practice, can reduce the risk of stress caused by hypothermia.

Invasive monitoring of blood pressure is imperative in these patients to identify and aid management of hypotension which may be secondary to anaesthetic induction agents or carcinoid crisis. Hypotension tends to occur when large neuroendocrine tumours are manipulated; resulting in the increased release of vasoactive substances. Inotropes can be used acutely to manage the hypotension but the peri-operative use of somatostatin analogues (eg Octreotide) aims to reduce the risk of its occurrence. Sympathomimetic morphine and histamine releasing drugs should be used with caution.

### Post-operative considerations

The use of somatostatin analogues should continue in the initial post-operative period and they then may be weaned off, often in the first postoperative week. Hypovolaemia and pain can cause sympathetic stimulation. Pain increases the body's stress response; hence adequate pain relief by the way of epidural and paravertebral infusions will decrease risk of developing a carcinoid crisis.

## Post-resection follow-up

There is little consensus between key international groups on the most appropriate follow up for patients after surgical resection of a pulmonary neuroendocrine tumours[1,4]. This is largely because these tumours are rare and so there is little evidence to support one follow up regime over another. There is general agreement that these patients should have 'long-term' follow up, given the possibility of delayed recurrence. Again, there is little agreement over what defines 'long-term'. Surveillance with repeated CT scans is advised by most groups but the frequency of this is variable, as is the need for repeated chromogranin A levels, octreotide scans and bronchoscopies.

### Key Principles of Follow Up

- Follow up should be longer than other lung cancers post-resection given possibility of late recurrences.
- Individual clinicians may elect to perform more frequent imaging or a longer period of follow up if there is specific concern that an individual patient is higher risk for recurrence. Atypical and large cell neuroendocrine tumours are more likely to recur than typical carcinoid, likewise R1 (microscopically incomplete) resections and node positive disease are more likely to recur.
- Opinion is divided over the need for routine follow up bronchoscopies. They should be considered in central/bronchial lesions, particularly if R1 resection or other concern for higher recurrence risk.

- Routine repeat Octreotide scans are advised by European Guidelines but not by the American guidelines. They should be performed if CT/clinical symptoms suggest recurrence.
- Further resection should be considered for all recurrences.

Given the lack of consensus regarding post-surgical follow up, we devised our own, local, follow up guidelines which have been implemented regionally. For ease of introduction, the first 5 years follow up follows the same pattern as our standard lung cancer follow in terms of outpatient clinical review and repeat CT frequency.

The table below summarises the key points of follow up from the European and American guidelines as well as our local guidelines[1,4].

*Table 2: Follow up guidelines following resection of NETs*

| Follow up | European (ENETS)[1] | | North American (NANETS)[7] | Glenfield Hospital Regional Guidelines |
|---|---|---|---|---|
| Clinical Review | 3 monthly then annually | | 3-6 months then every 6-12/12 | 3 monthly for 2 years then annually |
| CT | TC: 3/12, 6/12, 12/12 and 24/12 then every 3 years (Annual CXR if no CT) | AC: 3/12, 6/12, 12/12, 18/12, 24/12 then every 6/12 until 5 years then annually | Recommended but specific frequency not defined | CT chest at 6/12 & 12/12<br>CT chest, abdomen & pelvis at 24/12 and then every 3 years |
| Octreotide Scan | At 12/12 and repeat if concern of recurrence | | Only if concern of recurrence | Only if concern of recurrence |
| Bronchoscopy | TC: Every 5-10 years | AC: Every 1-3 years | - | Only if concern of recurrence |
| Chromogranin A | Repeat with each CT | | Monitor if abnormal at baseline | At 6/12, 12/12, 24/12 and 5 years if baseline levels raised |
| Total follow up duration | 'long-term' | | 'At least 7 years' | 20 years |

## Prognosis

Prognosis of NETs is determined by the size of the tumour, the type of tumour (typical or atypical) and lymph node metastases[43].

Pulmonary NET grading has significant influence on clinical behaviour of the tumour. Nevertheless, histologically low-intermediate grade tumours such as TCs or ACs can spread to regional lymph nodes and distant metastasis[8].

Typical carcinoid (TC) tumours are considered low grade tumours, generally slow growing and late to metastasise, whereas atypical carcinoids (AC) are intermediate grade tumours

and more likely to metastasise. Both typical and atypical carcinoids can present with regional lymph node or distant metastasis (5-20% for TC and 30-40% for AC)[49].

Low-grade TCs are associated with better survival and a longer disease-free period, whereas intermediate-grade ACs are more aggressive tumours with a greater incidence of lymph node and distant metastases, as well as a higher rate of local and distant disease relapse compared to TCs[8,49]. Similarly, disease-free and overall survival is better with TCs than ACs, with overall 5- and 10-year survival ranges of 87-100% and 87-92%, respectively, described for TCs, and 25-78% and 35-67% for ACs[5,26,50,51,52]. These findings highlight the importance of long-term surveillance in patients with pulmonary carcinoid tumours.

Conversely, LCNC and SCLC carry a poor prognosis owing to their highly aggressive nature, with median post-treatment survival in limited stage disease and extensive disease being 15-20 months and 8-13 months, respectively[53].

Many patients re-present with recurrent disease or metastases which often occur in the liver or bone. Median time to TC recurrence is 4 years and for AC is 1.8 years[54, 55].

5-year survival rate in pulmonary NETs is 78% - 95% and 10-year survival rate is 77% - 90%. Malignant carcinoid syndrome, carcinoid heart disease, high concentrations of tumour markers, urinary[5] – HIAA and plasma chromogranin A levels are adverse clinical indicators.

## Conclusion

Pulmonary neuroendocrine tumours are rare but represent an important cohort of patients. They behave differently from other, more common, lung cancers and sometimes are challenging if associated with carcinoid syndrome. Although the principles and techniques of surgical resection remain similar, pulmonary NETs require different pre-operative assessment, cautious peri-operative strategy and, perhaps most importantly, altered and prolonged post-operative follow up.

## Acknowledgements

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SECTION 2 THORACIC SURGERY

# Lung Cancer

*"Si post fata venit gloria, non prospero"*

*Marcus Valerius Martialis. 43 -104 AD.*

Chapter 13

# Screening for lung cancer – lessons learnt so far

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*"Aegroto dum anima est, spes est"*

## Introduction

Lung cancer remains a significant and devastating disease with a huge burden on global health and economy. It is the leading cause of cancer related death worldwide with more than 1.6 million deaths per year[1], accounting for approximately 20% of all cancer deaths globally[2]. In men, it is the commonest cause of cancer death and for women it is the second commonest cause of cancer death after breast cancer[3]. 60% of overall lung cancer related deaths are registered in less developed regions of the world. Worryingly, the burden of lung cancer is forecast to rise further in coming years despite the progress that has been made in diagnostics and treatments[4]. This is likely due to a combination of an overall aging population and a more recent peak in the tobacco epidemic in certain regions of the world[4]. On the whole, lung cancer outcomes have failed to improve significantly over the past four to five decades. 5-year survival remains very poor at an average of 12%[5] and a dismal 10-year survival of 6.8%. As can be expected, survival data does vary between countries and regions, with high income nations faring slightly better. For example 5-year survival in Canada has been quoted to be as much as 18%, still much lower than seen in other malignancies[3]. Survival in lung cancer is directly associated to stage at diagnosis[35,36] with five-year survival ranging from over 90% for stage 1A disease to only a few months for stage IV metastatic disease[7]. Surgery remains the only radical treatment with demonstrated long term survival despite recent significant advances in radiotherapy, immunotherapy and targeted therapy[6]. A major difficulty with earlier diagnosis is the lack of symptoms. Only a third of lung cancers are diagnosed at an early stage amenable to radical treatment, the remaining being diagnosed with advanced non-curable disease often dying within months of diagnosis[8]. It is therefore widely accepted that a large scale stage shift in lung cancer diagnosis is needed to play a key role in improving overall outcomes but how best to do this remains keenly debated. Screening high-risk asymptomatic individuals is one possible avenue to explore and will be discussed in this chapter.

## Low-dose CT screening

Screening for early stage lung cancer dates back to the 1960s. At the time focus was primarily on sputum cytology (SC) and chest x-ray (CXR). Several groups including the Memorial Sloan-Kettering team in New York[77], The John Hopkins Lung Project[9] and the Mayo Lung Project[10,11] collectively recruited >30,000 male smokers over the age of 45 exploring the role of SC and CXR in lung cancer screening. However, these studies compared one form of screening with another, rather than no screening at all. These studies recruited by either randomising to CXR versus CXR and SC, or randomising to CXR and SC every four months versus every 12 months. Whilst there were clear improvements in incidence, number of resections and survival in the intervention arms, no mortality benefit was demonstrated. There were marginally more lung cancer related deaths in the SC arm / more intensive screening arm compared with the CXR alone arm / less intensive screening arm. So what is the potential role of CXR alone compared with no screening in lung cancer screening. The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial[12,13] was set-up in 1993, and ran until 2001, looking at screening in the four named malignancies. A total of 154,901 (77,445 intervention and 77,456 control) subjects aged 55-74 were randomised to annual CXR for four years or usual care only. For the first time women were also included, as well as never smokers (45% of the subjects), and the control arm did not receive any form of imaging. Median follow-up was good at 12 years. Eventually, there were 1,213 lung cancer deaths in the intervention arm and 1,230 lung cancer deaths in the control arm, once again demonstrating no mortality benefit with annual screening with CXR (Mortality RR 0.99; 95% CI, 0.87-1.22). There were similar results in terms of lung cancer stage and histology between the two groups when matched for co-variables and it was concluded that screening with annual CXR was of no benefit.

The role of Computed Tomography (CT) in the detection of lung cancer was first described in the 1990s and was shown to be superior to CXR in a number of subsequent observational studies. The most recognisable of these was the Early Lung Cancer Action (ELCAP) study in 1999[14,15]. In this project 1000 high-risk participants aged ≥60 were randomised to CXR vs low-dose CT (LDCT). LDCT was found to be superior to CXR in not only identifying malignant nodules but also detecting earlier stage lung cancer more amenable to surgical resection. These studies ignited a renewed interest in lung cancer screening by displaying early promise that perhaps LDCT would be an effective tool for lung cancer screening.

The landmark moment in image-based lung cancer screening arrived in 2011 with the publication of the National Lung Screening Trial (NLST). This large American randomised controlled trial (RCT) of 53,454 participants, aged 55-74 with at least a 30 pack year smoking history and who had smoked within 15 years, demonstrated for the first time a mortality reduction (20%) from screening with LDCT vs CXR on an annual basis[16]. Additionally, the trial also demonstrated a 6.7% reduction in all-cause mortality within the LDCT group. Since the publication of NLST, several American bodies, including the US Preventive Services Task Force (USPSTF), have recommended screening with LDCT be offered to individuals that match the NLST eligibility criteria extended to age 80[17]. Several smaller European studies (Table 1) have further demonstrated LDCT screening's ability to create a stage shift towards earlier detection of lung cancer but have not had the statistical power to further demonstrate mortality reduction. Many of the European countries have been awaiting results from the Dutch-Belgian NELSON study, the second largest ever lung cancer screening RCT. This trial was designed with a statistical power to detect a 20-25% reduction in lung cancer mortality at 10 years[18]. The full publication of the final results are

*Table 1: Selected European lung cancer screening studies*

| Study | Screening Methods (duration) | Number Enrolled | Age eligibility criteria (years) | Smoking eligibility criteria | Baseline Cancer Detection Rate (%) | Proportion of Early Stage (I+II) Cancers (%) | Surgical Resection Rate (%) |
|---|---|---|---|---|---|---|---|
| DANTE | Annual LDCT vs No Screen (4 years) | 2,472 | 60-74 | ≥20 PY; Ex-smokers quit within 10 years | 2.2 | 57.0 | 67.9 |
| ITALUNG | Annual LDCT vs No Screen (4 years) | 3,206 | 55-69 | ≥20 PY; Ex-smokers quit within 10 years | 1.5 | 47.6 | 81.0 |
| DLCST | Annual LDCT vs No Screen (5 years) | 4,104 | 50-70 | ≥20 PY; Ex-smokers quit within 10 years | 0.8 | 53.0 | 65.0 |
| MILD | Annual LDCT vs Biennial LDCT vs No Screen (5 years) | 4,479 | ≥49 | ≥20 PY; Ex-smoker quit within 10 years | 0.8 | 63.0 | 84.0 |
| LUSI | Annual LDCT vs No Screen (5 years) | 4,052 | 50-69 | At least: a) 15 CPD for 25 years OR b) 10 CPD for 30 years; Ex-smoker quit within 10 years | 1.1 | 80.0 | Not stated |
| UKLS | Single LDCT vs No Screen (single round) | 4,055 | 50-75 | LLPv2 ≥5% | 1.7 | 85.7 | 83.0 |
| NELSON | LDCT at 1, 2, 4 & 6.5 years vs No Screen | 15,822 | 50-75 | At least: a) 15 CPD for 25 years OR b) 10 CPD for 30 years; Ex-smoker quit within 10 years | 0.9 | 70.8 | Not Stated |

*PY=Pack years; LDCT=Low-dose computer tomography; CPD=Cigarettes per day; LLP=Liverpool Lung Project risk model; $PLCO_{m2012}$=Prostate, Lung, Colorectal and Ovarian trial risk model, the 2012 model; PanCan=Pan-Canadian study risk model*

still awaited but were presented at the plenary session of the World Conference on Lung Cancer 2018 in Toronto, Canada, and demonstrated a 26% mortality rate reduction at ten years in males (95%CI 0.60-0.91, p=0.003) who formed the majority of the recruited participants. Interestingly a more significant 39% mortality reduction (95%CI 0.35-1.04, p=0.0543) was seen at 10 years in female participants[19]. Additionally the 10-year results of the Italian MILD study have since been published also demonstrating a lung cancer mortality reduction of 39% (0.61; 95%CI: 0.39-0.95)[20], further adding to the evidence from RCTs that LDCT screening for lung cancer can save lives. Subsequently focus has shifted from whether LDCT screening can reduce lung cancer mortality to how best to implement such a screening programme in a safe and cost-effective manner on a large scale.

