The Right Ventricular Response to Lung Resection

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Dedication:

To Sophia, Hamish and Euan

This is all for you. Thank-you for your endless patience and continuous encouragement.

To my Parents

This is only possible because of you. Thank-you for everything.

Abstract

Lung cancer is the most common cause of cancer death in the UK and although the best opportunity for cure is provided by lung resection, surgery is associated with high rates of cardiorespiratory complications and long-term morbidity. Existing studies indicate right ventricular dysfunction occurs following lung resection and may be implicated in any post-op deterioration. Evaluation of right ventricular function is challenging, with its complex shape, marked load dependence and retrosternal position meaning there is no reliable, non-invasive method of assessment. The majority of previous work examining right ventricular function in the lung resection population has been performed using the volumetric pulmonary artery catheter, the reliability of which has been challenged.

The first section of this thesis reviews the right ventricle in terms of anatomy, physiology and assessment, providing context for future investigations (Chapter 1). A review of the literature examining the right ventricular / pulmonary vascular response to lung resection is then presented, along with the rationale for further investigations (Chapter 2).

As there is a high frequency of complications in this population, often requiring critical care support, the first investigation (Chapter 3) of this thesis characterises those patients admitted to intensive care following surgery. It also examines the incidence of right ventricular dysfunction in this population.

Given the methodological concerns regarding the techniques previously used to assess right ventricular function following lung resection, cardiovascular magnetic resonance imaging was used to sequentially assess the right ventricular response to surgery (Chapter 5). Cardiovascular magnetic resonance is a reference method for assessment of right ventricular function and has not previously been used sequentially in this population. This investigation demonstrates right ventricular function (measured by right ventricular ejection fraction) deteriorates following lung resection with impairment still evident two months following surgery. There were no changes in left ventricular function over the same period.

With the difficulties associated with cardiovascular magnetic resonance imaging in this population and its limited use outside of research settings, an alternative

method for assessment of right ventricular function would have utility in this population. Trans-thoracic echocardiography is the most commonly used non-invasive method for assessment of right ventricular function with widespread availability and low cost. Chapters 6 and 7 attempt to validate conventional and novel echocardiographic methods for assessment of right ventricular function in this population. The main finding is that established echocardiographic methods; fractional area change, tricuspid annular plane systolic excursion and S' wave velocity at the tricuspid annulus, are not suitable for assessment of right ventricular function in this population. Speckle tracked strain echocardiography is a novel method of assessing right ventricular function that has shown promising results in other patient groups. Chapter 7 demonstrates that right ventricular *global* strain is not useful, but that right ventricular *free-wall* strain may have value in this population.

Biomarkers of myocardial dysfunction (B-type natriuretic peptide and high sensitivity troponin-t) were measured contemporaneously with the imaging studies (Chapter 8). This investigation demonstrates that both biomarkers increase following lung resection and that their plasma concentration two days following surgery are associated with right ventricular function. There was no association with parameters of left ventricular function suggesting the biomarkers are released in response to changes affecting the right ventricle. On an exploratory basis the association between the peri-operative biomarkers and functional capacity following surgery is also assessed.

Finally, potential mechanisms of right ventricular dysfunction following lung resection are explored (Chapter 9). This demonstrates that as pulmonary artery acceleration time (a surrogate measure of right ventricular afterload) increases, right ventricular ejection fraction deteriorates. Using a cardiovascular magnetic resonance surrogate, a deterioration in the matching of right ventricular function with right ventricular afterload (coupling) is also demonstrated.

In combination these studies provide a robust answer to the question "what happens to right ventricular function following lung resection?" It provides validated methods for future work in this population and suggests an association between post-operative right ventricular function and right ventricular afterload.

Table of Contents

List of Tables

List of Figures

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Author's Declaration

I declare that, except where reference is made to the contribution of others, this thesis is a result of my own work, written entirely by myself and has not been submitted for any other degree at the University of Glasgow or any other institution.

Dr Philip McCall (MBChB, FRCA)

Word Count: 67,400

Definitions/Abbreviations

A4C	Apical 4 chamber
AF	Atrial fibrillation
ALI	Acute lung injury
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARDS	Adult respiratory distress syndrome
ASA	American society of anesthesiologists
ASE	American society of echocardiography
AUROCC	Area under the receiver operating characteristic curve
BA	Bland Altman
BMI	Body mass index
BNP	B-type natriuretic peptide
BSA	Body surface area
BSE	British society of echocardiography
CC	Conductance catheter
CI	Confidence interval
CMR	Cardiovascular magnetic resonance
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
CVP	Central venous pressure
Ea	Effective arterial elastance
EDPVR	End diastolic pressure volume relationship
EDV	End diastolic volume
Ees	End systolic elastance
$\mathbf{E_{max}}$	Maximal systolic elastance
EQ5D	EuroQol 5 domain
ESP	End systolic pressure
ESPVR	End systolic pressure volume relationship
ESV	End systolic volume
ET	Echocardiography technician
FAC	Fractional area change
FEV1	Forced expiratory volume in 1 second
FEV1%	Percent predicted forced expiratory volume in 1 second
FVC	Forced vital capacity
hsTnT	High sensitivity troponin T
ICC	Intraclass correlation coefficient
ICU	Intensive care unit
IQR	Inter quartile range
IVC	Inferior vena cava

LADCA	Left anterior descending coronary artery
LV	Left ventricle
MAP	Mean arterial pressure
mPAP	Mean pulmonary artery pressure
MPI	Myocardial performance index
MRC-DS	Medical Research Council dyspnoea scale
MVO2	Myocardial oxygen consumption
NPV	Negative predictive value
NYHA	New York Heart Association classification
OLV	One lung ventilation
PA	Pulmonary artery
PAAT	Pulmonary artery acceleration time
PAC	Pulmonary artery catheter
PASP	Pulmonary artery systolic pressure
PAWP	Pulmonary arterial wedge pressure
PE	Pulmonary embolus
PFT's	Pulmonary function tests
POD	Post-operative day
PPO	Predicted post-operative
PPV	Positive predictive value
PRSW	Preload recruitable stroke work
PV	Pressure volume
PVR	Pulmonary vascular resistance
RA	Right atrium
RAP	Right atrial pressure
RCA	Right coronary artery
RV	Right Ventricle
RVEDP	Right ventricular end diastolic pressure
RVEF	Right ventricular ejection fraction
RV-FWPLS	Right ventricular free wall peak longitudinal strain
RV-GPLS	Right ventricular global peak longitudinal strain
RVP	Right ventricular pressure
RV-PA Coupling	Right ventricular / pulmonary artery coupling
SV	Stroke volume
S'Wave	S'Wave velocity at the tricuspid annulus
TAPSE	Tricuspid annular plane systolic excursion
TIVA	Total intravenous anaesthesia
TLCO	Transfer factor for carbon monoxide
TLCO%	Percent predicted transfer factor for carbon monoxide
TOE	Transoesophageal echocardiography
TRJ	Tricuspid regurgitant jet

TTE	Trans thoracic echocardiography
VATS	Video assisted thoracoscopic
WHO-PS	World Health Organisation performance status

Chapter 1 Introduction

1.1 General introduction

1.1.1 Lung cancer

Lung cancer is the most commonly diagnosed cancer worldwide, accounting for 1,825,000 cases in 2012 (about 13% of total cancer cases). It represents the leading cause of cancer in men, and the third most common in females[1]. Lung cancer is also the most common cause of death from cancer internationally, accounting for 19% of cancer deaths in 2012[2]. This pattern is similar in Scotland where lung cancer is the second most common cause of cancer (behind non-melanoma skin cancers) and the most common cause of cancer death. Over the last ten years (since 2004) there has been an overall decrease in the incidence of lung cancer with rates down by 5.2%. This reduction is mainly due to the decrease in the number of cases in men (also down 5.2%). In the same time period, there has been a 14.2% increase in the number of cases in females[3]. Lung cancer survival is poor with one, five and ten years survival figures of 32.1%, 9.5% and 4.9% respectively[4].

A link between smoking and lung cancer was observed in 1950 and smoking prevalence largely dictates lung cancer trends, with observed variation in incidence reflecting differences in the stage of the tobacco epidemic. This is true in the UK, and as smoking rates have fallen, lung cancer rates have fallen in the later years (Figure 1, pg 21). Advancing age is also a significant risk factor associated with diagnosis (89% of cases in Scotland in 2012 were in patients over the age of 60) and despite a fall in the incidence of lung cancer, absolute numbers are expected to increase (Figure 2, pg 21) [3, 5-7]. Projections suggest that absolute numbers in the UK will increase by 35.4% (compared to 2014 figures) by 2035[8].

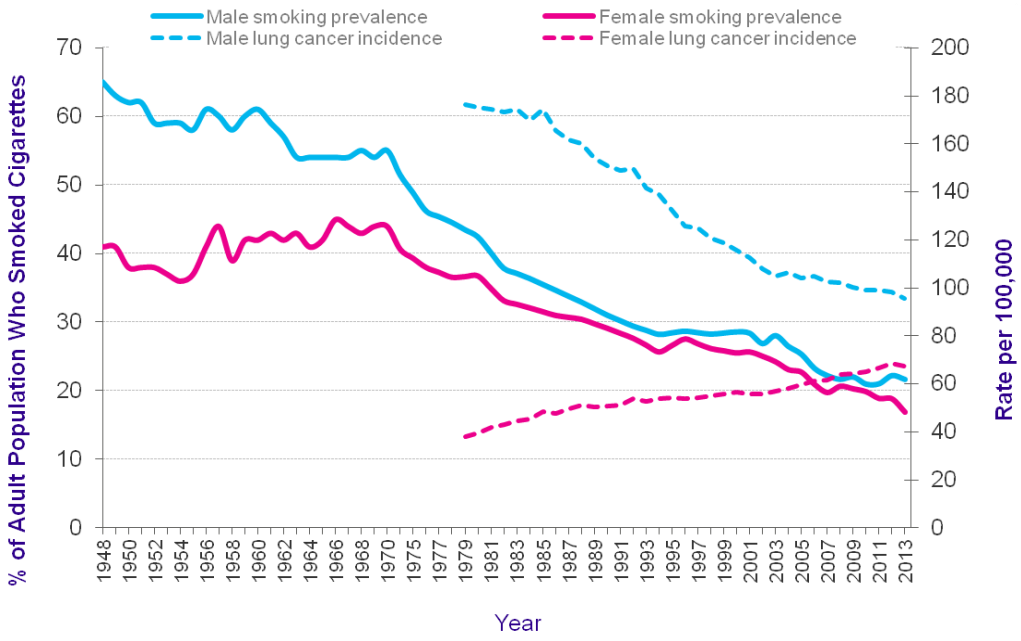

Figure 1. Lung cancer incidence and smoking trends, Great Britain, by sex, 1948-2013
From Cancer Research UK[9].

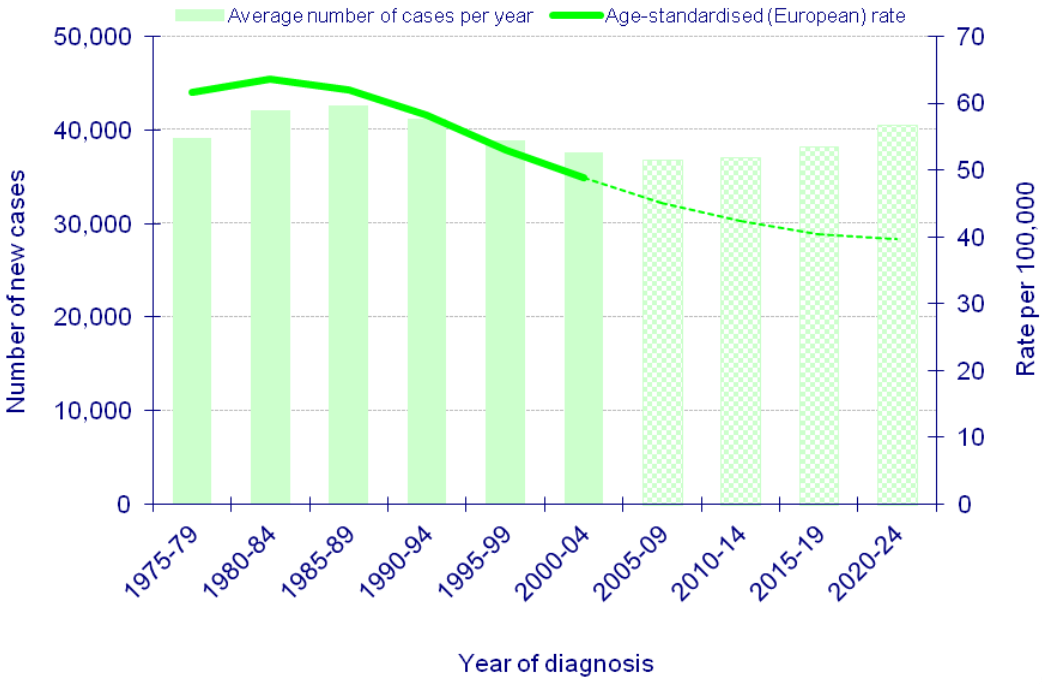

Figure 2. Lung cancer incidence projection to 2024, age standardised (European) rate and number of new cases, all person, Great Britain (Based on 1975 to 2004 data)
From Cancer Research UK[6].