## Selecting high-risk participants

The benefits of lung cancer screening differ significantly depending on the participants' risk of developing lung cancer. USPSTF or NLST criteria of age and smoking pack-years alone are sub-optimal for identifying high-risk individuals for LDCT screening[21]. Only an estimated 40% of lung cancer patients in the United States (US) and Canada would meet the USPSTF screening criteria had screening been available prior to diagnosis[22]. In the United Kingdom (UK) this value is estimated to be at a maximum of 58.6% depending on the inclusion criteria selected[23]. In NLST only 1% of the prevented deaths occurred in the lowest quintile of 5-year lung cancer risk compared with 88% of prevented deaths in the 60% highest risk participants[24]. The number needed to screen (NNS) to prevent one death in the highest risk quintile was 161 compared with 5,276 in the lowest risk quintile, clearly demonstrating a vast difference in the benefits gained from screening between risk groups. Furthermore screening with LDCT has downstream implications including further investigations and potential surgery, therefore appropriate selection of participants will be essential in terms of maximising benefits and minimising harm. To date all but one lung cancer screening RCT have used selection criteria based on primarily age and smoking history alone. Age inclusion criteria have varied significantly between screening trials ranging between 50-80. The median age of lung cancer diagnosis is 70 yet the median age of the biggest observational trials is significantly lower at 59[25]. Less than 10% of NSLT participants were aged ≥70. Whilst smoking tobacco is accepted as the dominant risk factor for lung cancer, not everyone with lung cancer will have smoked. Other risk factors including socioeconomic status, Body Mass Index (BMI), ethnicity, gender, family history of lung cancer, personal history of cancer (both lung and non-lung) and previous respiratory disease also play a role. Numerous lung cancer risk prediction models which incorporate the above variables have been developed attempting to improve selection performance for screening[26] (Table 2).

Whilst no prospective study has compared performance between these risk prediction models, microsimulation work has repeatedly suggested that the majority of these models outperform age and smoking history alone (i.e. NLST criteria) and that the $PLCO_{m2012}$ model performs best in external validation with the highest sensitivity, specificity and positive predictive values[27,28]. At a $PLCO_{m2012}$ threshold of ≥1.51%, lung cancer specific mortality rates in the NLST population were consistently lower in the LDCT arm than the CXR arm and the NNS to prevent one lung cancer death reduced from 963 to 255[29]. Given the potential logistical challenges for lung cancer implementation, in terms of available work force and facilities, the use of risk prediction models can also influence the potential downstream workload of a programme by increasing the inclusion threshold to reduce the number of eligible participants. Currently, no risk prediction model is validated for never

*Table 2: Selected lung cancer risk prediction models*

| Risk Model | Incorporated variables | Estimated risk |
|---|---|---|
| $PLCO_{m2012}$ | Age, smoking history, socioeconomic status, BMI, ethnicity, gender, family history, previous cancer diagnosis, respiratory disease history | 6-year risk of developing lung cancer |
| LLP | Age, smoking history, family history, previous cancer diagnosis, pneumonia, asbestos exposure | 5-year risk of developing lung cancer |
| Bach | Age, smoking history, gender, asbestos exposure | 10-year risk of developing lung cancer |
| Spitz | Smoking history, family history, respiratory disease history, dust exposure | 1-year risk of developing lung cancer |
| Etzel | Smoking history, COPD, hay fever, asbestos exposure, dust exposure | 5-year risk of developing lung cancer |
| Hoggart | Age, smoking history | 5-year risk of developing lung cancer |

*$PLCO_{m2012}$=Prostate, Lung, Colorectal and Ovarian trial risk model, LLP=Liverpool Lung Project risk model; BMI=Body Mass Index; COPD=Chronic Obstructive Pulmonary Disease*

smokers or specific to an Asian population where the incidence of lung cancer is on the rise including amongst female never smokers[30]. Recently published data from Canada suggests a significant association between cumulative air pollution exposure and lung cancer risk in female never smokers[31]. If lung cancer screening is to be implemented amongst such populations, improved risk stratification tools are required and variables such as outdoor/household air pollution and genetic susceptibility may need to be considered in the development of future risk stratification models.

## Lung Cancer Screening Engagement

For lung cancer screening to be effective it must be accessible to those at highest risk and therefore most likely to benefit. In the United States, uptake of lung cancer screening has been poor with only an estimated 3.9% of potential participants receiving LDCT screening in 2015[32]. Demographic factors associated with increased lung cancer risk such as older age, active smoking, lower socioeconomic status (SES) and lower educational attainment are also associated with poor lung cancer screening uptake[33,34]. Reaching these high-risk populations has been highlighted as a key challenge for successful implementation of lung cancer screening[35,36]. Participants from the larger trials, including NLST, UKLS and NELSON, had high levels of educational attainment and affluence[37,38]. Lung cancer screening decision making is complex and multifactorial[39,40] and research into reasons for a lack of participation amongst such high-risk populations reveals repeated themes of 'practical barriers', including travel and costs, and 'emotional barriers' including fear and anxiety[41,42]. The use of mobile-units have recently been explored in terms of addressing some of these

barriers. Setting up such units in community settings addresses issues around travel and costs and also eliminates the need to attend hospitals which can elicit emotional stress for some participants. In the UK, recent pilot programmes utilising the use of community-based mobile screening in deprived areas was able to enrol participants from deprived backgrounds with high current smoking rates and low educational attainment levels[43,44]. This programme also introduced the concept of 'Lung Health Checks' (LHC), as opposed to 'lung cancer screening', which is likely to further reduce some of the psychological barriers to cancer screening. This will be discussed in more detail later in this chapter.

## Reducing Screening Associated Harms

The successful implementation of lung cancer screening should adhere strictly to the Wilson & Junger criteria for screening. As a consequence, engaging those most at-risk and employing systematic strategies to reduce the leading causes of harm (overdiagnosis, false positives, radiation induced cancer, benign resection) in a screening programme from participation through to treatment will maximise the available benefits and life years gained.

## Overdiagnosis

Overdiagnosis is the finding of a cancer through screening that would have never caused harm within the patient's lifetime, either due to the indolent biology of the tumour or due to death from competing causes of mortality. Concerns of overdiagnosis exist in all screening programmes and have done so in lung cancer screening ever since the early studies detected more early stage lung cancer but without a corresponding reduction in mortality. Overdiagnosis is primarily caused by diagnosis and treatment of indolent disease and this must be avoided in an effort to reduce potential overdiagnosis. Within a RCT, the excess number of lung cancers in the intervention arm as compared with the control arm is deemed to be an estimate of overdiagnosis. The estimated rate of overdiagnosis across screening trials varies significantly. In NLST, the rate of overdiagnosis was initially estimated to be around 18%[16]. This figure however was after a median follow-up period of only 6.5 years, not long enough to overcome lead-time bias, and included treatment of bronchioloalveolar carcinoma (BAC) which accounted for almost 80% of the overdiagnosed cases. These entities are now managed conservatively due to their reclassification to in-situ disease, slow progression and excellent prognosis. Recent publication of updated NLST follow-up data after a median period of 11 years suggests the overdiagnosis rate to be closer to 3%[45]. Long term follow-up from the ITALUNG study has recently reported an almost non-existent overdiagnosis rate after 8 years[46]. This data confirms the efficacy of CT for identifying nodule morphology and the efficiency of modern day nodule management algorithms to avoid treatment of indolent disease and thereby reducing the risk of overdiagnosis. Furthermore, there is potential to reduce the risk of overdiagnosis further from competing causes of death within a lung cancer screening programme by addressing tobacco addiction, COPD, & cardiovascular disease as core components within screening programmes. This will be discussed in more detail later in the chapter.

### False Positives

LDCT scans detect benign nodules as well as cancer. Positive results cause participants anxiety, fear and psychological stress and in the context of no eventual cancer diagnosis this is deemed to be a harm of screening[47,48]. The rate of positive and false positive results varies

significantly across screening trials, partly due to the inconsistent definitions of positive, and subsequently false positive, LDCT results. For example NLST defined a positive scan as any with a non-calcified nodule ≥4mm resulting in 39% of participants having at least one positive result over the course of three rounds, of which 96% were false positives. In contrast, NELSON and UKLS used volumetric measurements, larger positive size definitions, and defined an 'indeterminate group' that simply required surveillance, and both reported much lower false positive rates. Robust nodule management has significant implications for downstream investigations and therefore potential harms including that of surgery for benign disease. In the US, the 'Lung-RADS' nodule management guidelines[49] are recommended to aid management of nodules and retrospective application of lung-RADS to the NLST cohort lowered the false positives rate by 52% whilst increasing the positive predictive value (PPV)[50]. The NELSON group have provided strong evidence that the use of a 2-step nodule management algorithm which applies volumetric measurement and close interval imaging is an effective way of managing nodules and superior to the use of mean diameter alone[51]. The use of their 2-step nodule algorithm has shown impressive sensitivity (84.6%) and specificity (98.6%) with a negative predictive value (NPV) of 99.8% and PPV of 40.4%. This data played a key role in the development of the British Thoracic Society (BTS) nodule management guidelines[52] which are now in use in the UK and Europe. In an effort to reduce potential harm from false positive results future screening programmes will need to incorporate such nodule management algorithms as well as nodule risk stratification models, such as the BROCK score[53], and in the near future incorporation of artificial intelligence (AI) algorithms.

### Radiation

Whilst radiation from LDCT is approximately 70-90% less than a standard CT Thorax (1.5-mSv vs 7-8-mSv), there remains a population risk of radiation induced cancers. Exposure from a single LDCT is less than the average exposure from natural sources over the course of 12 months[54,55] however repeated scanning poses a more significant threat. Additionally, positive results within a screening programme would expose a participant to further sources of radiation from downstream investigations such as Positron Emission Tomography (PET) CT and image guided biopsies. Nonetheless, several studies have defined the risk of radiation induced cancer deaths as a consequence of LDCT lung cancer screening to be very low and not enough to outweigh the potential benefits[56-58]. This risk can be reduced further with the use of ultra-low dose CT scanning, achieving a dose one-tenth of the conventional LDCT[59].

## Lung Health Checks

Inviting individuals to cancer screening can be daunting and illicit fear and anxiety leading to a lack of willingness to participate[42]. Patient-focussed work has demonstrated the decision to participate in screening to be complex, emotional and multifactorial. An approach that downplays 'cancer screening' can be seen as less likely to illicit emotional barriers to participation. A novel approach to this is by inviting participants to a 'Lung Health Check' from which those at highest risk of lung cancer are invited to LDCT screening. Whilst one of the primary aims of the LHC concept is to improve participation in lung cancer screening, it also provides an opportunity to address other significant smoking related morbidity and mortality such as cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD), whilst at the same time incorporating tobacco addiction treatment at a

teachable moment. In such programmes ever-smokers are invited to attend a free LHC and undergo an assessment which includes spirometry, CVD risk assessment and tobacco addiction treatment. The LHCs include lung cancer risk prediction models which are used to select participants that are high risk of lung cancer who are invited and consented to LDCT screening.