1.1.2 Lung cancer management and surgery

Following diagnosis, management of lung cancer is multimodal and ranges from smoking cessation to the use of chemotherapeutic agents and radiotherapy. Despite advances in the non-surgical management of lung cancer, in suitable cases the mainstay of *curative* treatment is lung resection.[10] This offers the best opportunity for prolonged survival, with five year survival figures of 54-80% in patients with stage Ia (the earliest stage) lung cancer. Surgery has progressed since the first successful pneumonectomy (removal of an entire lung) was performed in 1933 and procedures now include lung sparing options such as lobectomy, segmentectomy and wedge resection[11]. In the UK, the number of resections for primary lung cancer have increased significantly over recent years and approximately 8500 lung resections take place in the UK each year (2011)[12]. In Scotland, the total percentage of lung cancer cases having surgery has increased from 10.6% in 2008 to 15.7% in 2014[13]. This has been driven by a number of factors including efforts to increase resection rates in the UK, which are low compared to other countries with equivalent healthcare systems[14]. In addition, guidelines by the National Institute of Clinical Excellence (NICE, UK, 2011) and Scottish Intercollegiate Guidance Network (SIGN, Scotland, 2014) have recommended increasing the availability of surgery to older patients with more comorbidities (and conventionally thought of at increased risk for post-op complications and long-term morbidity, including dyspnoea) if they are prepare to accept these higher risks[15].

> *"Offer patients with predicted post-operative FEV_1 or TLCO below the recommended limit of 30% the option of undergoing surgery if they accept the risk of dyspnoea and associated complications."*
>
> NICE (2011)[15]

1.1.3 Lung cancer surgery morbidity and mortality

The majority of patients undergoing lung resection represent a high risk surgical population, they are generally over 60 years old, have a significant smoking history and are at high risk of heart disease. For that reason, lung resection is associated with significant morbidity in addition to the effects of the underlying disease[16]. Post-operatively this includes high rates of cardiorespiratory complications such

as; pneumonia, lobar collapse requiring bronchoscopy, adult respiratory distress syndrome (ARDS), pulmonary oedema, pulmonary embolus, myocardial ischaemia, cardiac failure, arrhythmias (both atrial and ventricular), stroke and renal failure[17-19]. All of these may need interventions and support that will contribute to a significant peri-operative patient burden and increased hospital resource requirement. In-hospital mortality following lung resection (for all procedures) is 1.7%[20].

Although improved survival is the goal of surgical treatment, health related quality of life is an important long-term outcome and lung resection is associated with significant long-term morbidity. Many survivors will have a decline in their underlying functional health status. Quality of life following surgery has been assessed using multiple scores, with patients having a decline in numerous indicators including; physical function, ability to undertake usual activities, pain, persistent cough, mental function, fatigue, sleeping, vitality, sexual activity, dyspnoea and overall quality of life. This decline is present immediately post-operatively and although there does seem to be an improvement with time, many patients continue to report functional limitations and symptoms two years after their surgery [16, 21-23]. Sarna et al.[24] followed survivors up at five years and found disabling respiratory symptoms contributed to diminished quality of life. Up to two-thirds of patients reported at least one symptom of cough, phlegm, wheezing or dyspnoea and 11% of patients described themselves as being so breathless that they couldn't leave the house.

1.1.4 Predictors of morbidity and mortality

As may be expected, both the extent of the surgical procedure and the underlying health status of the patient contribute to how a patient will progress peri-operatively. Predictors for mortality (in hospital or within 30 days) and post-op morbidity include: pneumonectomy, bilobectomy, higher American Society of Anesthesiologists (ASA) rating, Zubrod performance status, renal dysfunction, induction chemoradiation therapy, steroid use, advancing age, urgent procedures, male gender and low body mass index (BMI)[25, 26].

The use of pre-op pulmonary function tests: Forced Expiratory Volume in 1 second as a percentage of predicted (FEV_1%) and the Transfer factor for Carbon

Monoxide as a percentage of predicted (TLCO%) are key tests in the evaluation of patients for lung resection, with lower values indicating higher risk[15, 27-29]. These are often corrected to the predicted post-op lung function values by calculating the amount of functional lung that will remain following resection (Equation 1)[30].

$$PPO\ value = \frac{preoperative\ value}{T} x\ R$$

Equation 1. Predicted post-operative (PPO) values
T = total number of functioning segments prior to resection, R = number of functional segments remaining following resection.

It would seem logical that those patients with larger lung resections and poorer respiratory function would be more likely to suffer from peri-operative morbidity, and decreased long-term quality of life. Although FEV_1%[25, 26, 31], ppoFEV_1%[32-34], TLCO%[31, 35] and ppoTLCO%[32-34, 36] have all been shown to be predictive of post-op morbidity and mortality following lung resection, there is a significant body of work demonstrating they are non-predictive, or their value is limited to particular sub-groups[15, 33, 35-38]. Whilst less work examines *long-term outcomes*, there is a similar picture, with some studies showing a link between poor pre-op PFT's and reduced quality of life[24, 39] and others showing no association[23, 40]. It would seem that normal lung function is a predictor of good outcome, but there is no reliable lower limit for those who will suffer peri-operative complications or long-term disability[37].

It would appear that pulmonary function is not the only factor contributing to post-op outcomes. The 2013 American College of Chest Physicians guidelines for the physiological assessment of the patient with lung cancer being considered for resection surgery explains;

> *"Ultimately though, the factors that contribute to long-term pulmonary disability, either individually or in concert, remain largely unknown. This makes predicting who exactly will suffer long-term pulmonary disability following lobectomy or pneumonectomy largely speculative."*
>
> Brunelli et al. (2013)[27]

It is when examining what other factors could be working in concert with respiratory function to contribute to post-op morbidity and mortality, that the potential role of cardiac function, particularly that of the right ventricle (RV) is considered. Due to common aetiological factors, cardiopulmonary dysfunction often coexists with primary lung cancer[41]. It had been noted by the author and his colleagues during the course of their clinical work (in the cardiothoracic intensive care unit at the Golden Jubilee National Hospital) that a number of patients following lung resection were developing acute RV failure. Requirement for critical care following lung resection and the incidence of RV failure in this population is investigated in Chapter 3.

The importance of the RV in health is increasingly recognised and its major role in disease states is increasingly appreciated[42]. As the RV and pulmonary vasculature are coupled together as a unit it would seem intuitive that resection of large amounts of lung tissue would have an impact on RV function. The literature investigating RV function following lung resection is and its relationship to early and late post-op complications is explored in Chapter 2[41, 43-45].

1.2 The right ventricle

1.2.1 General introduction

The primary function of the RV is to receive systemic venous blood from the right atrium and pump it to the pulmonary circulation where gas exchange with the environment occurs. In 1628, the English physician Sir William Harvey published his work describing the human circulation, *Exercitatio anatomica de motu cordis et sanguinis in animalibus* (concerning the motion of the heart and blood). In this work, the RV and pulmonary circulation were described, but its importance was perhaps not appreciated [46-48].

> *"...again I ask, when the lungs are so near, the blood vessel to them of such size, and themselves in continual motion, what is the object of the beat of the right ventricle? And why did nature have to add this other ventricle to the heart for the sake of nourishing the lungs?"*
>
> William Harvey (1628)[47]

For many years and well in to the 20th century, an emphasis in cardiology was placed on the left ventricle (LV), overshadowing the study of the RV. The RV was long considered a passive chamber for blood flow between the systemic and pulmonary circulations. The focus on the LV echoes William Harvey's comment from 1628 when he describes the RV as a servant to the left [47, 49-51].

> *"...the right ventricle is a sort of servant to the left, it doesn't reach to the apex, its walls are three fold thinner and it is somehow joined on to the left..."*
>
> William Harvey (1628)[47]

The importance of the RV and its function has been increasingly recognised[52] and it has been identified as an important prognostic factor in many disease states; heart failure[53, 54], pulmonary hypertension[55], myocardial infarction[56], valvular heart disease[57] (particularly mitral valve), pulmonary embolism[58, 59] and obstructive sleep apnoea[60].

1.2.2 Normal right ventricle structure

1.2.2.1 Macroscopic anatomy

The term "*right*" ventricle is probably incorrect; as in the normally connected *in vivo* human heart, the RV is anteriorly situated, in front of the LV and immediately behind the sternum[46, 61]. It could perhaps be more accurately termed the anterior, or pulmonary ventricle. The RV does not contribute to the cardiac silhouette on chest x-ray[62].

The RV is delineated by the annuli of the tricuspid (or atrioventricular) and pulmonary valves[46]. The shape of the RV is complex; the thin RV free wall wraps around the LV giving it a crescent shaped appearance. When viewed in long axis the RV appears triangular and under normal conditions the septum is concave towards the LV throughout systole and diastole. Although traditionally divided into two components (the sinus and conus), it is *functionally* better viewed as three main regions:[62]

1. The sinus (inflow / inlet) which consists of the tricuspid valve apparatus, chordae tendinae and papillary muscles (red region Figure 3).

2. The anteroapical region which is characterised by a complex meshwork of muscle bundles with coarse trabeculations that make up the trabeculated myocardium. It is this component that allows distinction between morphologically right, left or indeterminate ventricles, irrespective of the chambers location (orange region, Figure 3)[63].

3. The conus or infundibulum (outflow), this is the smooth RV outflow tract (green region, Figure 3).

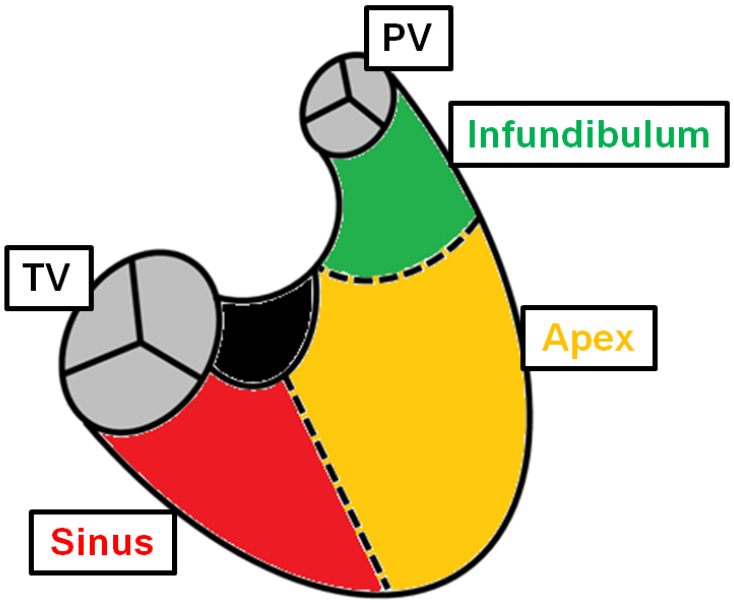

Figure 3. Macroscopic anatomy of right ventricle
Adapted from Haddad et al.[46]. TV = tricuspid valve, PV = pulmonary valve. Red (Sinus) = inflow region. Orange (Apex) = trabeculated apical region. Green (infundibulum) = outflow region.

Along the outflow tract, an arch of muscle separates the tricuspid and pulmonary valves. This arch consists of: the parietal band, the septo-marginal band and the moderator band. The parietal band and the infundibulum make up the crista supraventricularis (supraventricular crest) which separate the sinus and conus

regions. The moderator band crosses the RV septum from the base of the anterior papillary muscle to the ventricular septum. The entire heart is enveloped within the fibrous pericardium, this serves to hold the heart in a fixed position and protect it from other thoracic structures. The pericardium is resistant to acute distension, meaning acute alterations in pressure or volume of either chamber can affect performance of the other ventricle, so called ventricular interdependence[64, 65].