COPD and lung cancer are strongly interlinked. COPD is an independent risk factor for the development of lung cancer and there is a high burden of COPD amongst those diagnosed with lung cancer. Undiagnosed COPD is known to be associated with increased risk of exacerbations, pneumonia and mortality[60,61] and continues to be a major source of morbidity and mortality globally[62]. Performing spirometry in such a high-risk population of current or former smokers has the potential to identify previously undiagnosed symptomatic COPD. Similarly, those at risk of lung cancer are also at risk of CVD related morbidity and mortality. CVD was the leading cause of death in the NLST population[63]. The concept of a LHC allows the opportunity to combine addressing previously unrecognised CVD risk with lung cancer screening and in doing so also provides an evidence-based opportunity to minimise overdiagnosis from competing causes of mortality. This can be done either non-radiologically through CVD risk prediction models, such as QRISK[64] or Framingham[65], where an evidence base exists for pursuing statin therapy[66], or through the detection of coronary artery calcification (CAC) on LDCT which is strongly correlated with cardiovascular events and all-cause mortality, although it remains unclear how best to approach this entity[67,68]. Smoking contributes significantly towards healthcare inequalities[70] and is an established and leading cause of morbidity and mortality[71]. Lung cancer and smoking are strongly linked[72]. Smoking is thought to be the primary cause of almost 90% of lung cancer cases in the UK[73]. Addressing smoking is imperative to any lung cancer screening programme and successfully doing so provides an opportunity to increase the mortality reduction from screening[74,75]. For example, modeling work in the United States has suggested that a 10% quit rate within a screening programme with 40% uptake could lead to 160,000 fewer lung cancer deaths and 1.4 million life years gained by 2060[76]. Data from the larger lung cancer screening trials have shown mixed results to date with regards to the impact of screening on smoking habits. NELSON data suggests a possible negative impact on smoking habits as although the quit rates amongst participants was higher than the national average (17% vs 3-7%), screening was associated with a lower prolonged abstinence rate compared to the control group (14.5% vs 19.1%; OR 1.40, 95%CI 1.01-1.92; $p<0.05$)[77]. The Danish DLCST trial showed no significant positive or negative impact on smoking cessation from screening[78], neither did the recently published Alberta Lung Cancer Screening Study[79]. Encouragingly, data from UKLS has demonstrated a positive impact of screening on smoking quit rates with a quit rates of 14% vs 8% at 1-year and 24% vs 21% at 2-years in the intervention vs control arms. This effect could be improved further by incorporating pharmacotherapy[80]. Addressing these additional causes of smoking related morbidity and mortality within the context of lung cancer screening not only has potential clinical benefits but is also likely to improve the cost-effectiveness of such a programme[81].

## Manchester Lung Health Checks – a pragmatic evidence-based real-world modern day example

The novel concept of LHCs incorporating lung cancer screening has recently been successfully demonstrated in UK-based pilot programmes such as the Manchester Lung Health Checks[43,82]. This pilot programme took a pragmatic evidence based approach and

created a programme that was acceptable to their local population and addressed the leading causes of morbidity and mortality in the city whilst delivering LDCT screening for lung cancer. The Manchester programme used mobile units to provide community-based LHCs in some of the most deprived parts of the city. Participants were invited to attend a 20 minute LHC which included spirometry, CVD risk assessment and smoking cessation. The PLCOm2012 risk prediction model was incorporated into the LHCs and those with a score of ≥1.51% proceeded to LDCT screening in a co-located mobile scanner following a shared-decision making consultation. BTS guidelines were used to manage LDCT detected nodules.

Across two rounds of annual, 65 lung cancers in 61 individuals were diagnosed through LDCT screening equating to a lung cancer detection rate of 4.4% (3% in the baseline prevalence round and 1.6% in the incidence round). 80% of screen detected cancers were diagnosed at an early stage (I-II) demonstrating an almost 5-fold reduction in stage 4 disease compared with age-equivalent lung cancer diagnosis across Manchester. 89% of cancers received curative intent treatment including a surgical resection rate of 60%. The overall false positive rate across the pilot was 44.5% of those seen in the lung cancer clinic and 3.5% of the overall screened population. There was only one benign surgical resection, a growing PET-positive pulmonary nodule that was not amenable to biopsy that was identified as a granulomatous nodule after surgery. Screening performance was good with a sensitivity of 89.5%, specificity of 97.1% and negative predictive value (NPV) of 99.6%.

One of the primary aims of the Manchester pilot was to engage with high-risk participants most likely to benefit from lung cancer screening. Demand for service exceeded capacity. 75% of participants were from the lowest quintile of deprivation for England. 82% of participants had left school by the age of 16 without any significant educational qualifications. One in five (22%) had a family history of lung cancer and a personal history of COPD, one in four (24%) had a previous exposure to asbestos and one in ten (12%) had a personal history of cancer. A third (35%) of LHC attendees were current smokers and of those that qualified for LDCT screening more than half (53%) were current smokers. All of these demographical characteristics are known to be associated with increased lung cancer risk and reduced screening participation.

Additionally, almost one in five (18.6%) of all service attendees had evidence of previously undiagnosed airflow obstruction and, therefore, likely COPD. More than half of these individuals had associated symptoms and therefore a tenth (9.9%) of all screening attendees had evidence of undiagnosed symptomatic COPD, known to be associated with increased morbidity and mortality[60]. The Manchester pilot was also able to identify a third of its lung cancer screening participants as at high risk of CVD, defined as a QRISK2 score of ≥10%, who were not on primary prevention as recommended by national guidelines[69]. Such individuals were referred back to the primary care physicians for a more detailed assessment and provision of primary prevention. By the second round of screening, one in ten (10.2%) baseline round current smokers had stopped smoking, most (78%) for six months or more which is associated with an increased likelihood of successful long-term cessation[83]. The positive impact of the pilot has led to commissioning by the Manchester Health and Care Commissioning group of an expanded £4.2 million service across the north and east Manchester regions to carry out over 10,000 LHCs and an estimated 5,000 screening LDCT scan. The results have also significantly contributed to NHS England's decision to announce plans for £70 million funding to rollout similar LHC programs across 10 sites across the country[84].

## Conclusions

A mortality reduction from LDCT screening has now been demonstrated in three RCTs providing the evidence required to suggest implementation of lung cancer screening. This should help tackle the global health and economic burden of lung cancer. Emerging data from pilot programmes suggests this can be done in a safe and effective manner attracting high-risk participants, detecting significant numbers of early stage lung cancers amenable to curative treatment, all whilst minimising potential harms of screening. The novel concept of incorporating lung cancer screening into so-called Lung Health Checks has been found to be acceptable to local populations and allows the opportunity to address other competing causes of smoking related morbidity and mortality such as CVD and COPD. Ensuring that screening is considered as a concept that includes identification and engagement of participants, the LDCT and its evaluation, and the diagnostic and treatment components is critical for the highest quality implementation and associated harm reduction. Lung cancer screening questions must now be redirected from asking if lung cancer screening can save lives to focus more on the logistical challenges of delivering screening on a large scale and in a high quality manner accounting for the shortage in resources, both in terms of facilities and staffing.

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Chapter 14

# Lung Cancer: Current Therapies and New Targeted Treatments

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*"Audentes fortuna juvat"*

## Introduction

Lung cancer is the commonest malignancy worldwide, and accounts for the majority of cancer-related deaths. Approximately 85% of lung cancers are classified as non-small cell lung cancer (NSCLC), and the rest are small cell lung cancers (SCLC). In most cases, lung cancer is diagnosed at an advanced stage due to presentation with symptoms of local tumour or distant metastases. Lung cancer is currently staged according to the Union for International Cancer Control (UICC) eighth edition of the tumour, node, and metastasis (TNM) classification[1]. The data on which this system was based come from the International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee's retrospective and prospective databases of more than 100,000 patient cases diagnosed between 1999 and 2010 to predict overall survival (OS). According to these outcomes, the 5-year survival for patients with stage IVA disease is 10%, and those with Stage IVB, 0%.

## Newer therapeutic strategies: molecular targeted therapy

The fundamental basis for treating patients with stage IV NSCLC has previously been rooted in chemotherapy. However, over the past few decades, NSCLC systemic therapy has rapidly evolved, initially with the development of molecular targeted therapies and now checkpoint inhibitor therapy both as monotherapy and in combination with chemotherapy. These initial changes in systemic therapy, away from a global use of chemotherapy for all NSCLCs, with the introduction of molecular targeted therapies, were only made possible due to a better understanding of somatic molecular genetics. The publication of the first draft sequence of the human genome occurred over 18 years ago and provided a crucial insight into the normal human genome sequence, thereby allowing mapping differences in sequence variants in tumours (somatic vs germline variants)[2,3]. In parallel, sequencing the human kinome (1.7 percent of all human genes) thereby allowed a broader understanding of molecular abnormalities identified in these key signal transduction proteins in tumours

and their potential role as viable targets for the emerging field of kinase inhibitors[4]. In 2004, the discovery that sensitising mutations in the EGFR gene were fundamentally responsible for the dramatic responses observed with gefitinib (Iressa) coupled with results of the IPASS (Iressa Pan-Asia Study) trial led to implementation of tumour genetic testing as standard care for patients with advanced NSCLC[5,6,7,8].

At the molecular level, NSCLC adenocarcinoma is now known to be a heterogeneous disease driven by multiple somatic aberrations. The most commonly identified oncogenic drivers are mutations in EGFR and KRAS genes. The rarer oncogenic fusions in ALK, ROS1, and RET, as well as MET exon 14 and BRAFv600E mutations, also fundamentally identify clinical benefit to their paired kinase inhibitors[8]. Sub-classifying NSCLC by molecular status is now, therefore, routine for stage IV disease, allowing matching of somatic aberrations to kinase inhibitor. Such kinase inhibitors are highly active for some sensitising somatic variants (eg osimertinib [Tagrisso] for EGFR mutations, crizotinib [Xalkori] for ALK and ROS1 fusions) and are licensed. Other molecular alterations such as RET fusions are rarer key NSCLC drivers with highly active kinase inhibitors in development that will likely soon be licensed, whereas others, eg HER2 amplification have targeted approaches that are highly active and approved for other solid tumours, but their clinical utility in lung cancer patients has yet to be proven. Thus, at time of diagnosis of stage IV NSCLC, a number of predictive biomarkers are recommended to be tested to allow optimal drug therapy, licensed for use by both European Medicines Association (EMA) and Food and Drug Administration (FDA), and recommended by both the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO), respectively[9,10]. These predictive biomarkers include EGFR, ALK, ROS1, and BRAF alongside PDL1 to predict magnitude of benefit from immune checkpoint inhibitors. Although molecular targeted therapy is highly effective in oncogene-addicted NSCLC - a term used to describe NSCLC driven by a key molecular aberration with deep and rapid responses (Figure 1), it is not curative, and acquired resistance to drug therapy is inevitable.

If the biological mechanism that underpins acquired resistance is identified and treated with next generation kinase inhibitors, a significant survival benefit for stage IV NSCLC can be observed: a huge change in survival metrics to the dataset that underpins the IASLC staging dataset. Thus, for example, the median overall survival (mOS) for advanced (stage IV) ALK positive NSCLC patients is now measured in years, with one institution reporting a mOS of

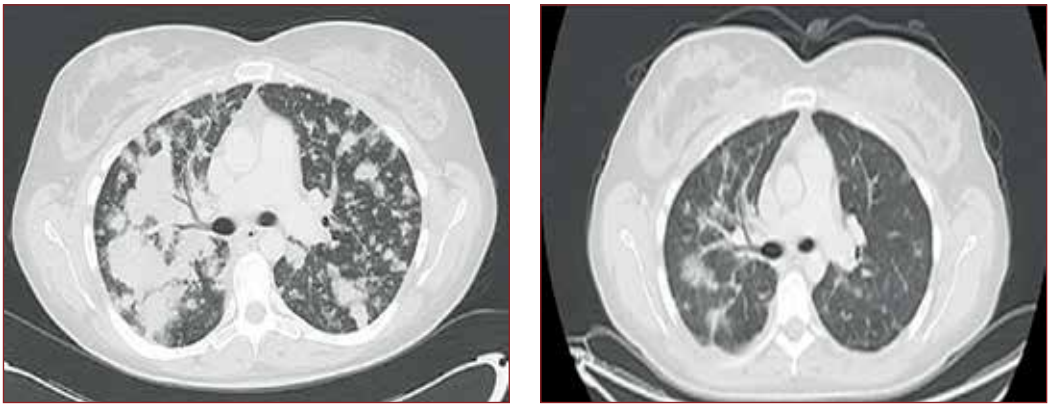

*Figure 1: Left:Patient with stage IVA ALK-fusion positive NSCLC treated with crizotinib. Right: Interval CT scan after 2 months of crizotinib shows partial response.*

6.8 years[11]. Indeed, by definition, whilst 50% of the population will live beyond this metric, predicting individual patient prognoses remains difficult. Like kinase inhibitors, cancer immunotherapy also has the ability to markedly increase OS in select NSCLC patients with metastatic disease. Long-term OS data from the CHECKMATE 003, the original multicentre phase 1 trial of nivolumab (Opdivo), including a NSCLC cohort expansion in patients relapsed post chemotherapy, has now demonstrated a 5-year absolute survival of 16% versus previous datasets eg the IASLC staging dataset demonstrating a 5-year OS rate of 0% for stage IV B[12]. Indeed, this long-term survival benefit has been observed in both squamous and nonsquamous NSCLC histologies. Moreover, the shape of the Kaplan Meier curve has demonstrated a long durable benefit for such patients, with those alive at year 3 most likely to still be alive at year 5: a major change to that previously seen for molecular targeted therapy.