1.2.2.2 Blood supply to the right ventricle

The main blood supply of the RV is from the right coronary artery (RCA) which arises from the right coronary sinus[61]. The lateral wall is supplied by the marginal branches of RCA while the posterior wall and infero-septal region are supplied by the posterior descending artery (PDA). In the majority of cases (80%) who have a right dominant system the RCA supplies the PDA, but in the other 20% with a left dominant system, the left coronary artery supplies the PDA. The RV also receives blood from the left coronary artery with the anterior wall of the RV and the antero-septal region receiving blood from the left anterior descending artery (LAD). The infundibulum derives its supply from the conal artery which has a separate ostial origin in 30% of cases[46]. Venous drainage is accomplished through a complex network of Thebesian veins, which drain directly in to the ventricular chamber and from anterior cardiac veins[66].

1.2.2.3 Muscle fibre architecture

The overall muscle mass of the RV is only about one sixth that of the LV but the volume is larger[64, 66]. The ventricles are not composed of single muscle layers but of a complex three dimensional network of myocytes in a matrix of fibrous tissue. These were described in detail by Ho and Nihoyannopoulos[63]. In the muscular wall of the RV, which is 3-5mm thick and composed of two layers with superficial (sub-epicardial) and inner (deep) muscle layers, circumferential and longitudinal orientations predominate. The superficial myofibres are arranged *circumferentially* in a direction that is parallel to the atrioventricular groove. On the sterno-costal aspect the superficial fibres turn obliquely towards the apex, to cross the interventricular groove and continue into the superficial fibres of the LV. At the RV apex, the superficial myofibres invaginate in a spiral fashion to form the deep or sub-endocardial fibres that line the cavity. The deep fibres of the RV are

longitudinally aligned base to apex. The arrangement of fibres contribute to RV function with longitudinal shortening a major contributor to overall RV contraction[51]. In contrast the LV has three layers with *obliquely* orientated myofibres superficially, *longitudinally* orientated fibres in the sub-endocardium and predominantly *circular* fibres in between, this contributes to a more complex movement which include torsion, translation, rotation and thickening[46].

1.2.3 Normal right ventricular physiology

Functionally the cardiac ventricles can be viewed as two hydraulic pumps in series, therefore they are obligated to eject, on average, the same stroke volume[65, 66]. The RV functions as a *low-pressure, high volume* pump, in contrast to the LV, which may be identified as a *high pressure, high volume* pump. The RV is attached to the high-compliance, low impedance pulmonary vasculature and the LV connected to the less compliant systemic vasculature[64]. This means, despite its thinner wall, the RV can pump the same blood volume as the LV. The RV's unique physiology is dependent on the low hydraulic impedance characteristics of the pulmonary vasculature[50]. Despite the structural and functional differences between the RV and LV, performance of both chambers is largely a function of the same factors: preload, contractility and afterload, the specific features of each vary between the chambers[67]. Performance is also influenced by heart rhythm, synchrony of ventricular contraction, RV force-interval relationship and ventricular interdependence.

1.2.3.1 Preload

RV preload represents the sarcomere length at the end of diastole, just prior to contraction[67]. Within physiological limits an increase in preload increases myocardial contraction based on the Frank-Starling mechanism[46]. Just as the LV has a point where increased sarcomere length results in reduced contractility, so does the RV. This means that excessive and prolonged RV sarcomere stretch reduces RV contractility[51]. Chamber volume is often considered an index of preload however, the relationship between volume and sarcomere length is also influenced by pressure[67]. This means that RV preload is influenced not only by intravascular volume status but also by the diastolic compliance of the ventricle. In the thin walled RV, diastolic compliance is significantly influenced by the pressure

exerted by the pericardium, intra-thoracic pressure and left ventricular pressure. Heart rate and atrial characteristics also contribute.

Compared with LV filling, RV filling is longer, normally starting before and finishing after the LV. RV isovolumetric relaxation time is shorter and RV filling velocities lower. The respiratory variations in RV filling velocities are more pronounced when compared with the LV. Filling period is an important determinant of ventricular preload and function and the RV follows a force-interval relationship in which stroke volume increases above baseline after longer filling periods, as seen in post extra-systolic beats[46].

The geometric configuration of the RV is more suited to ejecting large volumes of blood with minimal myocardial shortening. The RV is considered to be *tolerant of preload*, meaning it can cope with considerable changes in systemic venous return, without large changes in filling pressures because of the greater ratio of volume to surface area in the right compared with left ventricle[68].

1.2.3.2 Contractility

Contractility is the basic property of the myocardium that reflects its active state and is distinct from its loading conditions (preload and afterload)[69]. The RV contracts sequentially in a peristaltic pattern that proceeds from the sinus, via the trabeculated myocardium to the infundibulum[46, 50]. Approximately 50 milliseconds separates contraction of the sinus and the infundibulum[66].

Ejection of blood from the RV chamber emanates from an interaction of 3 difference sources: free wall, interventricular septum and conus[66]. Due to the higher surface to volume ratio of the RV, a smaller inward motion is required to eject the same stroke volume[46]. The RV contracts by 3 separate mechanisms:

1. Inward movement of the free wall which produces a bellows effect

2. Contraction of the longitudinal fibres which shortens the long axis and draws the tricuspid annulus towards the apex

3. Traction on the free wall at the points of attachment secondary to LV contraction.

1.2.3.3 Afterload

RV afterload represents the load that the RV has to overcome when emptying and is the opposition to sarcomere shortening and chamber ejection[67]. The efficiency of the RV to pump blood comes from its 'coupling' to the low impedance pulmonary vasculature. This means that compared to the LV, the less muscular RV is *intolerant of afterload*. This is demonstrated in Figure 4 with a large drop of RV stroke volume in response to experimental increases in RV afterload. This is in contrast to smaller decreases of LV stroke volume in response to increases in LV afterload. This response is particularly relevant in situations where afterload increases acutely, such as following pulmonary embolism.

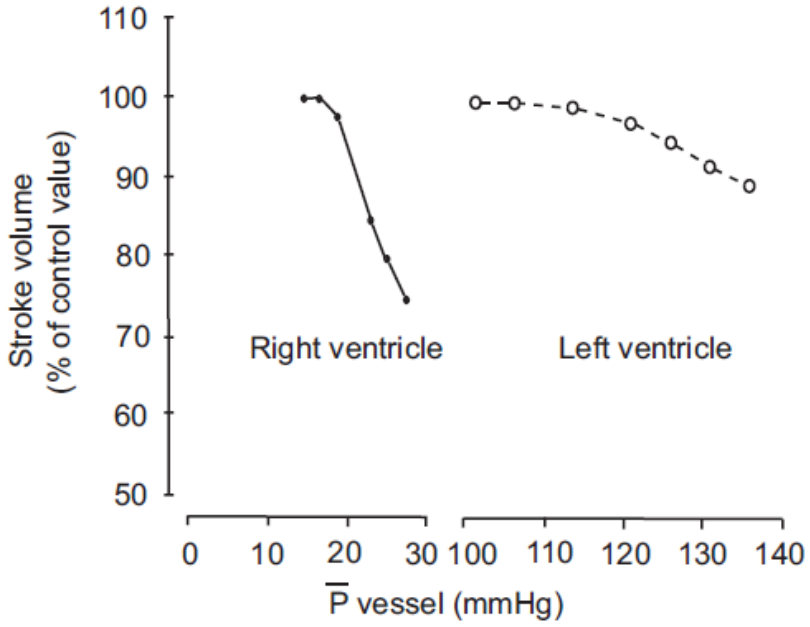

Figure 4. The stroke volume response of the right ventricle and left ventricle to experimental changes in afterload.
Image from Haddad et al.[46], adapted from MacNee et al.[68] P represents mean pulmonary artery pressure (right ventricle) and aortic pressure (left ventricle).

In clinical practice, pulmonary vascular resistance (PVR) is the most commonly used index of afterload (Equation 2, pg 32).

$$PVR\ (\mathrm{dyn \cdot s \cdot cm^{-5}}) = \frac{mPAP - PAWP}{CO}\ x\ 79.9$$

Equation 2. Pulmonary vascular resistance (PVR)
mPAP = mean pulmonary artery pressure; PCWP = pulmonary arterial wedge pressure; CO = cardiac output.

Although most commonly used in clinical practice, PVR is a measure of opposition to *mean* flow, meaning it represents the static element of afterload and does not include the dynamic or pulsatile component[70]. The pulsatile resistance to flow (incorporating resistance, capacitance, inertia and pulse wave reflection) is particularly important in the RV where up to 30% of the work performed by the ventricle goes to overcoming the elastic and reflective forces of the pulmonary vasculature[67]. Pulmonary vascular impedance is a more comprehensive model and represents the *true* opposition to ventricular ejection[66, 70]. Impedance has the same units as resistance (dyn·s·cm^{-5}) but in addition, it has a term that describes the opposition to and energy costs of pulsations in the pulmonary vascular bed. Impedance is frequency related and is modulated by heart rate, vessel stiffness and wave reflections.

Acute increases in afterload lead to a major decline in RV performance but with a slowly progressive rise, the RV is able to adapt and there is progressive change towards an "LV" pattern of pressure-volume loop[50, 71]. Adaptation is initially with increased contractility followed by RV hypertrophy and remodelling[72].

1.2.3.4 Pressure volume loops

The complex interaction of preload, contractility and afterload can be better understood using the pressure-volume (PV) relationship. This can be determined for both the RV and LV by simultaneous measurement of pressure and volume[73].

1.2.3.4.1 Left ventricle pressure volume loop

PV loops are commonly used to describe the function of the LV, the shape and features of which are described here to allow comparison with the RV. Figure 5 (pg 33) demonstrates a single cardiac cycle as it moves (anti-clockwise) from 1

(end-diastole) through to 3 (end-systole) and back to 1, with the cardiac cycle commencing again.

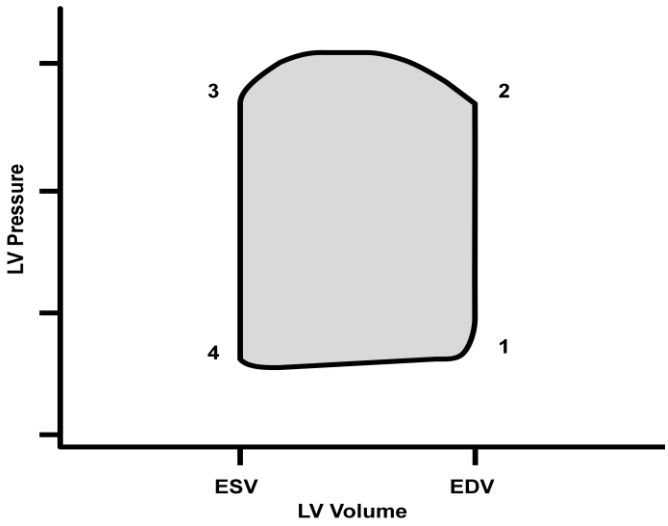

Figure 5 Left Ventricular Pressure Volume Relationship.
Image adapted from Chantler et al.[74] 1 = end diastole (MV closes), 1 to 2 = isovolumetric contraction, 2 = start of ejection (AV opens), 2 to 3 = ventricular ejection, 3 = end-systole (AV closes), 3 to 4 = isovolumetric relaxation, 4 = start of ventricular filling (MV opens), 4 to 1 = ventricular Filling. Stroke volume can be calculated by (EDV - ESV). Area shaded by grey represents ventricular stroke work. LV = left ventricle, MV = mitral valve, AV = aortic Valve, EDV = end diastolic Volume, ESV = end Systolic Volume.

The LV PV relationship is typically rectangular with well defined periods of isovolumetric contraction and relaxation. It was first shown by Suga et al.[75] in the isolated canine LV that the end-systolic pressure volume relationship (ESPVR, Figure 6, pg 34) can be approximated by a linear relationship. This slope is ventricular elastance (change in pressure per unit change in volume) and due to its load independence is considered a reliable index of LV contractility. The ESPVR can be derived by experimentally altering LV loading conditions (preload by modifying end diastolic volume, or afterload by altering resistance to ejection). The end-diastolic pressure volume relationship (EDPVR) is at a tangent to the PV loop at the end-diastolic point and is a measure of ventricular compliance.

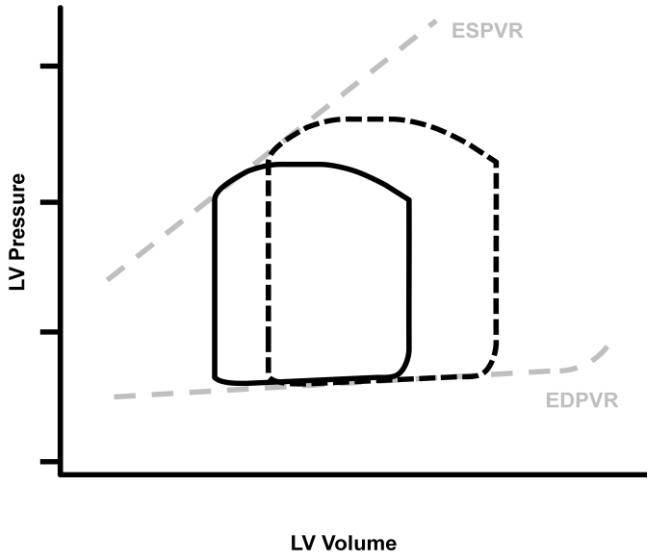

Figure 6 End Systolic and End Diastolic Pressure Volume Relationships
Image adapted from Chantler et al.[74] Two Pressure volume loops under different loading conditions (continuous and dashed lines) demonstrating linearity of ESPVR. ESPVR = end systolic pressure volume relationship, EDPVR = end diastolic pressure volume relationship.

1.2.3.4.2 Right ventricle pressure volume loop

The RV PV loop is a different shape to that of the left and reflects the difference in the work it has to perform and the circulation it is coupled with. As can be seen from Figure 7, in contrast to the well defined square waveform of the LV, the RV PV relationship has a triangular shape, with ill defined periods of isovolumetric contraction and relaxation[50, 76]. It can also be seen that RV ejection occurs over a much lower pressure range than LV ejection.

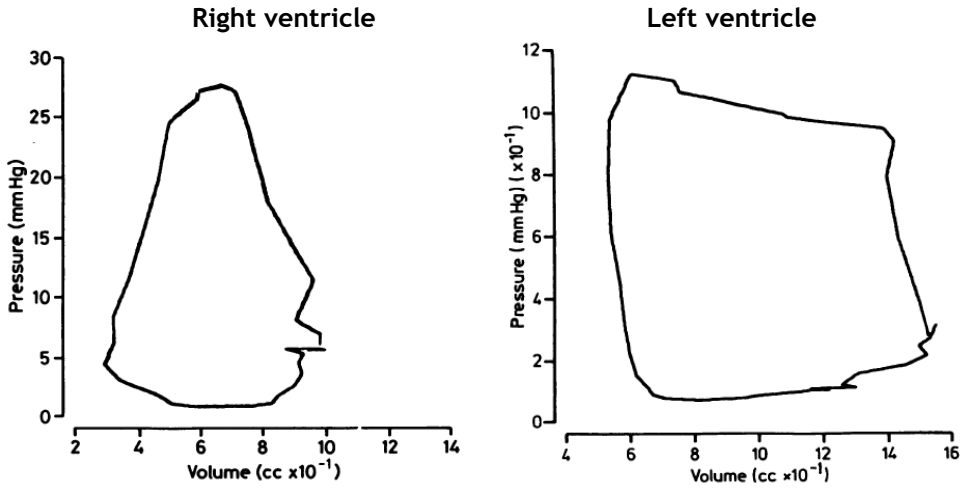

Figure 7. Right and left ventricular pressure volume relationships in sheep
From Redington et al. (1988)[77] Note pressure difference between left and right ventricles.

It can be seen from Figure 7, RV ejection continues as RV pressure declines, this phenomenon is as a result of the highly compliant pulmonary vasculature, with this "hangout" period shortening as RV afterload increases[50, 76]. Similarly to as described in section 1.2.3.4.1 for the LV, the ESPVR and EDPVR reflect contractility and compliance in the RV (Figure 8). Compared to the square shape of the LV, it is difficult to identify the precise end systolic point in the RV PV loop giving uncertainty in the estimation of the ESPVR. *Maximal* elastance (E_{max}) as opposed to *end-systolic* elastance is often described as the best measure of RV contractility[50].

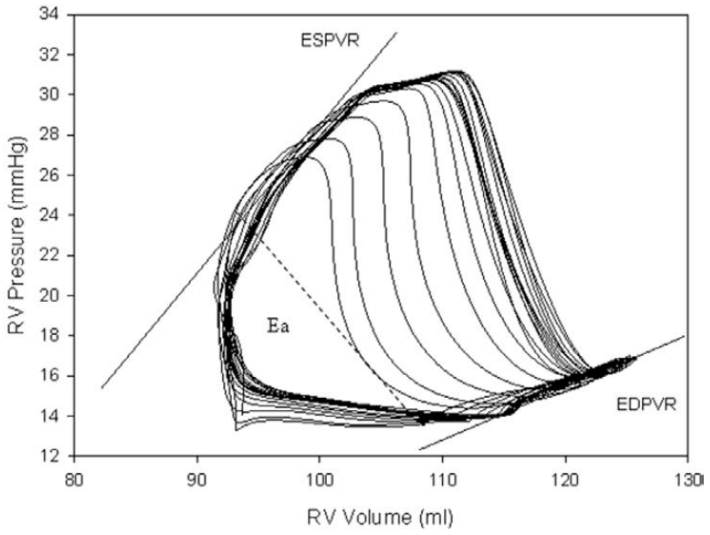

Figure 8. Right ventricle pressure volume loops
From McCabe et al.[76]. Contractility (E_{max}) is derived from the end systolic pressure volume relations ship (ESPVR). The dashed line is the ratio of end systolic pressure to stroke volume and is the arterial elastance (E_a).

Effective arterial elastance (E_a) of the pulmonary artery is a parameter that offers an assessment of afterload, incorporating resistance, compliance and backward reflective waves[76]. Pressure volume loops allow E_a to be obtained from the ratio of end systolic pressure (ESP) and stroke volume (dashed line, Figure 8)[71].

1.2.3.5 Perfusion and cellular biology of the right ventricle

The mitochondrial density and the mitochondrial to myofibril ratio of the LV and the interventricular septum are similar to each other, but much greater than in the RV. This ratio is a marker for myocardial oxygen consumption (MVO_2) and workload, indicating comparatively lower values in the RV[64, 66].

Unlike the LV where perfusion of the left coronary artery occurs predominantly in diastole, in the absence of severe hypertrophy or pressure overload, epicardial coronary artery flow to the RV occurs throughout the cardiac cycle. Beyond the RV marginal branches however, flow is predominantly diastolic. Under baseline conditions coronary blood flow is lower in the right coronary artery (RCA) compared with the left anterior descending coronary artery (LADCA)[61, 66]. Putting both ventricles under stress results in increased blood flow in the LADCA with no increase in LV MVO_2 whereas there is an increase in both RV MVO_2 *and* blood flow in the RCA[66, 78].

The decreased oxygen demand of the RV myocardium at baseline, along with a lower blood flow rate results in an oxygen consumption that is approximately half that of the LV. These properties, along with higher coronary vasomotor tone at baseline (allowing an increase in blood flow with increased oxygen demand), provide the RV with a more favourable supply/demand profile compared to the LV and explain its ability to increase O_2 extraction in response to ischaemia[66].

1.2.3.6 Biventricular function / ventricular interdependence

The concept that the ventricles can be viewed as *independent* entities is flawed, they are constrained by the same visceral cavity (the pericardium), have a common interventricular septum, share coronary blood flow and have common myofibres (particularly superficially). So although *anatomically independent* cavities, there is continuous interplay and they are *functionally inter-dependent* meaning the size, shape and compliance of one ventricle may affect the function of the other through direct mechanical interactions[50, 64, 66]. The two chambers are also connected in series, meaning a decrease in RV output results in decreased LV preload, thus reducing LV output[49].

In the normal heart, contraction of the LV is a significant contributor to ejection of blood from the RV, this is mediated through the interventricular septum[51 64]. Damiano and colleagues demonstrated in a canine model that LV contraction in the presence of an electrically isolated and inert RV, with an open pericardium, led to pronounced pulmonary artery pressure generation (Figure 9, pg 37). The authors estimated that 30-35% of the measured RV pressure and volume output

were generated by the LV and septum. The converse was not true with RV contraction contributing little to LV pressure development[79].

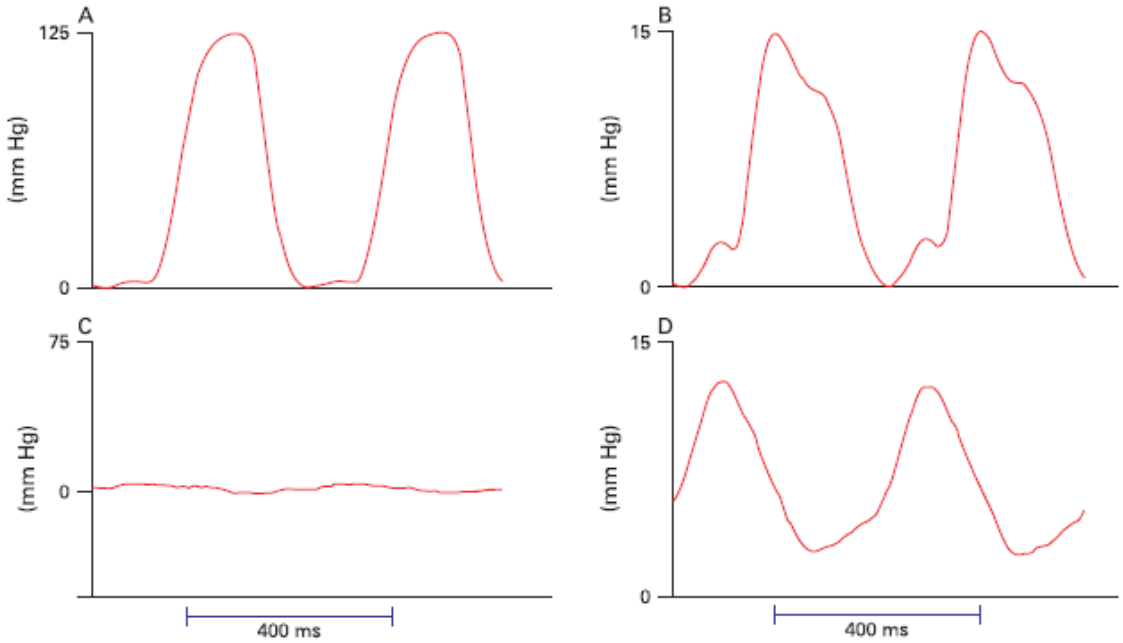

Figure 9 Pressure recordings from the electrically isolated canine right and left ventricles. Image from Sheehan et al.[50] adapted from Damiano et al.[79] Note the difference in pressure scale between the left (A and C) and Right (B and D) ventricles. A = pressure generated in the LV during LV contraction, B = pressure generated in the RV during LV contraction, C = no pressure generated in LV during RV contraction, D = pressure generated in the RV during RV contraction.

Diastolic ventricular interdependence is mediated mainly through the pericardium and occurs when pressure or volume overload of the RV shifts the interventricular septum towards the LV, altering LV geometry and reducing LV distensibility[51]. Brookes et al. demonstrated in a swine model with PV loop analysis of both ventricles, that changes in RV geometry directly affected LV contractile performance. This indicated that impairment of LV function during RV dilatation was not *only* as a result of reduced LV preload but also as a direct result of changes in RV geometry. This effect was attenuated by pericardotomy[80].

The LV is a significant contributor to RV ejection and although RV function does not contribute to LV ejection, RV dysfunction can have both a negative *series* and *parallel* effect on LV function. LV pressure generation can be reduced as a result of reduced preload (series effect) but also as a result of changes in RV geometry directly affecting LV performance (parallel effect).

1.2.3.7 Right ventricular-pulmonary vascular unit (ventriculo-arterial coupling)

Efficient RV function relies on effective interaction between the RV and the low resistance, high compliance pulmonary circulation. This matching of contractility and afterload is known as coupling and its preservation is important for ventricular efficiency[81]. Contractility and afterload can both be altered by pathology but coupling and efficiency is maintained if, as afterload increases, there is a matched increase in contractility[82]. As a disease process progresses, with further increases in afterload, the RV starts to fail as a pump and contractility falls, leading to inadequate coupling and reduced efficiency[83]. Effective right ventriculo-pulmonary artery (RV-PA) coupling ("coupling") maintains cardiac output while maximising the efficiency of the RV.