The subsequent routine implementation of immune checkpoint inhibitor therapy has therefore marked a major milestone in the lung cancer therapeutics. Rather than reserving immune checkpoint inhibitors to patients relapsing after first-line chemotherapy, these are now used in the first-line setting as monotherapy, with the results of the KEYNOTE 024 randomised phase 3 trial in previously untreated advanced NSCLC patients with PDL1 expression ≥50% (those previously identified from phase 1 studies as most likely to benefit from immune checkpoint inhibition) and without EGFR mutation or ALK fusion demonstrating a mOS of 30 months in the pembrolizumab (Keytruda) group versus 12.2 months in those randomised to chemotherapy (HR=0.63; 95% CI: 0.47 to 0.86; nominal p=0.002)[13]. This result is more impressive noting that cross-over was allowed on progression for the chemotherapy control arm, and the trial was stopped early given the large benefit for pembrolizumab. With a favourable safety profile and no new safety concerns, these data led to the global licensing of first-line pembrolizumab and reinforced the routine implementation of PDL1 testing.

The current landscape of metastatic drug therapy for NSCLC is therefore functionally divided into two categories: oncogene- and immune-addicted lung cancers and their respective treatments, kinase inhibitors and checkpoint inhibitors, respectively. Although these new therapies have the potential for major clinical benefit in the front-line advanced NSCLC setting, a major question remains regarding the ability of these new drugs to improve the curability of radically treatable NSCLC for operable patients. The focus of drug development has now therefore shifted to early-stage (IB - IIIA) patients with resectable lung cancer where chemotherapy has already become established as providing a small but clinically meaningful survival benefit. A number of key clinical trials over the past decade have been conducted, and many are ongoing, with a view to potentially markedly change the face of drug therapy for operable NSCLC patients.

## Will molecular targeted therapy improve NSCLC curability?

Trialling molecular targeted therapy for patients with radically treatable NSCLC was first formally evaluated in the SWOG S0023 randomised phase 3 trial[14]. Here, gefitinib was evaluated in the maintenance setting for stage III NSCLC[15,16,17]. Patients completing radical chemoradiotherapy for stage III NSCLC were randomised to either maintenance gefitinib for up to 5 years versus placebo. Unfortunately, an unexpected survival detriment for gefitinib was observed (mOS 23 vs 35 months for gefitinib vs placebo, respectively: HR=0.633; 95%CI: 0.44-0.91, p=0.013), with no obvious cause and no new toxicity concerns[14]. However, this trial was performed in an era when EGFR mutations had not been

well characterised, and recruited all comers, unselected for EGFR mutational status, likely therefore recruiting predominantly EGFR wild-type patients. This negative trial therefore resulted in significant caution in evaluating kinase inhibitors further in the radical setting, especially after radical radiotherapy.

For patients with resected stage II or III NSCLC the standard of care is currently adjuvant chemotherapy, specifically adjuvant cisplatin-doublet chemotherapy, based on the results of the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, reporting a 5.4% 5-year absolute OS benefit[18]. Nevertheless, the magnitude of this benefit is modest and toxicities can be prohibitive. Given the survival benefits observed with molecular targeted therapy for stage IV NSCLC, their role as adjuvant therapy in resected NSCLC has been evaluated in a number of trials, noting their relatively favourable toxicity profile.

To date, three randomised trials have evaluated first generation EGFR kinase inhibitors: RADIANT, ADJUVANT and EVAN, all demonstrating a disease-free survival (DFS) benefit, but no OS benefit[19,20,21]. Briefly, in the EGFR mutation positive subset of the phase 3 RADIANT trial, where completely resected IB-IIIA NSCLC patients were randomised to either erlotinib (Tarceva) or placebo for 2 years, whilst median DFS was markedly improved for erlotinib (46.4 vs 28.5 months; HR=0.61, 95%CI: 0.38-0.98, p=0.039), this was not statistically significant, likely due to study power, and importantly, there was no OS benefit[19]. Most worryingly, the commonest site of relapse in those receiving erlotinib was the brain (37.1% vs 12.9%).

ADJUVANT (CTONG1104) was a large randomised phase 3 trial of patients with completely resected stage II-IIIA (N1-N2) and EGFR-mutant (exon 19 deletion or L858R) NSCLC run in China, randomising patients between gefitinib alone (without chemotherapy) for 24 months and cisplatin-vinorelbine chemotherapy for 4 cycles[20]. Whilst a significantly longer DFS for gefitinib was observed (28.7 vs 18.0 months; HR=0.60, 95%CI: 0.42-0.87, p=0.0053), again there was no OS benefit. Indeed, there has been some concern about the durability of benefit with gefitinib based on 24 months follow-up data.

Another Chinese trial, EVAN, investigated the role of adjuvant erlotinib for in stage IIIA EGFR mutation-positive (exon 19 deletion or L858R) NSCLC patients who had undergone complete resection[21]. In this open-label phase 2 trial, patients were randomised to adjuvant erlotinib for 24 months or four cycles of cisplatin-vinorelbine chemotherapy. Adjuvant erlotinib again improved DFS (HR=1.823, 95% CI: 1.194-2.784; p=0.0054). OS data were immature at time of reporting but currently favour adjuvant erlotinib (HR=0.165, 95% CI: 0.047-0.579; p=0.0013). Thus, whilst trials of first generation EGFR kinase inhibitors have consistently demonstrated a DFS advantage, no mature OS benefit has been demonstrated to date. Coupled with the higher intracranial progression rate, these drugs have not yet been licensed for this indication and neither are they recommended by international society guidelines[22,23]. However, results of the ongoing ADAURA phase 3 trial, randomising patients with common EGFR mutations between adjuvant osimertinib (a third generation mutation-specific EGFR inhibitor, highly effective and now considered to be standard for front-line metastatic use and with strong CNS penetration) and placebo (after completion of adjuvant chemotherapy where indicated), are eagerly anticipated[24]. Unfortunately, the study primary endpoint is DFS, and whether an OS benefit will be identified for this disease where control patients will crossover to receive osimertinib on relapse, is debatable. Similarly, in the United States (US), the phase 3 ALCHEMIST trial is molecularly stratifying resected patients and for ALK positive NSCLC randomising to crizotinib or placebo for 2 years[25].

## Will immune checkpoint inhibitors improve NSCLC curability?

Despite definitive platinum-based doublet chemotherapy plus concurrent radiation therapy (chemoradiotherapy) as standard of care, most NSCLC patients with locally advanced, unresectable (stage III) disease will progress. The Aupérin meta-analysis demonstrated a significant benefit of concomitant chemoradiotherapy on OS (HR=0.84; 95% CI: 0.74-0.95; p=0.004) with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years among these patients, and only 15% alive at 5 years[26]. Aiming to improve outcomes further, using the immune checkpoint inhibitor durvalumab (Imfinzi) has demonstrated a marked survival advantage for inoperable stage III NSCLC treated with concomitant radical chemoradiotherapy in the randomised phase 3 PACIFIC trial[27].

Here, durvalumab was administered two-weekly for up to one year to patients with inoperable Stage III NSCLC with involved N2 nodes who had previously received platinum-based chemotherapy concurrently with definitive thoracic radiation therapy (54-66 Gy) starting within 42 days after completion of chemoradiotherapy. The median progression-free survival (PFS) was markedly improved (17.2 vs 5.6 months, HR=0.51; 95%CI 0.41-0.63) as was mOS (NR vs 28.7 months, HR=0.68; 95%CI 0.47-0.997, p=0.0025). Importantly, durvalumab improved both local control (ORR=17.8 vs 30.0%) and distant control (a marked reduction in incidence of new metastatic lesions, including the CNS (6.3 vs 11.8%). Durvalumab therefore improves both locoregional and distant control compared with placebo[27].

When evaluating outcomes of previous phase 3 trials of multimodality therapy (RTOG 0617, PROCLAIM and INT0139), PACIFIC had both a better median and 2-year OS. Specifically, durvalumab significantly increased the 2-year OS from 55.6% to 66.3%, whilst the other trials did not reach the 60% mark 28, 29, 30. Briefly, in RTOG 0617, high-dose (74 Gy in 2 fractions) radiotherapy in inoperable stage III NSCLC proved potentially harmful when compared with standard dose radiotherapy (60 Gy) with median OS 20.3 months in the high-dose versus 28.7 months in the standard dose group (HR=1.38, 95% CI: 1.09-1.76; p=0.004)[28]. The 2-year survival rate for the control arm was 58%. In the PROCLAIM trial, concurrent pemetrexed-cisplatin and thoracic radiation therapy followed by consolidation pemetrexed did not show superiority to the standard chemoradiotherapy with etoposide-cisplatin in stage III unresectable nonsquamous NSCLC (OS HR 0.98; 95% CI: 0.79-1.20; p=0.831)[29]. The 2-year survival rate for the control arm was 52%. Likewise, in the earlier phase 3 trial, INT0139, chemotherapy plus radiotherapy with consolidation resection in operable stage III NSCLC did not produce an OS advantage in the intention-to-treat (ITT) population to standard concurrent chemoradiotherapy alone, with a 2-year survival rate of 48%[30]. However, the exploratory analysis of the tri- versus bimodality treatments did show that OS was improved in the lobectomy, but not the pneumonectomy, group.

Although the checkpoint inhibitor durvalumab has proven efficacy and safety in unresectable Stage III NSCLC, there are other emerging trials exploring the strategy of adding consolidation immunotherapy to enhance the antitumour effect of radical concurrent chemoradiation. In the phase 2 trial, LUN 14-179, consolidation pembrolizumab is being investigated in unresectable stage III NSCLC patients following completion of concurrent chemoradiation with carboplatin-paclitaxel, cisplatin-etoposide, or cisplatin-pemetrexed and 59-66.6 Gy thoracic radiotherapy, if no progression, 4 to 8 weeks after completion of therapy. Patients were consolidated with the anti-PD1 agent pembrolizumab for up

to 1 year. The two-year survival rate was an impressive 61.5%, underpinned by a median PFS of 15.0 months[31]. The median OS is yet to be reached and mature follow-up data are anticipated.

ETOP 6-14 NICOLAS is an ongoing phase 2 trial designed to evaluate the safety and feasibility of nivolumab given concurrently with radical radiotherapy when delivered either sequentially or concurrently with chemotherapy in unresectable stage III NSCLC. Safety data on the first 21 patients presented at the ASCO 2018 meeting confirmed feasibility with no grade ≥ 3 pneumonitis and a 6-month pneumonitis rate consistent with that expected from historical data[32]. Accrual continues and efficacy data are awaited.

Similarly, the anti-PDL1 atezolizumab (Tecentriq) is currently being investigated in the phase 2 DETERRED trial again in unresectable stage III NSCLC patients. This single institutional trial is assessing the safety and efficacy of adding the anti-PDL1 atezolizumab either sequentially with carboplatin-paclitaxel after completing chemoradiotherapy only or concurrently with chemoradiotherapy followed by consolidation atezolizumab with carboplatin-paclitaxel. Importantly, initial results of both arms show that atezolizumab administration is safe, particularly when administered concurrently with chemoradiation. Similarly, DETERRED has also so far demonstrated promising efficacy with a one-year OS rate of 77% for those receiving concurrent chemoradiotherapy and atezolizumab[33].