Coupling is the ratio of contractility (E_{max}, section 1.2.3.4.2, pg 34) and afterload (E_a, section 1.2.3.4.2, pg 34) and gives an index of the matching between the RV and pulmonary circulation[71, 76, 81, 84]. *Theoretical* optimal coupling occurs when the ratio of E_{max}/E_a is equal to 1 and the RV is able to generate maximal flow with minimal energy loss[83, 84]. Stroke work is the work performed by the ventricle to eject stroke volume into the pulmonary circulation. There is a broad range of E_{max}/E_a of 0.5 to 2.0 where stroke work is close (<5% decrease) to optimal [85, 86].

Myocardial efficiency is the ratio of stroke work to myocardial oxygen consumption and this is optimal at E_{max}/E_a=2. Myocardial efficiency is maintained close to optimal over a broad range of E_{max}/E_a values from 1.0 to 3.0[85]. As mentioned above, coupling is maintained if as afterload increases, there is a matched increase in contractility however, this is often at the expense of myocardial efficiency which would increase oxygen consumption with maintained coupling[83]. There are no reference values for coupling and results may be dependent on the methods used in its calculation, however values are generally larger than one in healthy groups and closer to, or lower than one in disease states [81].

1.2.3.8 Right ventricle and pulmonary interaction

It would seem intuitive that given their close proximity and interaction with the pulmonary circulation that pulmonary function would interact with RV function. The mechanical work of breathing has a major impact on beat-by-beat and breath-by-

breath right heart haemodynamics. During spontaneous breathing, the 2-5cmH_2O decrease in intra-pleural pressure with inspiration leads to an increase in preload and therefore RV cardiac output, accounting for the waxing and waning of RV stroke volume during the respiratory cycle[50]. Conversely, during mechanical ventilation, RV stroke volume falls as mean airway pressure increases, preload is reduced and afterload is increased. Although not usually important in health, the small changes may be amplified in any situation where RV function is already compromised[50].

1.2.3.9 Regulation of right ventricular function

The main mechanisms that regulate RV function are heart rate, the Frank-Starling mechanism and the autonomic nervous system. The autonomic nervous system has a differential effect on the inflow and outflow regions of the RV [46].

Two methods act to preserve cardiac function when afterload or preload are altered. The first is *heterometric autoregulation* (changes in contractility are dependent on myocyte length), this is based on the Frank-Starling mechanism with increased preload increasing contractility. This occurs on a beat to beat basis[71, 81]. The second mechanism is *homeometric autoregulation* (changes in contractility are independent of changes in myocyte length). This response is based on the Anrep effect, or slow force response, and reflects an increase in contractility associated with increased afterload. This occurs over a longer time period (minutes) and is initiated by stretched myocardium leading to increased contractility[81]. This is an autocrine and paracrine controlled chain of events which begins with Angiotensin II release and culminates in increased cardiac myocyte intracellular Ca^{2+} concentration and a progressive decline in RVEDP (elevated as a result of increased afterload).[87] These responses are unlikely to happen completely in isolation, for example, in response to increased afterload the RV is likely to dilate and trigger the Frank-Starling mechanism first and then the slower homeometric autoregulation response develops[85].

1.2.3.10 Right ventricle vs left ventricle

Characteristics	Right Ventricle	Left Ventricle
Structure	3 component parts[63]: 1) Inlet (inflow region) 2) Trabeculated myocardium 3) Outlet (infundibulum)	Inflow region, myocardium, no infundibulum
Coupled circulation[82]	Short vessels repeatedly dividing into daughter vessels. Vasoconstricts in response to hypoxia	A large main artery (aorta) with multiple side branches Vasodilates in response to hypoxia
Location	Most anterior cardiac structure, Immediately behind the sternum[61]	Posterior to RV
Shape	Crescenteric in cross section triangular when viewed from the side[46]	Elliptical / conical[46, 63]
Blood supply (depends on dominance of the coronary system)	Majority of cases from right coronary artery. Perfusion throughout entire cardiac cycle	From left coronary artery Perfusion predominantly during diastole
Muscle fibre orientation	Superficial circumferential deep longitudinal myofibres predominate (no middle layer)[63]	Superficial obliquely orientated with longitudinally orientated fibres in the sub-endocardium circular fibres in between[63]
Contraction	Longitudinal shortening[51]	Twisting, rotational movements[51]
End diastolic volume (mm^3)	Larger 75 ± 13 [49 - 101][46]	Smaller 66 ± 12 [44 - 89][46]
Mass (g/m^2 BSA)	Smaller 26 ± 5 [17 - 34][46]	Larger 87 ± 12 [64 - 109][46]
Thickness of ventricular wall (mm)	2-5[46]	7-11[46]
Ventricular pressures	25/4 ([15-30] / [1-7])	130/8 ([90-140] / [5 - 12])
EF (%)	61 ± 7 [47-76]	67 ± 5 [57-78]
Ventricular elastance (E_{max}), mmHg/ml	1.30 ± 0.84	5.48 ± 1.23
End diastolic compliance	High	Low
Filling profiles	Longer. Starts earlier finishes later with lower filling velocities	Shorter. Starts later, finishes earlier, higher filling velocities
Afterload ($dyn \cdot s \cdot cm^{-5}$)	PVR. 70 [20-130]	SVR. 1100 [700-1600]
Resistance to ischaemia	High	Low
Adaption to disease state	Tolerant of volume overload	Tolerant of pressure overload

Table 1. Comparison of normal RV and LV structure and function
Values presented as mean ± SD [range]. Adapted from Haddad et al.[46]. RV = right ventricle, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance.

1.3 Assessment of the right ventricle

Determination of RV function is important for management of many clinical conditions. The RV can be assessed using a number of imaging and functional modalities, with each providing its own strengths and limitations. The assessment of RV structure and function is challenging with a number of factors contributing to this difficulty[46, 88]:

1. The complex geometry of the RV; It is triangular when viewed from the front and crescenteric when viewed in transverse section. This means that measures using geometric assumption for volume quantification have limited application[88].

2. The heavily trabeculated myocardium; When using imaging techniques this limits accurate endocardial visualisation and delineation. This is in contrast to the smoother LV endocardial border.

3. The retrosternal position; This applies mainly to echocardiographic assessment and means the RV, particularly the free wall, is hidden behind the sternum (which acts as an acoustic barrier) limiting its visualisation[61].

4. Marked load dependence; RV function is sensitive to changes in both preload and afterload. The ideal measure of function would be independent of loading conditions but due to the difficulties in obtaining load independent measures of contractility, many of the most commonly used parameters for assessing RV function are load dependent[46, 88].

Due to the fundamental difference between the pulmonary and systemic circulations, the parameters that have been historically used to assess LV function cannot readily be applied to the RV. Pressure-volume loop (PV loop) analysis (as described in section 1.2.3.4.2 pg 34) is the gold-standard method for load-independent assessment of RV function but is technically challenging to perform.

Methods of RV assessment can be broadly divided into invasive and non-invasive.

1.3.1 Invasive assessment

1.3.1.1 Conductance catheter

This technique has been widely used in assessment of LV function and involves placement of a catheter in to the RV and allows continuous and instantaneous measurement of ventricular volume. The conductance catheter (CC) consists of a number of equidistant electrodes and utilises the principle of the time-varying conductance of blood within the ventricle, with conductance linearly related to ventricular volume. Blood is a good conductor of electricity and the ventricular wall relatively poor, meaning when the ventricle is full (end diastole), the conductance is higher than end systole[76, 89]. These catheters also contain a high fidelity sensor which simultaneously measures pressure, allowing the construction of pressure-volume loops. A family of pressure-volume loops can be obtained by altering preload (e.g. balloon occlusion of the inferior vena cava) or afterload (e.g. occlusion of the pulmonary artery). From this family of curves, maximal systolic elastance (E_{max}), effective arterial elastance (Ea) and RV-PA coupling (ratio of E_{max}/E_a) can be obtained (section 1.2.3.7, pg 38).

In addition to E_{max} and E_a, pressure-volume loop analysis allows calculation of other parameters describing RV function including; Stroke work (the area enclosed by the P-V loop and a measure of kinetic energy within the RV), dP/dt_{max} (maximum rate of pressure change in the RV, a measure of systolic performance), preload recruitable stroke work (PRSW, a relationship of stroke work and end diastolic volume that represents ventricular contractility), dP/dt_{min} (maximum rate of pressure decline which gives an idea of ventricular compliance) and End Diastolic Pressure Volume Relationship (EDPVR, ventricular compliance)[76, 90].

Conductance catheterisation is considered the gold standard for assessment of RV function, however the requirement for specialised equipment, along with its complex measurement and technical difficulty means its use is limited to a small number of specialist research centres[46, 73, 85, 91]. In addition, this is an invasive technique requiring placement of an intra-cardiac catheter with incorporated risk.

1.3.1.2 Pulmonary artery catheter

The pulmonary artery catheter (PAC) also known as the right heart catheter (RHC), has been used in medical practice since 1970 and allows direct measurement of right sided haemodynamics with calculation of cardiac output and resistances[92]. Although its use has diminished in recent years, especially in critical care, it is still the reference standard for diagnosis and assessment in a number of clinical settings, particularly pulmonary hypertension[93-95]. Parameters that can be measured from the PAC include; right heart pressures (right atrial pressure [RAP] and RV pressure [RVP]), pulmonary artery pressures, pulmonary arterial wedge pressure (PAWP), trans-pulmonary pressure gradient (TPG) and diastolic pressure gradient (DPG). By calculation of flow (cardiac output) other parameters can be derived; pulmonary vascular resistance (see Equation 2, pg 32) and systemic vascular resistance (SVR)[96].

Some novel PACs allow measurement of additional parameters[97]. A spectrophotometry sensor at the tip of the catheter can allow continuous mixed venous oxygen saturation measurement which can provide information on global oxygen delivery and consumption[98]. Continuous cardiac output (CCO) can be measured using thermodilution techniques. RV end diastolic volume (RVEDV) can purportedly be determined by fast response thermodilution systems and allows calculation of RV ejection fraction (RVEF) and RV End Systolic Volume (RVESV)[99, 100]. A more in depth discussion of these 'volumetric' PACs is provided in section 2.3.2, pg 77.

Measurements of pressure and PVR are an important diagnostic tool, giving some insight into the RV, but their measurement alone allows only an indirect description of RV function[72, 81]. RAP could be considered a surrogate of RVEDV or preload, with PAP or PVR as an estimate of afterload and stroke volume as an approximation of contractility. *Volumetric* measures provide much more information on RV function and can be used to compliment the information provided by PAC measurements[72].

Although rates are low, complications of PAC occur and can be related to the introduction of the catheter (arterial puncture, pneumothorax, haemothorax, thoracic duct lesions, infection), or from the PAC itself (valve lesion, catheter

knotting, PA rupture, RV perforation and cardiac arrhythmias)[96, 101-104]. The complications associated with PAC insertion would also be expected to apply to the introduction of the conductance catheter discussed in section 1.3.1.1, pg 42.

1.3.2 Non-invasive assessment

1.3.2.1 Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance (CMR) imaging utilises the interaction between a static magnetic field generated by a magnetic resonance imaging (MRI) scanner and the tiny magnetic fields that arise from the individual atomic nuclei of hydrogen atoms within free water or lipid molecules[105-107]. CMR is ideally suited to assessment of the RV as it allows measurement of ventricular parameters overcoming most of the limitations to RV assessment that are described in section 1.3, pg 41. There is no reliance on acoustic windows, meaning no matter the position or orientation of the heart within the thorax, it is possible to obtain high resolution, time resolved images free from geometric assumptions which limit other modalities[108]. There is no exposure to ionising radiation, no risk associated with intra-cardiac catheter placement (in contrast to the PAC and CC) and non-contrast imaging can even be completed without the need for intra-venous access making it *genuinely* non-invasive.

Volume measurements of all cardiac chambers are obtained from cine imaging; these consist of anatomical images acquired at consecutive frames throughout the cardiac cycle that when played back show a movie of heart motion[109]. These cine images 'slice' the heart from base to apex and are performed during breath holds. A 'stack' of these images can be subsequently analysed offline and the endocardium contoured at both end systole and end diastole (manually or automatically depending on software) to provide an accurate measure of volumes using the summation of discs method (illustrated in *Methods, section 4.3.2.3, pg 143)*. These volumes (end systolic and end diastolic) permit calculation of ejection fraction and a volumetric estimation of RV-PA coupling. Although it is load dependent, RV ejection fraction is the most commonly used measure of RV contractility and is widely accepted[46]. RVEF is *load* dependent as it does not measure *intrinsic* contractility and situations may arise where contractility is reduced but as a result of loading conditions (decreased afterload or increased

preload) ejection fraction remains unchanged. Interventricular septum geometry can be determined from cine imaging allowing calculation of the eccentricity index, which quantifies the septal bowing that occurs during RV pressure and volume overload states[110].

In addition to providing detailed information on the structure, volume and mass of the RV from cine imaging, CMR can provide further insights into RV and pulmonary vascular function. Velocity encoded imaging can provide information on blood flow velocity and blood flow rate within the heart and vasculature. This can provide information on valve function and blood flow patterns within the pulmonary vessels. T2-weighted imaging can be used to assess myocardial oedema. First pass myocardial perfusion imaging allows assessment of perfusion of the myocardium in real time[111].

T1 weighted perfusion and late enhancement imaging following administration of gadolinium contrast allows characterisation of RV tissues, showing oedema, fibrosis, inflammation and scarring[112]. Interpretation can be difficult in the thin-walled RV however. Additional information can be provided by simultaneous use of pressure catheters to provide pressure-volume loops and give a more in depth assessment of RV function, this technique has only been utilised in a research setting[88, 113].

Consensus guidelines from the Society of Cardiovascular Magnetic Resonance (SCMR) for standard post-processing and interpretation of CMR imaging were published in 2013 and help ensure consistent quality and reproducibility[114]. CMR assessment of RV volumes is reproducible with low inter-observer and intra-observer variability[108]. Mooij et al. examined 60 patients (20 '*normal*' and 40 with RV dilatation) using CMR and showed low inter and intra-observer variability[115]. This was signified by high intraclass correlation coefficients (ICC) for inter-observer (ICC 0.94-0.99) and intra-observer (ICC 0.97-0.99) variation for comparison of RV volumes (RVEDV, RVESV and RVSV). ICC for RVEF was lower with ICC's for inter-observer and intra-observer variability of 0.81 and 0.87 respectively. There is also some data (published in abstract form) to suggest that following a training period, with a standardised protocol, there is little difference between novice and experienced CMR readers[116].

CMR is considered a reference method for non-invasive evaluation of RV function and is an important tool for assessment in many clinical conditions, such as heart failure, congenital heart disease, pulmonary hypertension and ischaemic heart disease[108, 117-119]. It is also commonly used as the reference method for validation of echocardiographic methods[120-122].

CMR does have a number of limitations, it is expensive, especially when compared to other imaging modalities (echo or CT)[88, 108, 123]. Lower availability means that not every hospital will have access to CMR imaging. Lack of portability means its use is limited in the sickest of patients who would be unsuitable for safe transfer to the scanner. Claustrophobia in combination with long scan duration means that some patients will decline imaging. The need for breath holds during cine imaging, used to reduce respiratory motion artefact, may hinder its use in the very sickest patients and provides a unique challenge in the lung resection cohort[76]. Contraindications as a result of implantable devices that are MRI incompatible are less frequent with modern materials, but still mean some patients will be permanently unsuitable for scanning. When contrast is required, there is risk of renal injury or allergy from gadolinium based agents[124]. Manual segmentation is time consuming although automated software has been developed[125]. Expertise is required for imaging to be performed and for robust assessment of findings, meaning CMR imaging is often limited to specialist centres[51].

1.3.2.2 Echocardiography

Trans thoracic and transoesophageal echocardiography (TTE and TOE respectively) can both be used to assess RV function. TOE is usually reserved for the intra-operative assessment of cardiac function and assessment of complex valvular disease. For this review, discussion will focus on TTE imaging. TTE assessment of the RV is challenging, it's retrosternal position meaning visualisation of the anterior RV free wall is difficult. As described in section 1.3, pg 41, the RV has complex geometry meaning summation disc type volume calculations (in contrast to Simpsons bi-plane measurement of the LV) are not easy to perform and ultimately inaccurate[126]. In addition, many of the commonly used indices of RV performance are markedly load dependent[88]. TTE can provide information on RV dimensions, RV function and right sided pressures.

Despite the difficulties associated with TTE, it is by far the most commonly used modality in clinical practice; it is portable, widely available, inexpensive, non-invasive with no exposure to ionising radiation. The British Society of Echocardiography have published a minimum dataset for standard TTE assessment which incorporates all aspects required for comprehensive evaluation of the RV[127]. Consensus guidelines have also been produced by the American Society of Echocardiography (ASE) for assessment of the right heart in adults and these have been endorsed by the European Association of Echocardiography and the Canadian Society of Echocardiography[128]. This guideline recommends that any report on right heart function should represent an assessment based on both *qualitative* and *quantitative* measures.

Given the difficulties in assessing RV volumes using TTE, there had been a previous reliance on *qualitative* assessment with it still recommended for estimation of RV size. The RV should appear smaller (and usually no more than 2/3 the size) than the LV when viewed in the standard apical 4-chamber view. If it appears larger in this view, it is likely to be significantly enlarged. RV assessment in this view is very sensitive to angular change and should be interpreted with caution. A subjective assessment can also be made of global function and septal bowing (which can additionally be quantified with the eccentricity index)[129]. Patterns of RV wall motion abnormality can be useful, such as in acute pulmonary embolism and McConnell's sign, which is signified by akinesia of the mid-free wall with normal motion at the apex[130]. Any qualitative assessment of RV function should be complemented with objective, quantitative, standardised measures. As there are difficulties in obtaining reliable views of the whole RV, quantitative assessment of systolic function often relies on surrogate parameters, or extrapolating regional assessment to reflect the entire ventricle[61].

As per ASE guidance for the assessment of the right heart in adults, the parameters to be obtained should include a measure of right heart size, a measure of RV systolic function (at least one of fractional area change [FAC], tricuspid annular plane systolic excursion [TAPSE], S' wave velocity at the lateral tricuspid annulus [S' Wave] or the RV myocardial performance index [RV-MPI]) and an estimate of right sided pressures.

1.3.2.2.1 Right heart size

In addition to qualitative assessment, RV linear dimensions should be obtained from the apical 2-dimensional 4-chamber (A4C) view. Caution should be exercised here as the view is very dependent on probe position/rotation meaning RV width can be underestimated. RV basal, mid-cavity and longitudinal dimensions should be recorded.

1.3.2.2.2 Fractional area change (FAC)

FAC is a measure of the change in RV area and can be obtained from 2-D imaging in the A4C view. FAC is calculated as described in Equation 3 (Determination of FAC is illustrated in *Methods, section 4.4.2.2.1 pg 150).*

$$FAC = \frac{EDA - ESA}{EDA} \times 100$$

Equation 3. Fractional area change (FAC)
EDA = end diastolic area, ESA = end systolic area.

EDA and ESA are obtained by tracing the RV endocardium from the annulus, along the free wall to the apex and then back along the interventricular septum to the annulus again. In a mixed population of 63 patients[A] Focardi et al. demonstrated strong association of FAC with $RVEF_{CMR}$ (r=0.77) and that it had an area under the receiver operating characteristic curve (AUROCC) of 0.78 for predicting an $RVEF_{CMR}$ of <45%[121]. This finding is supported by other studies, albeit with a lower correlation coefficient (r=0.47) but similar AUROCC for ability to predict poor $RVEF_{CMR}$ (0.88-0.89)[122, 131]. Other work however, including that by Kjaergaard et al. in 34 participants[B], has shown that FAC does *not* associate with $RVEF_{CMR}$ (r=0.34, non-significant [exact p-value not provided in paper])[120, 132].

The limited range of RVEF assessed by Kjaergaard et al. meant that they were unable to evaluate FAC in those with very large or very small RVEF. The range

[A] Referred for clinical assessment, 8 with suspected myocarditis, 8 with idiopathic dilated cardiomyopathy, 10 with hypertrophic cardiomyopathy, 10 with arrhythmogenic right ventricular dysplasia, 5 with infiltrative cardiomyopathy, and 9 for other reasons.

[B] 17 with prior ST-elevation myocardial infarction, 7 with a history of pulmonary embolism and 10 normal subjects.

assessed by Focardi et al. was much broader and could have contributed to the conflicting results of the two studies. The difficulties of RV visualisation and endocardial border contouring described above could also contribute to the inconsistency of FAC[112].

1.3.2.2.3 Tricuspid annular plane systolic excursion (TAPSE)

Given the predominantly longitudinal movement of the RV on contraction, the systolic movement of the base of the RV wall at the tricuspid annulus provides one of the most visibly obvious movements on echocardiography. TAPSE quantifies this movement towards the apex and is obtained by placing an M-mode cursor through the tricuspid annulus in the A4C view and measuring the amount of longitudinal motion at peak systole. It assumes that the greater the displacement of the base during systole, the better the systolic function. It also assumes that displacement of the base reflects function of the entire ventricle. TAPSE is sensitive to Doppler cursor alignment, loading conditions and heart rate[112, 131]. TAPSE is the most commonly used measure in clinical practice, has been extensively studied and has well defined normal ranges[51, 133]. Global cardiac movement can contribute to the movement of the tricuspid annulus during systole meaning TAPSE may not truly represent *solely* RV function. Giusca et al. attempted to correct for global cardiac movement by adding the change in position of the LV apex to TAPSE values, resulting in improved association with peak systolic strain (an alternative echocardiographic method of assessing RV function, see section 1.3.2.3.4, pg 53)[134].

TAPSE has been shown to be associated with $RVEF_{CMR}$ (r=0.45-0.48) and has shown variable predictive ability for RVEF <45% signified by an AUROCC 0.66-0.85[121, 122, 131, 132]. Measurement of TAPSE is illustrated in *Methods,* section 4.4.2.2.2, page 151.

1.3.2.2.4 S' Wave velocity at the tricuspid annulus (S'Wave)

This method, similar to TAPSE, utilises the longitudinal excursion of the ventricle at the basal free wall. S' wave velocity is the highest systolic velocity and is obtained from an A4C view of the heart with a tissue Doppler 'region of interest' highlighting the RV free wall. As with all tissue Doppler techniques, care must be

taken to ensure optimal image orientation to avoid underestimation of velocities. Similar to TAPSE, this method assumes that function of a single region represents the function of the entire ventricle and is influenced by global cardiac movement. Moderate association with $RVEF_{CMR}$ has been shown in a heterogeneous group of patients (r=0.48-0.52) with a good ability to predict poor RV function with an AUROCC of 0.80[121, 122]. Other work however, has shown that S'Wave does not relate to $RVEF_{CMR}$[131]. Colour coded tissue Doppler can be analysed offline and is a novel method that can also be utilised to determine tissue velocities and calculate S'Wave. Measurement of S'Wave is illustrated in *Methods,* section 4.4.2.2.3, pg 152.

1.3.2.3 Summary of TTE measures of systolic function

The measures of systolic function described (FAC, TAPSE, S'Wave) are all recommended for assessment of systolic RV function, however their ability to determine RV function from a reference method is inconsistent. There is association between $RVEF_{CMR}$ and the parameters in some studies, but not in others[121, 122, 131, 132].

Part of this inconsistency results from the range of RV function assessed. Correlation coefficients are often used to describe the relationship of two variables with higher coefficients often resulting from wider ranges of variables (a complete description of the use of correlation for validation of measurement is provided in the *literature review,* section 2.3.2, pg 77). In a study of 223 patients[c] Pavlicek et al. demonstrated better predictive power in those with severely impaired RV function ($RVEF_{CMR}$<30%) in comparison to those with moderately impaired RV function ($RVEF_{CMR}$<50%) (Figure 10, pg 51)[122].

[c] Heterogeneous group with a mixture of Ischaemic heart disease, cardiomyopathy, valvular heart disease, congenital heart disease and pulmonary hypertension. Subdivided in to three groups based on RVEF 1)RVEF ≥50%, n = 129, 2)RVEF 30-49%, n = 67, 3) RVEF ≤30%, n = 27.