## Immune checkpoint inhibitors in operable NSCLC

Having established proven efficacy for multiply relapsed metastatic NSCLC, front-line metastatic NSCLC, stage III NSCLC receiving radical chemoradiotherapy, it is also being evaluated in patients with operable NSCLC, in both the neoadjuvant and adjuvant settings. Multiple commercial and academic trials of neoadjuvant checkpoint inhibitors are recruiting. These include Checkmate 816, a phase 3 trial evaluating nivolumab (anti-PD1) and ipilimumab (Yervoy; anti-CTLA4), nivolumab and platinum-doublet chemotherapy, and platinum-doublet chemotherapy alone in early stage (IB-IIIA) NSCLC[34]. The primary endpoints are event-free survival and pathological complete response.

In the adjuvant setting of resected NSCLC, several large randomised phase 3 checkpoint inhibitor trials are ongoing. These include trials of nivolumab, pembrolizumab, atezolizumab, and durvalumab being evaluated after completion of adjuvant chemotherapy if indicated[35,36,37,38]. The PEARLS trial (NCT02504372) randomises completely resected NSCLC to anti-PD1 pembrolizumab (MK-3475) or placebo for one year[36]. IMpower010 (NCT02486718) randomizes resected patients between atezolizumab versus best supportive care for 48 weeks[37]. Similarly, IFCT-1401 (NCT02273375) randomises between durvalumab and placebo for a maximum of 1 year[38].

Despite a similar OS benefit of neoadjuvant or adjuvant cisplatin-based chemotherapy in resectable NSCLC, the clinical standard has remained adjuvant cisplatin-based doublet chemotherapy. Two recent trials have evaluated the role of neoadjuvant checkpoint inhibitors in early stage operable NSCLC. Two recent studies to date have shown that giving two doses of nivolumab or atezolizumab prior to surgery is safe and potentially highly active in resectable NSCLC patients[39,40]. In the LCMC3 phase 2 trial, two doses of atezolizumab were given prior to surgery in stage I-III NSCLC, unselected by PDL1 status. The major pathological response rate (MPR, viable tumour cells in 10% or less of the resection specimen) was 22% but impressively nearly every patient had an element of pathological downstaging on the resection specimen, the magnitude of which was not correlated to

*Table 1: Clinical trials of neoadjuvant anti-programmed death receptor 1 (PD1) and programmed death-ligand 1 (PDL1) immune checkpoint inhibitors in early stage non-small cell lung cancer.*

| Strategy | Trial [Reference] | Clinical Phase | Treatment | Target Number of Patients | Primary Endpoint |
|---|---|---|---|---|---|
| Neoadjuvant IIIA | NCT03081689 [43] | 2 | Nivolumab +CHT | 46 | PFS |
| Neoadjuvant IA-IIIA | NCT03158129 [44] | 2 | Nivolumab or Nivolumab +ipilimumab | 66 | MPR |
| Neoadjuvant IB (>3cm)-IIIA | TOP1501 (NCT02818920) [45] | 2 | Pembrolizumab | 32 | Surgical feasibility |
| Neoadjuvant IB (>4cm)-IIIA non N2 | PRINCEPS (NCT02994576) [46] | 2 | Atezolizumab | 60 | Toxicities leading to surgical delay |
| Neoadjuvant IB-IIIA | MAC (NCT02716038) [47] | 2 | Atezolizumab +CHT | 30 | MPR |
| Neoadjuvant IB-IIIA | (NCT02927301) [48] | 2 | Atezolizumab | 180 | MPR |
| Neoadjuvant IIIA | SAKK 16/14 (NCT02572843) [49] | 2 | Durvalumab +CHT | 68 | EFS |
| Neoadjuvant I (>2cm)-IIIA | NCT02904954 [50] | 2 | Durvalumab or Durvalumab +SBRT | 60 | DFS |
| Neoadjuvant IB-II | IONESCO (NCT03030131) [51] | | | | |

*CHT=Chemotherapy; EFS= Event-free survival; SBRT=stereotactic body radiotherapy*

PDL1 status. 28% developed grade 3+ toxicities and there were no toxic deaths[40]. In a similarly designed phase 2 trial of two doses of nivolumab in stage I-III operable NSCLC, the MPR was 45%[39]. Again pathological downstaging occurred irrespective of PDL1 status. Interestingly, pathological response correlated poorly with radiological appearance[39]. Both nivolumab and atezolizumab did not delay surgery in both trials.

In the metastatic setting, combination chemotherapy-immunotherapy has demonstrated synergy with impressive response rates, and low progression rates. Building on this, the phase 2 NADIM trial evaluated combination neoadjuvant chemotherapy-nivolumab in

stage IIIA NSCLC[41]. Here, the primary endpoint was PFS at 12 months but MPR was also evaluated as an exploratory, early endpoint, given that it may be a surrogate marker of OS. Here, the MPR was 80% with complete pathological response observed in 75%[41]. This is a remarkable finding given historical MPR rates previously reported, eg the NATCH phase 3 trial a decade earlier[42], identifying a 10% pathological complete response for neoadjuvant chemotherapy. Therefore, the NADIM trial has suggested a potential major role for neoadjuvant combination chemotherapy-immune checkpoint inhibitor. Currently, there are several additional ongoing phase 2 trials investigating the use of checkpoint inhibitors for early NSCLC combining immunotherapy with chemotherapy, immunotherapy alone, combination immune checkpoint inhibitors, or immunotherapy with radiotherapy (Table 1). These results are eagerly anticipated, given those from NADIM.

## Conclusions

These are exciting times for the improved treatment of lung cancer patients. New highly effective drugs for NSCLC, beyond chemotherapy, have been rapidly evolving over the last few years. The discovery of driver mutations and their successful management with targeted therapies has revolutionised advanced disease in terms of improving long term responses and survival outcomes. Unfortunately, to date, molecular targeted therapy has not been shown to improve OS in radically treatable NSCLC. The identification of the escape mechanism by tumour cells from recognition by the immune system and the discovery of programmed death-1-receptor (PD1) and ligand (PDL1), as well as cytotoxic T lymphocyte antigen-4 (CTLA-4), as potential drug targets, has generated a plethora of possible immune-oncological therapies for cancer management. The use of immune checkpoint inhibitors in the metastatic stage IV NSCLC setting is now well established. Durvalumab is now standard of care to consolidate stage III NSCLC post chemo-radiotherapy following the impressive recent PACIFIC trial data. These results have opened the door for the use of immunotherapy in earlier stages of the disease to potentially offer the best chance for a cure. This review has summarised the recent trial data on novel therapeutic strategies in early stage NSCLC. Multiple ongoing phase 2 and 3 clinical trials of checkpoint inhibitors in adjuvant and neoadjuvant settings for stage I-III resectable and unresectable NSCLC patients are now recruiting, with exciting preliminary results thus far.

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Chapter 15

# Cost-Effectiveness in Minimally Invasive Thoracic Surgery

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*"Brevis oratio penetrat coelos longa portatio evacuat scyphos"*

## Introduction

In recent decades, minimally invasive thoracic surgery (MITS) has become a substantial portion of thoracic surgical practice - for many surgeons, minimally invasive approaches are preferred for the majority of diseases they manage. For anatomic lung resection, MITS is approaching a majority of reported cases while the rate of traditional thoracotomy approaches has decreased[1,2].

Simultaneously, there has been increasing scrutiny to decrease costs associated with surgery, including thoracic surgery[3]. Many authors have speculated that MITS would be associated with lower costs, given decreased pain, decreased length of stay, earlier return to work, and a likely modest reduction in surgical and post-surgical complications. However, it is possible that the costs of the materials required to perform minimally invasive surgery might outweigh any other areas in which cost savings is achieved. Furthermore, any decreased cost of MITS as compared to open thoracic surgery would not be inappropriate without equivalency in patient outcomes.

In this chapter, we will discuss some of the relevant literature regarding cost-effectiveness in MITS. Specifically, we will investigate cost-effectiveness in Video-Assisted Thoracoscopic (VATS) Lobectomy (VATSL) and in minimally invasive approaches to thymectomy. We will introduce these surgical methods, provide evidence for or against outcome equivalency, and discuss the studies addressing the cost-effectiveness of these methods, including those published and presented by our own thoracic surgery group. Along the way, we will make evidence-based suggestions for how cost-savings can be achieved without compromising patient outcomes.

## Cost-effectiveness in VATS Lobectomy

VATSL is one of the most common thoracic operations performed, and the techniques for its performance are now widely disseminated among thoracic surgeons. As centres across the country have become more comfortable with these techniques, most surgeons now consider VATSL ideal for clinical stage I lung cancer patients[4]. Many also consider it appropriate for patients with known or suspected N1 disease, and a substantial number will even use VATSL in the setting of N2 disease and centrally placed tumors in certain circumstances[5]. VATSL thus today represents a substantial portion of lobectomies performed in the United States. A recent study performed by Fernandez and colleagues found of 27,844 patients queried utilising the STS General Thoracic Surgery Database (GTSD) undergoing lung cancer resections, 62% of surgeries were performed utilising thoracoscopy[2]. This is substantially increased from a study published less than thirty years ago in 1993, in which of 1,820 patients undergoing a VATS procedure, only 38 (2.1%) underwent VATSL[6].

Recent studies have demonstrated improved patient outcomes associated with VATSL as compared to lobectomy by thoracotomy (THORL). VATSL has been associated with lower rates of complications and shorter length of stay (LOS)[7-17]. There is evidence to suggest similar and possibly better postoperative quality of life and oncologic outcomes associated with VATSL compared to THORL[15,18-23].

Given reduced pain, shorter LOS, and lower complication rates, it would be reasonable to conclude that the costs associated with hospital care for patients undergoing VATSL are lower compared to those associated with THORL. However, studies have shown conflicting results.

Swanson and colleagues in their 2012 retrospective cohort of 3,961 patients found that VATSL was associated with shorter LOS (6.15 days vs. 7.83 days, $p < 0.001$), and corresponding lower hospital costs ($20,316 vs. $21,016, $p=0.027$) compared to THORL[24]. However, other studies have found no impact on hospitalisation costs[15,25-27]. Golpaldas and colleagues utilised a large dataset of 13,619 patients and found no difference in hospitalisation costs between VATSL and THORL[25]. In 2009 Farjah and colleagues demonstrated lower mean LOS associated with VATSL but did not show decreased hospitalisation costs in a database of 12,958 patients[15]. In a similar analysis in 2014, Farjah and colleagues investigated both hospitalisation as well as 90-day costs[28]. In this study of 9,962 patients, VATSL was associated with lower rates of rates of prolonged LOS (greater than 14 days), as well as decreased emergency department utilisation and re-admission rates. In sum, average 90-day cost savings from VATSL were $3,476. Brunneli, in a 2016 review of costs of VATSL, notes that different cost outcomes in various studies could be attributed to differences in patient populations[29].

However, of more immediate interest to surgeons may lie with the fact that differences in costs may stem directly from variations in precisely how different surgeons perform these procedures. For example, Swanson and colleagues, in their previously discussed 2012 study, noted that surgical volume and experience significantly impacted costs[24]. In their dataset, hospitalisation costs for low-volume surgeons – defined as those with less than 16 surgeries in a 6-month period – had associated VATSL costs of nearly $4,000 higher than high-volume surgeons.

What more precisely might explain this drastic cost difference in VATSL hospitalisation costs between surgeons? Several authors have investigated the impact of intraoperative

costs in VATSL. Deen and colleagues found intraoperative costs constituted a substantial portion of VATSL hospitalisation costs, and Nakajima and colleagues demonstrated that intraoperative costs made up more than 60% of hospitalisation costs for their cohort[30-31].

## The Role of Intraoperative Costs in Overall Costs of VATS Lobectomy

Given that operating room costs are so significant in VATSL, perhaps differences in operating room practices could explain why VATSL has been shown to have lower hospital costs overall in only some, but not all, studies. Casali and Walker in 2009 compared VATSL and THORL costs and found THORL to be more expensive than VATSL[32]. This was explained by significantly reduced LOS associated with VATSL compared to THORL, although VATSL operating room costs were nearly twice as high as those of THORL. These operating room costs, they note, varied significantly by lobe and resection type, attributed to the differing needs of disposables such as stapler reloads. Khullar and colleagues also found that intraoperative costs, and specifically stapler utilisation, were a primary factor in VATSL cost, and were highly variable[33].

Our group has presented and published our data investigating the costs between VATSL and THORL [34]. We used prospectively collected data from our institution's modified Society of Thoracic Surgeons (STS) database between 2009 and 2013 to compare outcomes and costs associated with VATSL vs. THORL. We compared two surgeons from our institution, one a cost-conscious surgeon labelled "low-cost," and a less cost-conscious surgeon labelled "high-cost." The VATSL costs of the "high-cost" surgeon were compared against those of the "low-cost" surgeon, and both VATSL costs were compared against a combined pool of their THORL cases.