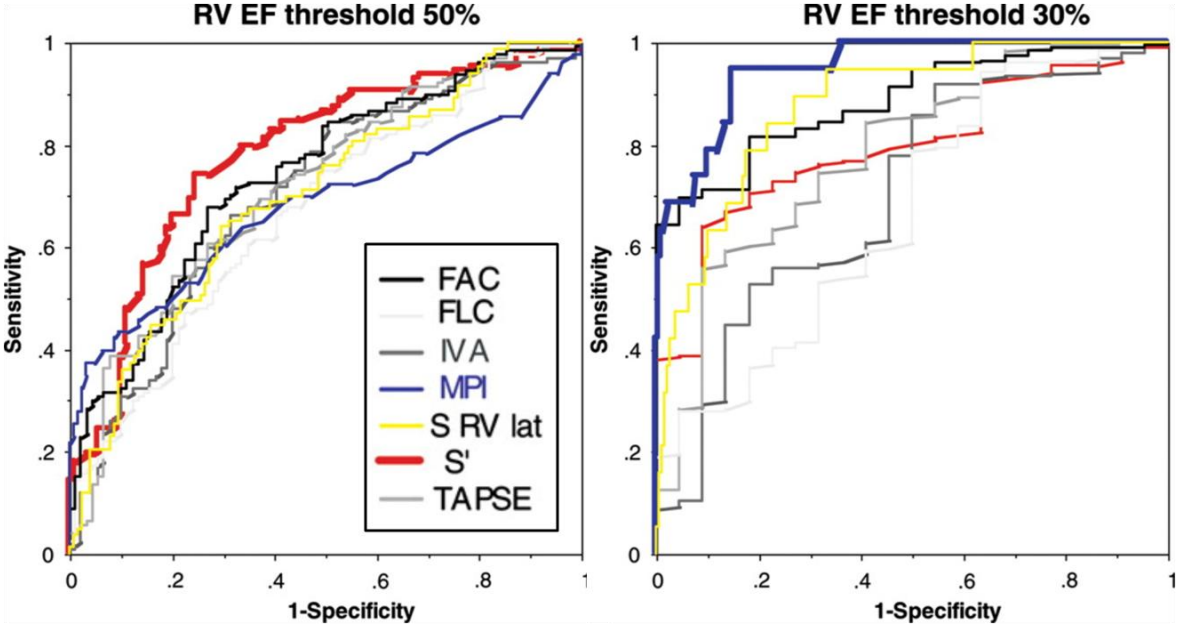

Figure 10. Receiver operating characteristic analysis for seven Doppler echocardiographic parameters from Pavlicek et al.
Adapted from Pavlicek et al.[122]. RVEF = right ventricular ejection fraction, FAC = fractional area change, FLC = fractional long axis change, IVA = isovolumic contraction acceleration, MPI = myocardial performance index, S RV lat = S'wave velocity at tricuspid annulus, S' = free wall peak systolic strain, TAPSE = tricuspid annular systolic excursion.

As can be seen from Figure 10 there is inconsistency between the echocardiographic methods. For $RVEF_{CMR}$ <50%, AUROCC ranged from 0.67 to 0.78 but for $RVEF_{CMR}$ <30%, they ranged from 0.66 to 0.95. For $RVEF_{CMR}$ <50% the AUROCC for FAC, TAPSE and S'Wave were 0.73, 0.71 and 0.78 respectively. For $RVEF_{CMR}$ <30% for FAC, TAPSE and S'Wave the AUROCC were 0.88, 0.79 and 0.80. This demonstrates that the parameters perform better for lower $RVEF_{CMR}$ but that there is also disagreement amongst them.

In 413 patients[D] presenting for cardiac surgery Peyrou et al. demonstrated discrepancy in results for FAC and S'Wave[135]. For 90.6% of participants there was concordance of results with *both* demonstrating normal or abnormal RV function (FAC>35% and S'Wave >10cm/s *or* FAC <35% and S'Wave <10cm/s). However, for the remaining 9.4% of participants there was disagreement between the two parameters with either FAC or S'Wave being '*normal*' but the other '*abnormal*'.

[D] Patients awaiting cardiac surgery. Consisted of 63% awaiting valve surgery, 49% coronary artery bypass grafting and 3% *other* cardiac surgery.

1.3.2.3.1 Inferior vena cava (IVC) diameter

IVC diameter and the presence of inspiratory collapse is commonly used to estimate right atrial pressure. As RAP increases, pressure is transmitted to the IVC which collapses less with inspiration. This method estimates well when RAP is low or high, but less well when intermediate[136]. IVC diameter of ≤2.1 cm that collapses >50% with a sniff suggests a normal RAP of 3mmHg. An IVC diameter >2.1cm that collapses <50% with a sniff suggests a high RAP of 15mmHg. In indeterminate cases that do not fit these groups, an intermediate value of 8mmHg is used[128]. Assessment of IVC diameter is illustrated in *Methods,* section 4.4.2.2.4, pg 153.

1.3.2.3.2 Pulmonary artery systolic pressure (PASP)

Pulmonary artery systolic pressure can be estimated using continuous wave Doppler analysis across the tricuspid valve[137]. The pressure gradient across the valve can be determined from the tricuspid regurgitant jet (TRJ) velocity and the simplified Bernoulli equation (Equation 4). This gradient combined with an estimate of RAP (from IVC diameter, above) is used to reliably determine RV systolic pressure. In the absence of a gradient across the pulmonary valve or RV outflow tract obstruction, PASP is equal to RVSP. In cases where RVSP is elevated, RV outflow obstruction should be excluded. It is recommended to gather TR signals from multiple windows and utilise the window with the highest velocity.

$$Tricuspid\ valve\ pressure\ gradient = 4(V)^2$$

Equation 4. Simplified Bernoulli equation
V = peak tricuspid regurgitant jet velocity from continuous wave Doppler

PASP by continuous wave Doppler echocardiography has shown strong association with invasively measured PASP (r=0.68±0.19 on pooled meta-analysis, p=0.003). This association is reduced in those patients with predominantly right sided heart disease or with normal PASP (in contrast to elevated PASP)[138]. TRJs are not visible in all patients; in those with PASP (measured invasively) >35mmHg, only 80% will have visible jets. This increases to more than 95% in those patients with PASP >50mmHg[137]. PASP by TTE tends to

overestimate PASP by PA catheter[70]. Measurement of PASP by TTE is Illustrated in *Methods,* section 4.4.2.2.5, page154.

1.3.2.3.3 Pulmonary artery acceleration time (PAAT)

Mean pulmonary artery pressure (mPAP) can be estimated from the acceleration time of the pulsed Doppler signal of the pulmonary artery during systole (PAAT is the time from onset of the Q wave on ECG to peak pulmonary flow velocity). Decreased PAAT is associated with increased wave reflection in the pulmonary artery which suggests increased pulsatile afterload[70]. A shorter PAAT is associated with higher pulmonary artery pressures and increased PVR in pulmonary hypertension [70, 139, 140]. Measurement of PAAT is Illustrated in *Methods,* section 4.4.2.2.6, page 155.

1.3.2.3.4 Strain

Strain and strain rate are parameters of deformation. It is important to make a distinction between myocardial *displacement* and myocardial wall *deformation*. Over time the myocardium may change its position (displacement) but may not undergo deformation if all parts move with the same velocity. Wall motion measurements (velocity and displacement such as S'Wave and TAPSE) cannot differentiate between active and passive movement of a myocardial segment, whereas deformation analyses (strain and strain rate) allow discrimination between active and passive myocardial tissue movement[69]. For example, as the apical parts of the ventricle contract they pull down the ventricular base, the wall motion velocity and displacement parameters of the basal segments will increase, even if these segments are completely passive (not contracting). Their velocity and displacement is tethered to apical contraction. Deformation parameters can overcome this problem by measuring the magnitude of regional myocardial fibre contraction and relaxation[141]. Lagrangian strain (Equation 5, pg 54) is deformation relative to the initial length and is mathematically defined as the change of (myocardial) fibre length during stress at end systole (L) compared to its length in a relaxed state at end diastole (L_0).

$$\varepsilon = \frac{L - L_0}{L_0} = \frac{\Delta L}{L_0}$$

Equation 5. Strain Calculation
ε = Strain; L_0 = baseline length; L = length at time of measurement.

The amount of deformation (positive or negative strain) is usually expressed in percent with positive values indicating myocardial thickening and negative values describing shortening in comparison to its original length[76].

Current methods allow strain to be calculated from echocardiography and CMR[142]. CMR tagged strain is considered the non-invasive reference method for strain measurement but due to its complexity and lengthy image acquisition and analysis times, its use is currently limited. Echocardiographic methods allow one-dimensional (1D) measurements of strain using tissue Doppler and two-dimensional measurements using speckle tracked imaging. The use of three-dimensional speckle tracked echocardiographic imaging is also developing[143].

Deformation parameters can be calculated for individual segments and specific directions. A good approximation of active cardiac motion can be made with the use of three components of contraction; longitudinal, radial and circumferential strains (Figure 11, pg 55). This still represents a simplification from true three dimensional strain, where shear strains would be used, in addition to these three '*normal*' strains[141].

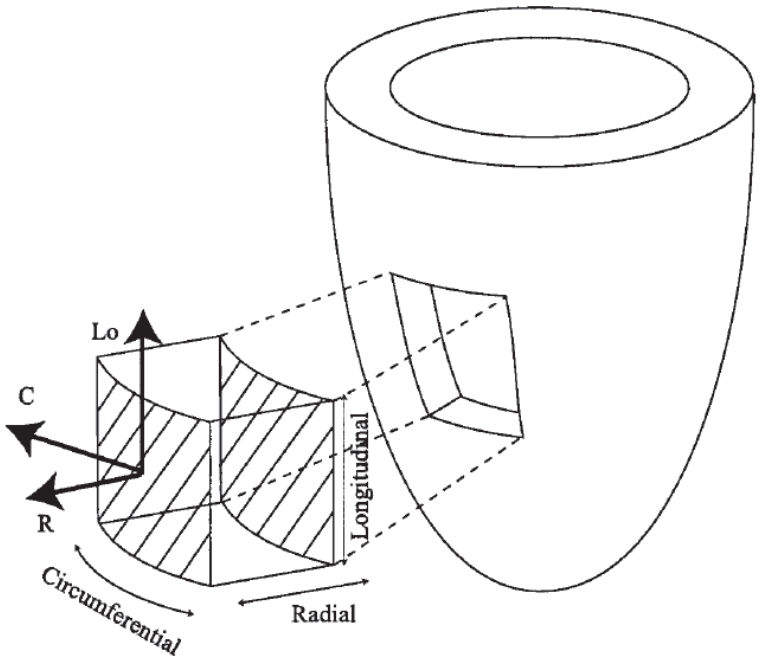

Figure 11. The heart coordinate system for interpretation of strain measurements
From D'hooge et al.[144] For each point to be interrogated in any myocardial wall, three perpendicular axes can be defined; ***Radial Axis (R)*** = perpendicular to the epicardium, away from the cavity; ***Longitudinal axis (L_0)*** = perpendicular to the radial axis, tangent to the epicardium and pointing towards the base of the ventricle, away from the apex; ***Circumferential axis (C)*** = perpendicular to both the radial and longitudinal axis.

Tissue Doppler imaging (TDI) is used for assessment of velocity and displacement and due to a relationship between velocity and strain rate (SR), it also allows the construction of strain curves[69, 145]. Assessment of strain by TDI is subject to multiple technical limitations. Firstly, an optimised 2D image with rapid frame rates (>150 Hz) to resolve regional velocities and calculate SR is required. Also, alignment of the Doppler beam with the region of interest is vital as results are very angle dependent. If the angle of incidence is >20^{o}, calculations become inaccurate[69, 141, 145]. Assessment of deformation parameters by TDI is only feasible if the echo beam can be aligned to the vector of contraction in the respective myocardial segment. Therefore, only longitudinal strain in the apical views, and radial strain in the parasternal views, can be calculated[146]. TDI requires considerable experience for correct interpretation and due to the analysis requiring operator dependent functions, including the positioning of sample volumes, TDI strain is semiobjective[141, 145]. Due to these multiple limitations, other methods to calculate myocardial deformation parameters have been developed.

1.3.2.3.5 Speckle tracked echocardiography

Speckle tracked echocardiography (STE) is performed as an offline analysis from cine loops of greyscale images. Semi-automated software uses speckle artefacts in the echo image which are generated at random due to reflections, refraction and scattering of echo beams. This interference pattern results in bright and dark pixels which remain relatively constant for any small region of the myocardium and can be tracked through the cardiac cycle. These speckles can be used as acoustic markers for tagging myocardial motion (Figure 12)[69, 128, 141].