In total, 269 patients were included: 100 THORL patients, 99 "high-cost" VATSL patients, and 70 "low-cost" VATSL patients. Patient characteristics which differed between VATSL groups at $p<0.20$ were used in a linear regression model to control for outcomes. Before and after applying this model to control for baseline characteristics, there were no differences in postoperative VATSL outcomes between the two surgeons.

VATSL costs for the "low-cost" surgeon were substantially lower than those of the "high-cost" surgeon – the "high-cost" surgeon had VATSL hospitalisation costs more than 20% higher than that of the "low-cost" surgeon (Figure 1 overleaf).

This difference was driven almost entirely by increased intraoperative costs. The "low-cost" surgeon did have lower stapler costs than the "high-cost" surgeon, however the largest difference in costs incurred by the surgeons was due to the use of other disposables such as energy devices, disposable ports, and surgical sealants by the "high cost" surgeon but not by the "low cost" surgeon (Figure 2 overleaf).

Significantly, the "low-cost" surgeon's VATSL total hospitalisation costs were approximately 30% lower than those of THORL, while the "high-cost" surgeon's VATSL costs did not differ from THORL costs. While both surgeons' VATSL bed costs and LOS were similar, these savings were lost in the case of the "high-cost" surgeon as a result of his utilisation of costly operating room (OR) supplies, which were nearly twice as expensive as those of the "low-cost" surgeon.

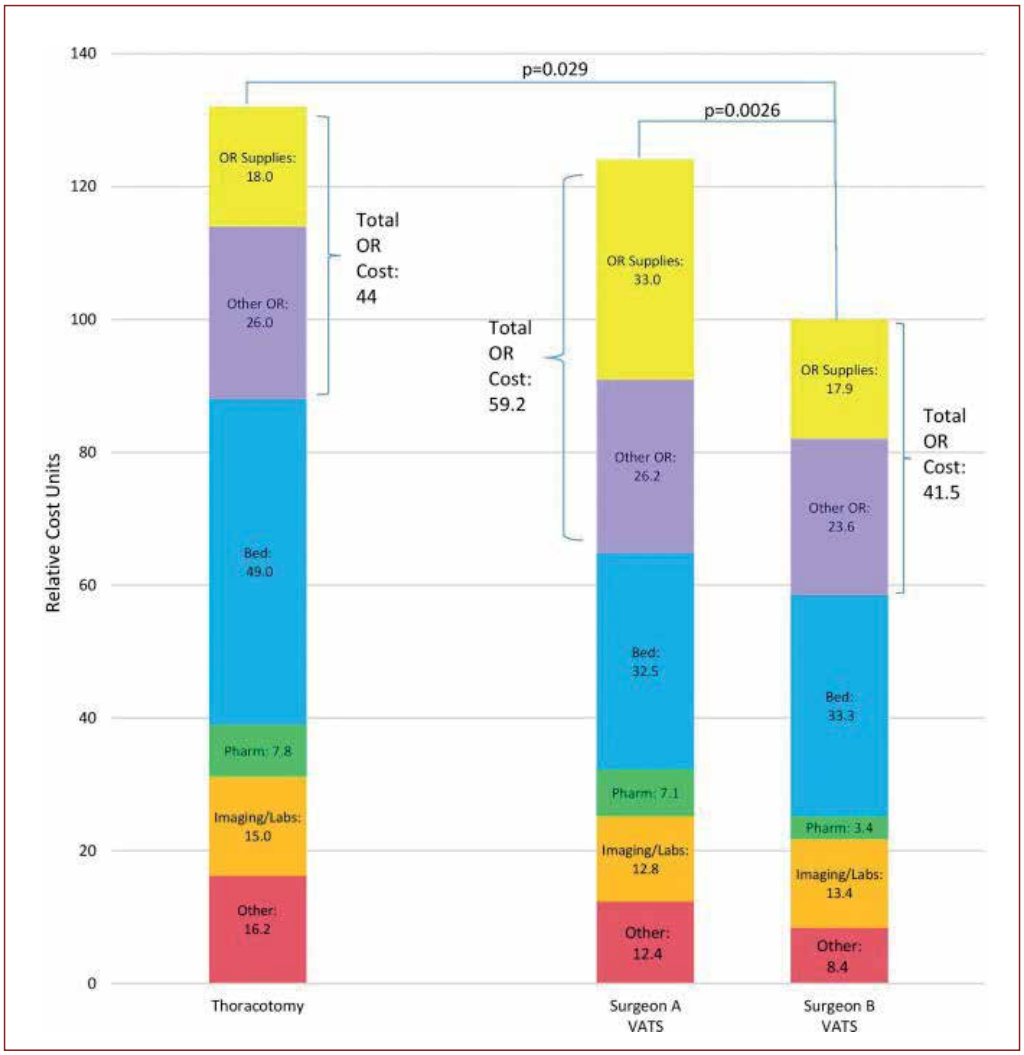


*Figure 1: Relative hospital costs associated with VATS lobectomy performed by 2 surgeons: a low-cost surgeon (surgeon B) and a higher cost surgeon (surgeon A). The leftward most bar represents the cost of lobectomy by thoracotomy by the 2 surgeons, combined. Surgeon B's VATS lobectomy costs were set at a value of 100 relative cost units. Each bar is separated into the costs of the variety of separate accounting categories that contribute to total hospital cost. Note that the high-cost surgeon incurred 24% greater costs per VATS lobectomy procedure than the low-cost surgeon, and that only the low-cost surgeon's VATS lobectomy costs were significantly less than lobectomies by thoracotomy. Further, intraoperative supply costs were the greatest contributor to the difference in costs between the surgeons (Reprinted from The Journal of Thoracic and Cardiovascular Surgery, Richardson MT et al, Intraoperative costs of video-assisted thoracoscopic lobectomy can be dramatically reduced without compromising outcomes, pp. 1267-77, 2017, with permission from Elsevier).*

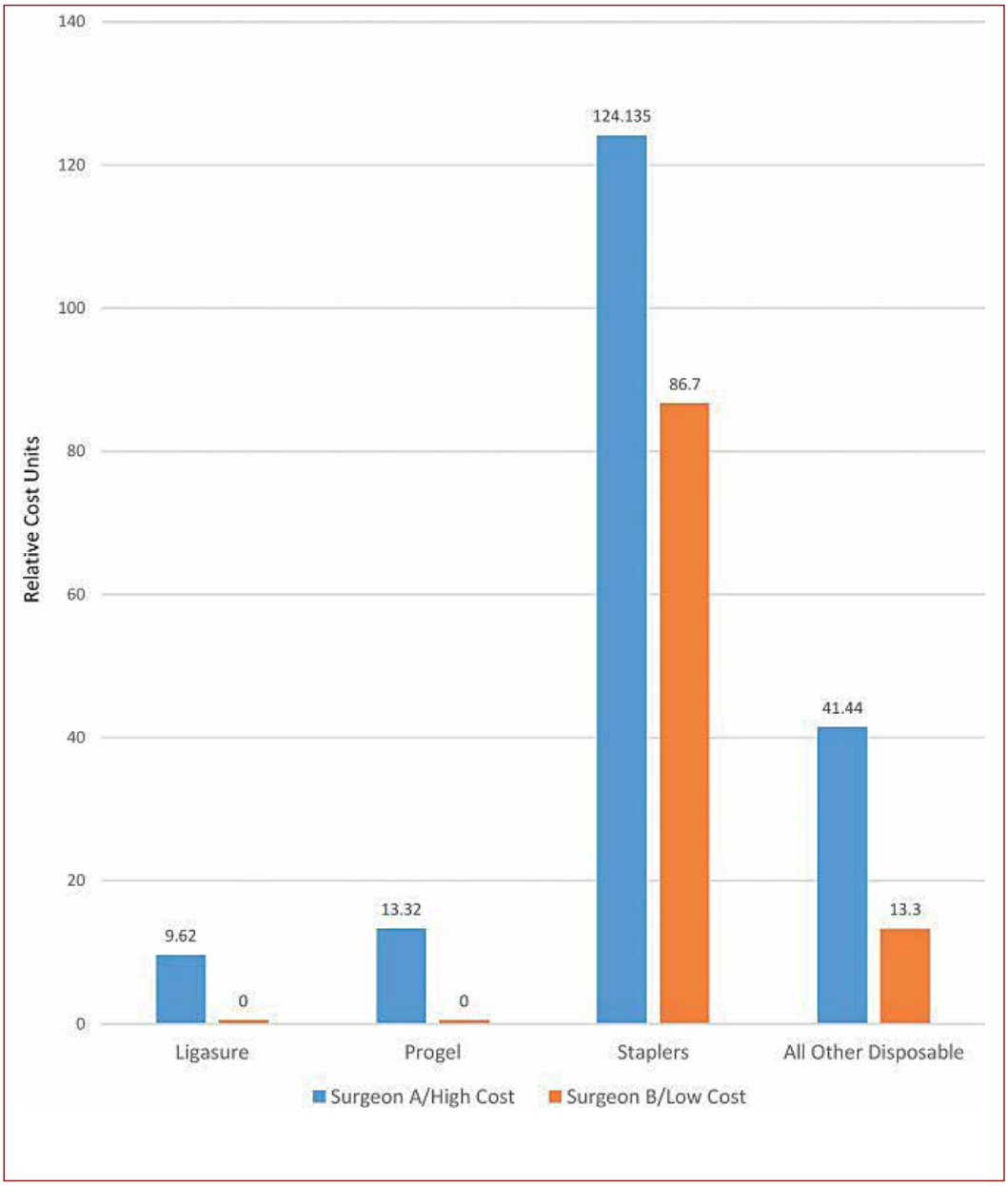


*Figure 2: Components of the intraoperative supply costs during VATS lobectomy by a high-cost (blue) and low-cost (orange) surgeon. The "all other" category includes all disposables besides those shown in the other bars in this figure. Note that although stapler use was a large contributor, the use of other expensive disposables such as energy devices, glues/sealants, and commercial ports combined to make up more than half of the difference in cost between the high- and low-cost surgeons (Reprinted from The Journal of Thoracic and Cardiovascular Surgery, Richardson MT et al, Intraoperative costs of video-assisted thoracoscopic lobectomy can be dramatically reduced without compromising outcomes, pp. 1267-77, 2017, with permission from Elsevier).*

## Surgeon-choices Dramatically Impact the Intraoperative Costs of VATS Lobectomy

From these results, it is apparent that surgeons can intentionally and dramatically impact the costs of the VATSL procedures they perform by avoiding expensive, disposable instruments and sealants that do not improve surgical results. Safe cost-savings achieved in this way in the operating room will ensure that overall, VATSL is indeed less expensive than lobectomy by thoracotomy. With careful selection of only truly necessary surgical adjuncts and disposables, VATSL costs can be reduced to levels well below that of THORL, given the significantly lower LOS associated with VATSL. Without this selection - without keeping intraoperative costs within reason – all cost benefits associated with VATSL are lost.

## Cost-effectiveness in Thymectomy for Myasthenia Gravis

For years, extended thymectomy has been considered a reasonable option to improve the course of disease for patients with myasthenia gravis (MG), although no level I data existed to prove that thymectomy was beneficial[35]. In 2016, a randomised trial of 126 patients finally provided definitive demonstration of improved clinical outcomes over a 3-year period after extended thymectomy in patients with non-thymomatous MG[36].

With this critical evidence now supporting thymectomy in MG, a new subject of debate is what is the optimal surgical approach to performing thymectomy in this disease. Traditionally, median sternotomy (MS) has been the standard of care, and MS was utilised in the aforementioned 2016 randomized trial[36]. However, MITS options for thymectomy have been developed and utilised as well, including VATS, robot-assisted thoracic surgery (RATS), combination VATS/RATS approaches, and transcervical thymectomy (TCT).

## Technique of Transcervical Thymectomy

While MS and VATS/RATS approaches to thymectomy are well-known and do not require review, the method for TCT is not as well disseminated, and so we will review it here. Transcervical thymectomy can be performed in patients who are not obese, can extend their necks well, and do not have a thymoma.

After general anaesthesia is induced and a single-lumen endotracheal tube placed, the patient is placed in a supine position with the neck hyperextended by placement of an inflatable bag beneath the shoulders. The neck and upper chest are prepared and draped. A curved, transverse skin incision is made about 2 cm above the sternal notch and extended for 5 cm along the skin folds such that the lateral edges of the incision are approximately 1 cm cephalad to the clavicular heads (Figure 3).

The caudal edge of the incision is elevated as a subplatysmal flap to the level of the sternal notch and the cephalad edge to the level of the thyroid cartilage. Gelpe retractors are placed and the strap muscles are separated in the midline. The superior poles of the thymus gland are identified just deep to these muscles by their salmon-pink colour and firmer texture than the surrounding investing tissue.

The left superior pole is typically more prominent and is dissected first. Dissection continues cranially to where the gland fuses with the thyrothymic ligament, which is ligated and divided. An 0 silk suture is placed on a sturdy portion of this superior pole and cut long as a “handle” to allow for retraction and manipulation of the gland during the remainder of the operation.

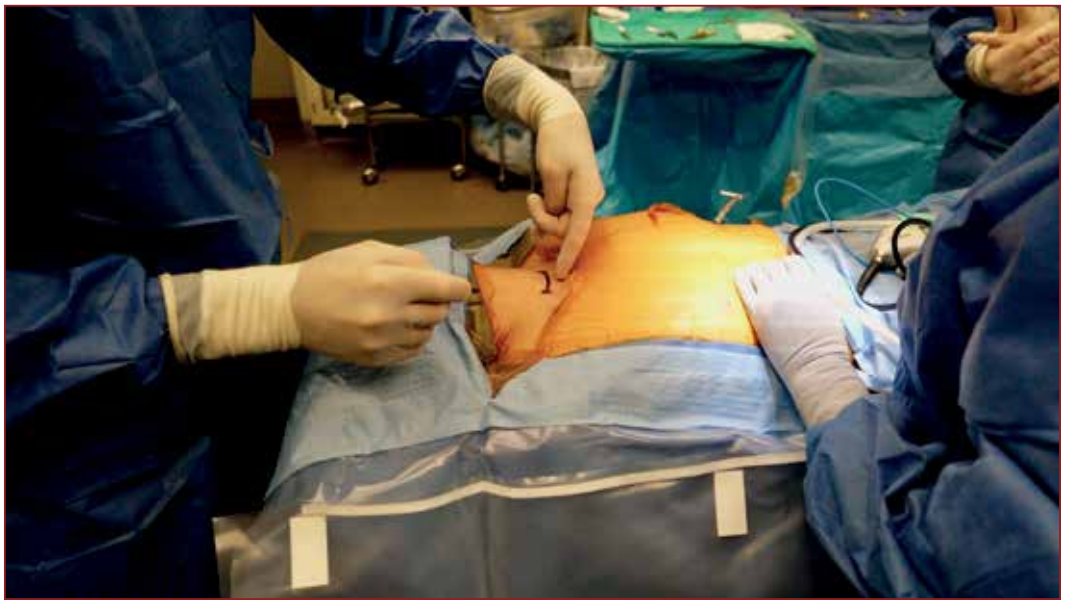

*Figure 3: The skin incision for transcervical thymectomy. The patient's head is to the left.*

The medial border of the left superior pole is now followed caudally to the body of the gland and then back cephalad along the right superior pole, which is then similarly dissected, ligated, and divided at the level of its thyrothymic ligament. Once both superior poles have been mobilised and secured with 0 silk "handles," the dissection proceeds down toward and into the mediastinum.

The prethymic plane is opened up by gently dissecting with a finger into the substernal space. The cleido-cleido ligament is divided. The sternum is now lifted anteriorly using the Cooper thymectomy retractor (Pilling Company, Ft. Washington, PA) (Figure 4), and the head and shoulders are allowed to fall back by deflating the shoulder bag.

This gives the surgeon, who from this point onward is seated at the head of the table, a direct view into the mediastinum with use of a headlight initially, and later with the thoracoscope providing a magnified view on a screen. It is usually helpful to place army–navy retractors in the corners of the incision to improve exposure. These can be secured with Penrose drains clipped to the drapes at the most cephalad corners of the operating table.

Just before or after placement of the retractor, the veins draining the thymus gland into the innominate vein are ligated and divided. This is completed by retracting the two upper horns anteriorly (using the aforementioned ligatures attached to each of the upper horns) to place mild stretch on the branches. There are almost always 2 veins branches, but occasionally there is only one or there may be[3]. These are sequentially double ligated with 00 silk ties and divided. Clips should not be used here as this region is the avenue through which dissecting instruments are subsequently placed into the deeper mediastinum, and clips can be easily dislodged, causing troublesome bleeding.

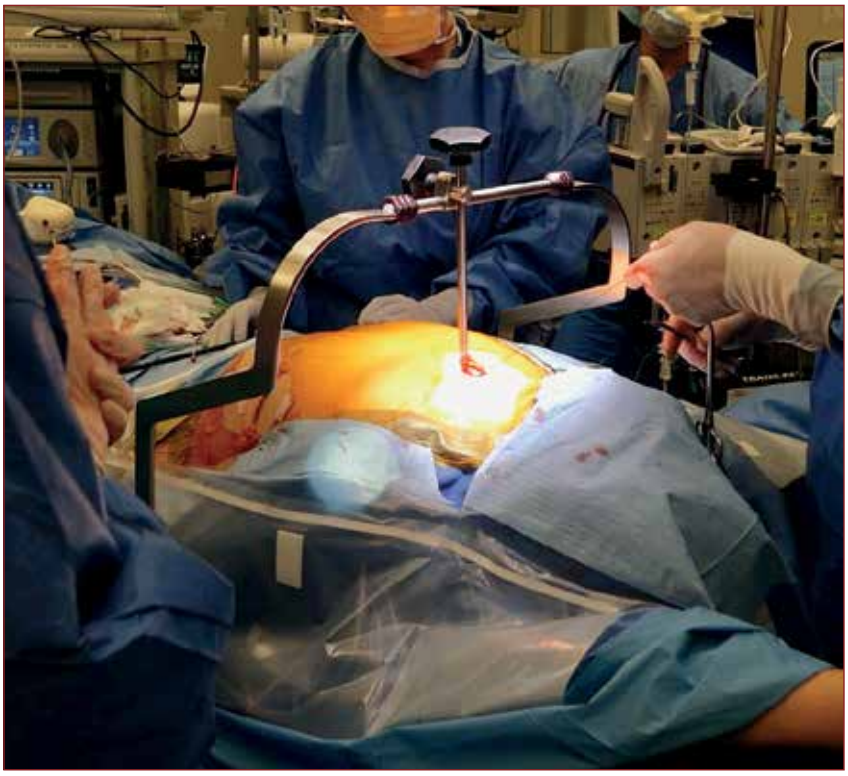

*Figure 4: The transcervical thymectomy operative field after placement of the Cooper retractor substernally and suspension of the patient by the sternum, creating the operative space through which to carry out the mediastinal portion of the dissection.*

The dissection is carried progressively deeper into the mediastinum, largely by blunt dissection under direct vision. Small cherry-ball-sponges on the ends of ring clamps, or Kittners are used, with one holding the innominate vein posteriorly while the other achieves the deeper dissection. At other times, one of the instruments will be used to push one tissue plane in one direction (for example, the mediastinal pleura laterally), while the other will be used to push the adjacent gland in the opposite direction (Figure 5).

A Yankau er sucker is also a useful device for blunt dissection in this area. Vascular attachments, such as the small branches of the internal mammary vessels, are easily cauterised or clipped and divided as encountered.

In this way, the gland and surrounding mediastinal fat is separated gradually from the surrounding structures. First, it is dissected from the pericardium posteriorly, allowing the anterior attachments to the chest wall to hold the gland anteriorly and out of the way as this posterior dissection is achieved. It is critical to be sure one dives posteriorly behind the thymus directly onto the white of the pericardium immediately after passing beyond the innominate vein, to avoid entering the posterior capsule of gland. After completing the posterior dissection as far caudally as possible, the thymus and surrounding fat are separated from the anterior chest wall, then from the pleurae bilaterally, and ultimately from the diaphragm. Retraction of the gland in the opposite direction of the focus of dissection, using the two ligatures attached to the upper poles, is helpful in facilitating the deeper mediastinal dissection. Ventilation is held intermittently to facilitate the view and for the dissection off the pleurae bilaterally. Although one attempts to keep the pleura intact initially in the classic approach, the breach in the pleura which frequently occurs allows a perfect view of the phrenic nerve to guide complete removal of the fat and pleura

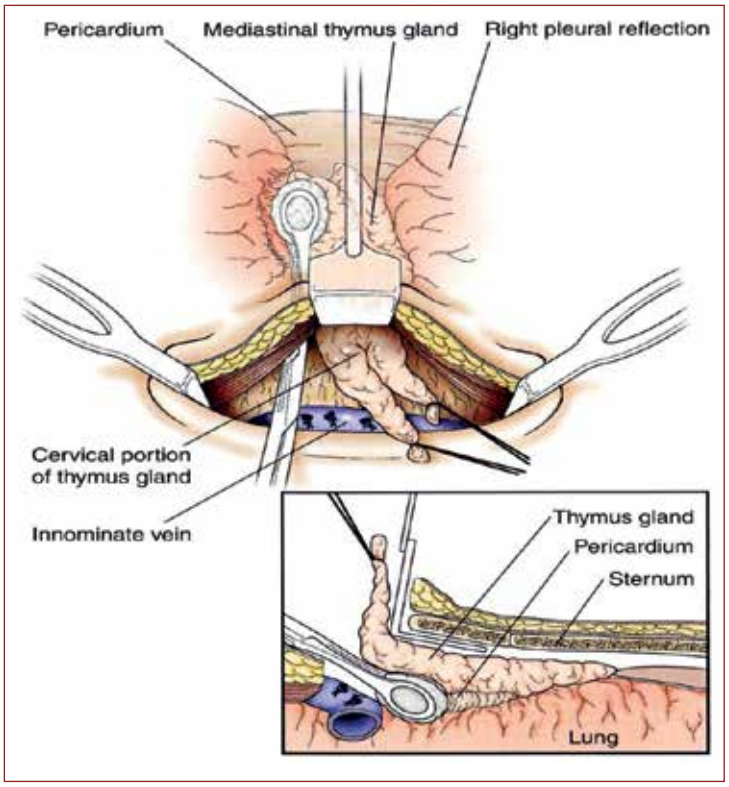


*Figure 5: The mediastinal dissection during Transcervical thymectomy. It is performed largely by blunt dissection using ball-sponges on ring-clamps (Republished with permission of Taylor & Francis Informa UK Ltd, from Operative Thoracic Surgery, Kaiser L.R. and Jamieson G.G., 5th Ed., 2006).*

to the level of the nerve, and thus opening the pleura is sometimes optimal to assure that all fat is removed. Toward the end of the dissection, it is sometimes helpful to gently grasp the gland with an empty ring clamp while dissecting the final attachments with the other hand.

Although performing TCT using the sternum-lifting retractor and direct, unmagnified visualisation was the approach initially described by Cooper, this has been improved in our hands with the adoption of the University of Toronto approach, introducing a 5 mm 30 degree videoscope through one or the other end of the neck incision, once having completed the initial stages of blunt dissection deep to the innominate vein[37,38]. The view provided by the video camera is superior to that which one can generally achieve directly through the neck incision with a headlight, and we believe it allows a more complete dissection of the extracapsular mediastinal fat.

An additional difference between our current approach and the traditional Cooper approach involves whether the mediastinal pleura is resected. Classically, TCT has not included resection of the pleural membranes. The above approach has evolved to include resection of the pleura when there is more than a minimal amount of mediastinal fat that remains adherent to it after initial dissection. In this circumstance, after opening the pleura beneath the sternal edge anteriorly, one can use the 30-degree thoracoscope turned downward to clearly see the course of the phrenic nerve from the pleural side. This allows a safe, posterior incision of the pleura to be made just anterior to the nerve, and allows removal of the pleural membrane and all associated mediastinal fat anterior to the phrenic nerve, just as in the classic transsternal extended thymectomy operation. With the pleurae opened, the entire pericardiophrenic fat pads can be removed as well.

After en bloc removal of the H-shaped thymic specimen, including the upper and lower poles and surrounding mediastinal fat, careful inspection for residual suspicious tissue in the mediastinum is performed. Any such tissue is removed at this point. For closure, the strap muscle and platysma are closed with running absorbable sutures. A red rubber catheter can be placed, depending on whether the pleural cavity has been entered, to remove air and the tube withdrawn just prior to rendering the deepest layer airtight, as the anaesthesiologists give a large positive-pressure breath.

Patients are almost always extubated in the operating room. After a chest radiograph confirms lung expansion, nearly all can be discharged home on the afternoon of the surgery, although to assure patient comfort we have generally kept patients overnight in our last few years of practice.

Notably, this entire procedure is performed without any disposable instruments or energy devices, other than a standard, monopolar, hook cautery.

## Costs of VATS/RATS vs. Sternotomy Approaches to Thymectomy

MITS thymectomy methods have been compared to MS with regard to remission rates from MG in several retrospective studies: VATS, RATS, and TCT have each demonstrated comparable complete stable remission (CSR) rates as compared to thymectomy by MS[37, 9-49]. The data simply do not support the contention of some that minimally invasive approaches offer only lower MG remission rates.

Studies have also demonstrated substantially shorter LOS with VATS and RATS, as compared to MS. Meyer and colleagues demonstrated a shorter LOS with VATS of 1.9 days compared to 4.6 with MS ($p<0.001$)[40]. Siwachat and colleagues also found shorter LOS (7 days vs. 10 days, $p<0.001$) as did Mineo and colleagues (3 days vs. 5 days)[41,43]. Additionally, a large systematic review by Hess and colleagues demonstrated decreased LOS associated with MITS thymectomy (VATS and RATS thymectomy included), in addition to decreased blood loss and chest tube duration 50. In this review, the average hospital length of stay ranged from 1 to 10.6 days with MITS, and 4 to 14.6 days following MS.

In several studies, minimally invasive approaches to thymectomy have been demonstrated to incur lower costs than MS. A 2018 study by Marulli and colleagues compared RATS to MS for early stage thymoma, finding MS average costs to be approximately 24% greater than RATS (€4194 vs. €3395, $p<0.001$), primarily attributed to significantly shorter LOS associated with RATS (3 days vs. 6 days, $p<0.001$)[51]. Another study by Augustin and colleagues found RATS thymectomy to be about 91% more expensive than VATS thymectomy[52]. This was attributed primarily to expensive robotic instruments which are of limited reusability, as hospital LOS was similar between groups. Additionally, their study included a review of literature comparing RATS and VATS and found hospital LOS of 2.65 days in the VATS group as compared to 2.6 in the RATS group and 10.3 in the MS group.

## Costs of Transcervical Thymectomy vs. other Approaches

TCT appears to allow a LOS even lower than that of other MITS thymectomy approaches, and certainly lower than MS – in our hands reliably 24 hours or less[49,53].

Although TCT LOS appears lower than that of MS and even other MITS approaches, and there do not appear to be expensive reusable devices used during the performance of TCT, does this indeed translate to lower costs? In his article on TCT, Calhoun concludes

that "because the operative time, length of stay, and morbidity rate of the transcervical approach are all less than with the more radical approaches, we can infer that the cost of the surgery is also significantly less 48."

However, there are currently no published studies directly evaluating the cost of TCT vs. other thymectomy approaches. Recently, our group investigated the cost-effectiveness of TCT in comparison to other techniques and presented our data at the Annual Meeting of the American Association for Thoracic Surgeons in 2019 (manuscript under review). We used prospectively collected data in our institution's modified STS database between 2007 and 2018 to compare peri-operative outcomes and costs between three thymectomy approaches: TCT, MS, and VATS and/or RATS (VRATS). Because TCT is generally reserved for patients with non-thymomatous MG, in order to control for operative difficulty and potentially associated resource requirements, we excluded patients in the MS or VRATS groups who had an invasive thymoma, tumour size larger than 4cm in diameter, received incomplete thymectomy, or underwent extended procedures (eg, pericardial or lung resection).

In total, after exclusions, there were 62 patients in the study: 25 TCT, 14 MS, and 23 VRATS. There was a higher incidence of MG in the TCT and MS groups as compared to VRATS and higher incidence of thymoma in VRATS and MS groups than in TCT, as expected. Patients in the MS group did have higher Modified Charlson Comorbidity Score than in the TCT and VRATS groups, although there were no differences between those in the TCT and VRATS groups. Perioperative complications were not significantly different between groups.

We next compared mean relative hospital costs associated with each surgical approach. TCT was associated with the lowest hospital costs of all surgical approaches, by a large margin: TCT total hospital cost was 45% of that of MS ($p<0.001$) and 58% of that of VRATS ($p=0.018$). VRATS costs were shown to be 78% of that of MS, but this difference did not reach statistical significance ($p=0.11$) (Figure 6).

The main driver for this drastic reduction in costs with TCT lies in the mean LOS associated with each procedure: LOS was significantly shorter for TCT (1.16 days) compared to VRATS (2.63 days, $p=0.02$) and MS (4.33 days, $p<0.01$). Bed costs alone accounted for 65% of the cost difference between TCT and MS and 44% between that of TCT and VRATS. Of note, only 2 of 25 TCT patients were hospitalised for more than a single night, and one was a patient who required conversion to MS (analysed in the TCT group as intention-to-treat). However, impressively, beyond reduced LOS, every single cost category that we measured was lower in the TCT group that in each of the VRATS and MS groups (Figure 6).

OR labour costs serve as a reasonable proxy for operating time. OR labour constituted 38% of VRATS cost and 45% of TCT total cost. This could be attributed to longer procedure times with VRATS (190 ± 70 minutes) as compared to MS (139.7 ± 46.6 minutes) and TCT (160.7 ± 29.8 minutes). VRATS OR times were likely inflated compared to those previously reported in the literature due to our institutional preference for a bilateral VATS/RATS approach to ensure total thymectomy in MG[45,46].

In conclusion, thymectomy by MITS appears to be significantly less costly than by MS while offering similar short-term and long-term outcomes. Of the available MITS approaches, TCT is the least expensive. This lower cost does not sacrifice patient safety in terms of perioperative complications, nor does it reduce long-term MG remission rates.

We believe that this cost savings is substantial enough that surgeons should seek out training opportunities to learn the technique of TCT, so that they can apply it when patient characteristics allow (non-thymomatous MG, non-obese, good neck extension).

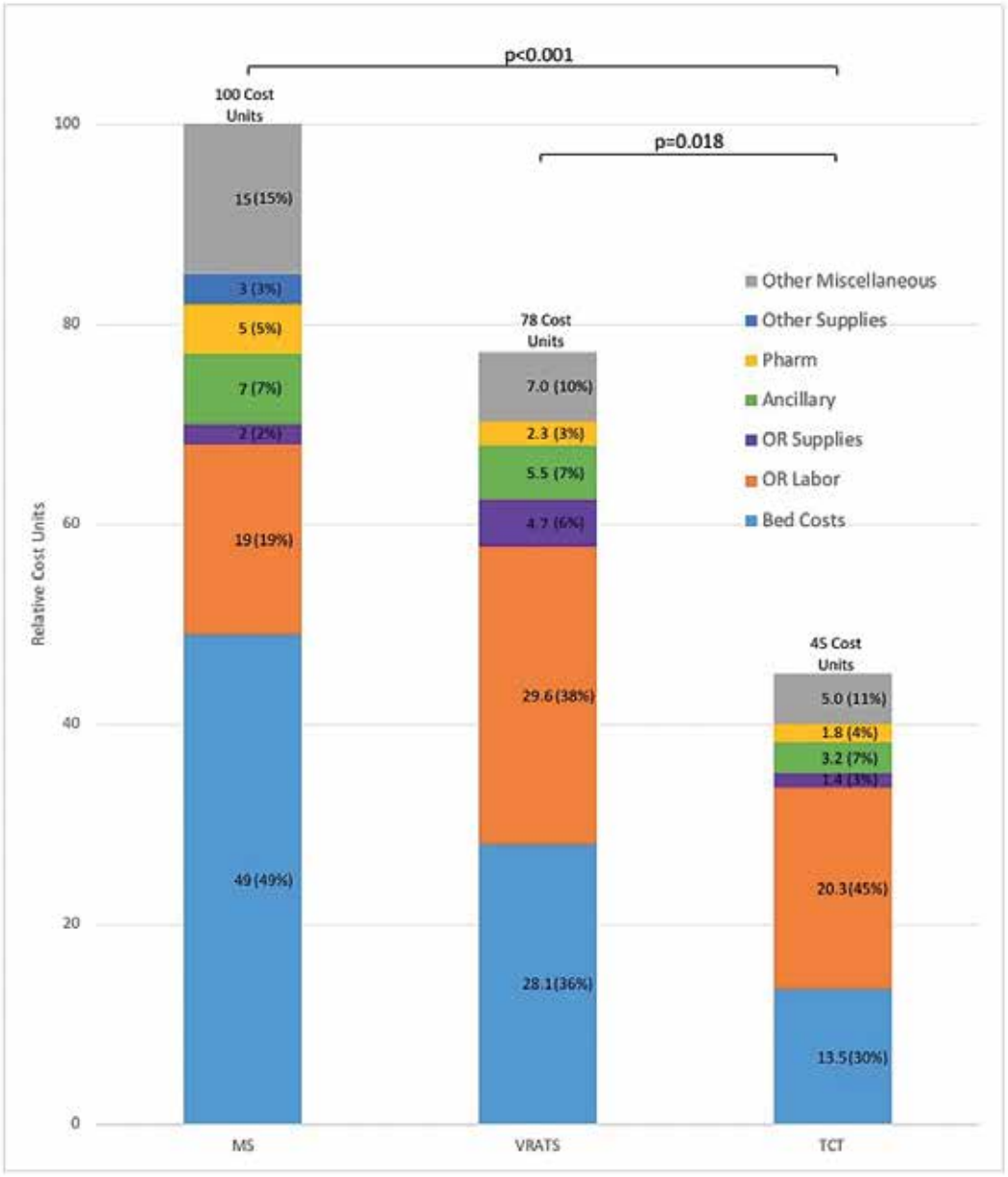


*Figure 6: Relative hospital cost associated with thymectomy via median sternotomy (MS), video-assisted thoracoscopic and/or robotic (VRATS), and transcervical (TCT) approaches. The total cost of thymectomy via MS was set at a value of 100. Total cost of VRATS was 77% of MS (77 cost units) and TCT was 45% (45 cost units). The relative cost of each category is indicated, followed by the percentage that each category makes up within that type of procedure's overall cost.*

## Conclusions and Next Steps

In this chapter, we have reviewed the literature on cost-effectiveness in MITS, focusing specifically on VATSL and thymectomy. Our work demonstrates that MITS approaches must be carefully dissected to accurately compare their costs and outcomes to traditional approaches, in order to determine whether, on balance, their use should be encouraged.

With regard to VATSL, we demonstrated that VATSL has the capability to be significantly less expensive than THORL, but that its cost-effectiveness is highly dependent on the surgeon's avoidance of expensive and apparently unnecessary energy devices, surgical sealants, and disposable devices. With careful, deliberate and cost-conscious selection of these surgical tools, VATSL costs can be significantly lower than those of THORL. We have also shown that not all MITS thymectomy approaches are equal in terms of cost-effectiveness, as TCT allows significantly lower costs, with the same short and long-term outcomes, as other methods.

Practically speaking, surgeons must remain aware of their contribution to healthcare costs in this era of, appropriately, increased scrutiny on costs. When health care represents 17% of the United States' gross domestic product, it is incumbent upon us to use health care dollars efficiently and not to waste society's precious resources. We have shown in this chapter that both choice of one particular minimally invasive surgical approach over others (e.g., TCT over VATS/RATS), as well as the precise techniques by which one chooses to perform a particular operation (e.g. VATSL with or without expensive adjuncts) can have major impacts on the costs associated with managing a surgical disease. Surgeons must discuss standardising surgical trays and be aware of the costs of disposable items that may not be needed in every case[54]. Additionally, we must be prepared to compare costs and outcomes between surgeons[55].

At our institution, we speak openly at our divisional meetings about how to safely minimise costs. We have also worked to make surgeons more aware of the cost of disposable instrumentation and adjuncts by: 1) having surgeons selectively remove as many devices from their sets as they believe they will not routinely require; 2) having the intraoperative circulating nurse read out loud the cost of any additional device that the surgeon is considering opening, giving him/her the opportunity to change this decision. Through this selective, cost-conscious approach, we hope to reduce costs of all procedures without sacrificing physician autonomy or patient outcomes.

As patient outcomes are the single most important measure for surgeons, we emphasise that patient safety must not be jeopardised in the name of cost-savings. For example, utilising fewer stapler reloads may result in lower costs in VATSL, but if done inappropriately it might increase the risk of prolonged air leak, among other complications, and would be counterproductive. Surgeons should first focus on low-hanging fruit such as shifting from disposable to reusable VATS ports, using cautery in lieu of expensive energy devices, and avoiding use of expensive glues/sealants. Other approaches may require larger shifts in thoracic surgery residency and fellowship training, such as encouraging TCT over VATS/RATS thymectomy.

Lastly, it is important to point out that one would not want to stifle innovation in the name of cost-savings. Many surgical devices that are today standard of care were, at the time of their introduction, considered to be overly costly and controversial. We simply encourage surgeons to be cognisant of costs as they evaluate novel devices and techniques and consider incorporating these into their practices.

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