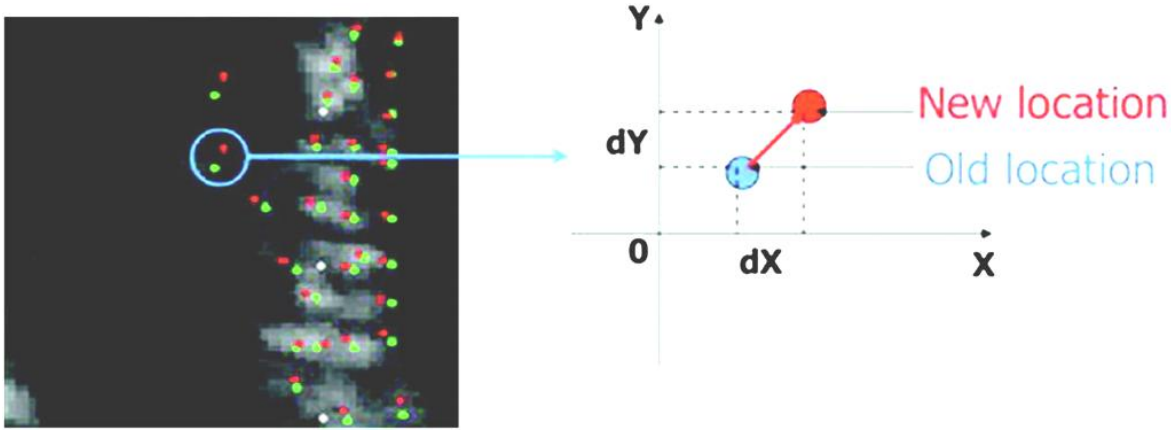

Figure 12. Displacement of acoustic markers from frame to frame
Image from Blessberger et al.[147] Green dots represent the initial position and red, the final position of the speckles. This displacement is represented as change in position on both the X and Y axis, from which strain can be calculated.

Post-processing software defines a 'cluster of speckles' (called a 'kernel') and follows it frame to frame trying to recognise the most similar speckle pattern from one frame to another. Detection of this 'fingerprint' during the cardiac cycle allows calculation of lagrangian strain parameters. Tissue velocity and strain rate analyses can also be performed[69, 141]. Before strain analysis can be performed the endocardial and epicardial borders need to be tracked to correctly define the region of interest (ROI). Post-processing software automatically divides the myocardium into segments. Depending on the software type, and echocardiographic view, varying degrees of user interaction is required[141, 148]. Results are displayed as strain curves, graphical colour encoded displays or raw figures. Values can be displayed for individual segments and algorithms allow them to be averaged over groups of segments (for example the RV free wall) or for the entire chamber.

By tracking in two dimensions, along the direction of the wall and not only along the ultrasound beam, this technique is angle independent. It does not require as high frame rates (50 to 90 Hz in contrast to >150Hz required for TDI) and also allows measurement of radial and circumferential strain, in addition to longitudinal strain[145].

STE is not without limitations. Different filtering algorithms are used by different software providers meaning there may be variation across platforms[141]. STE is still dependent on the quality of echocardiographic images, exact detection of borders is difficult and even though speckle tracking itself seems to enhance the capabilities of endocardial delineation, it is still necessary to correct contours manually. In addition, assessment of strain and SR also requires definition of epicardial borders. Inadequate tracking of speckles may occur due to out of plane movement meaning that it may not be possible to track speckles from image to image. STE also has operator dependent functions, such as the positioning of the region of interest and approval of myocardial tracking meaning that quantification of global and regional measures by this technique are still, to an extent, semiobjective[145, 149]. A further limitation that is not unique to STE, is that it is often difficult to image the entire myocardium, particularly the apical segments.

Two dimensional RV strain with STE is rapidly evolving, however use is still in its infancy. Due to the thin wall of the RV, only longitudinal parameters can be reliably calculated, this and the fact the RV mainly contracts in a longitudinal direction means most experience has been gathered using longitudinal strain. STE free-wall and global strain (incorporating the inter-ventricular septum) have both been used for assessment of RV function. Speckle tracked RV free-wall longitudinal strain has been shown to have a strong association with $RVEF_{CMR}$ ($r=-0.86$, $p<0.0001$)[121] with excellent predictive capability for poor $RVEF_{CMR}$ (AUROCC 0.88-0.96,Table 2)[121, 122, 150].

STE strain may overcome some of the difficulties associated with conventional parameters of RV systolic function, such as: angle dependence, reliance on function of a single region to represent the whole ventricle and global cardiac displacement. When $RVEF_{CMR}$ is used as a reference method, STE strain

parameters have been shown to perform better than these conventional methods for assessing RV function (Table 2).

	AUROCC		
	Focardi et al.[121].	Pavlicek et al.[122].	Park et al.[150].
RVEF cut-off	<45%	<30%	<50%
	n=63	n=223	n=57[E]
FAC	0.77	0.88	0.73
TAPSE	0.66	0.79	0.74
S'Wave	-	0.80	-
RV-GPLS	0.78	-	-
RV-FWPLS	0.92	0.88	0.96

Table 2. Predictive capability of conventional parameters and STE strain parameters for poor RV function
STE = speckle tracked echocardiography, AUROCC = area under the receiver operating characteristic curve, RVEF = right ventricular ejection fraction, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' wave velocity at the tricuspid annulus, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain.

1.3.2.3.6 Echocardiography summary

TTE offers anatomic and functional assessment of the RV and pulmonary circulation. Its non-invasiveness, widespread availability, low cost and portability mean it is an important tool for assessment of RV function. Although other methods may provide more accurate results, TTE is suited to the serial clinical examination of patients with RV disease.

The level of agreement between TTE variables and $RVEF_{CMR}$ depends on both the subjects included and the parameters measured. Each TTE measure of RV function has been validated in different conditions, meaning certain measures can be used in specific clinical situations but overall, a combined approach integrating several measurements is advocated[76, 112, 128, 151]. Emerging TTE techniques, such as speckle tracking are attempting to overcome some of the difficulties associated

[E] All with ischaemic cardiomyopathy

with imaging and will potentially offer a validated method for assessment of RV function. Further validation is needed before these novel techniques play a role in clinical decision making.

1.3.3 Biomarker assessment of right ventricular function

In other clinical settings (pulmonary hypertension, ischaemic heart disease and cardiac failure), imaging assessment is complemented with the use of biomarkers. Two of the most commonly used cardiac biomarkers are B-type natriuretic peptide (BNP) and troponin.

BNP is a 32-amino acid polypeptide hormone released in response to myocardial stretch with levels elevated in situations where a cardiac chamber is enlarged. It may be thought of a counter-regulatory hormone to the renin-angiotensin system promoting natriuresis, diuresis and vasodilatation[152]. BNP is easily measurable in plasma, either in its active form or as its inactive precursor, NT-pro-BNP[152]. BNP has been measured peri-operatively and in a non cardiac surgery setting, *pre-op* levels are predictive of major adverse cardiovascular events and mortality post-operatively[153]. A meta-analysis of natriuretic peptides in pulmonary embolism demonstrated that BNP is associated with adverse outcomes, including mortality and that it is able to detect RV dysfunction with an AUROCC of 0.92 in this population[154]. NT-pro-BNP has been shown to predict RV systolic dysfunction (defined as an RVEF <42%) with 100% sensitivity and 94% specificity in a population with pulmonary hypertension[155].

Troponins are released from cardiac myocytes following their necrosis and are most commonly used for the diagnosis of acute myocardial infarction. Elevations have been described for multiple cardiac and non-cardiac reasons. High sensitivity assays allow detection of very low levels of troponin[156]. Elevated troponins are commonly reported in pulmonary embolism and have been shown to be associated with RV dysfunction and adverse outcomes[154, 157].

BNP and troponin are not specific for RV failure, but their elevation can signal RV dysfunction or failure in the absence of left sided heart disease (Figure 13, pg 60)[158-160]. RV dysfunction following lung resection may be reflected with elevation of either cardiac biomarker.

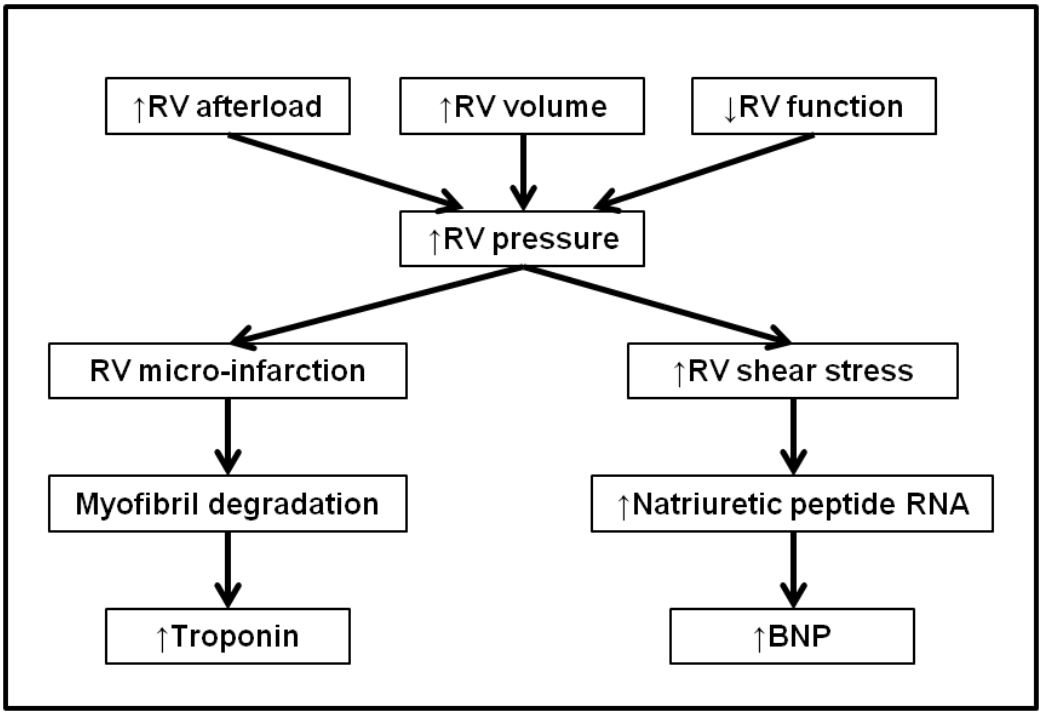

Figure 13. Mechanism of cardiac biomarker level elevation in RV failure
Redrawn from Piazza et al.[161]. and Kucher et al.[162]. RV = right ventricular, BNP = B-type natriuretic peptide.

1.4 Conclusion

A diagnosis of lung cancer is associated with significant mortality and although age adjusted incidence is falling, the total number of cases is expected to rise over the next 15-20 years. Lung resection offers the best opportunity for cure, but is associated with significant short and long-term morbidity. As a result of efforts to reduce historical inequalities in lung resection rates in the UK and changes in guidelines, increasing numbers of older and sicker patients will be presenting for surgery, at higher risk of post-op morbidity. A better understanding of the factors contributing to early and late post-op morbidity, not only has clinical importance but also resource implications as the costs of health care rise. Pulmonary function does not seem to be the only contributing factor, something else is limiting these patients. The importance of RV function in disease is increasingly recognised and its role in lung resection is not yet fully understood.

> *"Moreover, correction of the RV dysfunction after thoracic resection may result in reduced patient morbidity including a decrease in post-operative complications such as arrhythmias"*
>
> Reed et al. (1996)[163]

Historically, the RV is understudied when compared to the LV. Advances in imaging techniques and the recognition that RV function has an important prognostic role in many clinical conditions mean this is changing[51]. Despite a thinner myocardial wall and more complex shape, the RV ejects the same stroke volume as the neighbouring LV, albeit over a much lower pressure range. RV function is dependent on the same factors that govern LV function, namely; preload, afterload and contractility. Effective RV function is particularly dependent on its coupling to the low impedance (low afterload) pulmonary circulation. In contrast to the LV which is relatively resistant to increases in afterload, the RV is very sensitive to increases in afterload.

Assessment of RV function is challenging and no single technique has become the established method in clinical practice. Different techniques can be useful in specific clinical situations and can provide complementary information in others. Conductance catheterisation offers the ability to assess dynamic changes in ventricular volume and pressure, allowing pressure volume loop analysis and load independent assessment of RV function. Conductance catheterisation is a complex, technically challenging technique that is currently only performed in a small number of centres and is not used for the routine assessment of RV function in clinical practice. PA catheter assessment allows accurate assessment of pressures and flow but is unable to provide reliable measures of RV volumes so needs to be complemented with additional imaging techniques to provide more information. In addition, both these techniques are invasive and have small, but real, risks of complication and their regular use is limited.

CMR offers a validated reproducible method for assessing RV volumes and function and newer techniques allow more precise measurement of RV parameters. It is firmly established as the non-invasive *reference* method. Despite the limitations with TTE assessment, it is the most commonly used technique in clinical practice and the development of novel techniques, such as speckle tracked strain echocardiography, will continue to improve its role in assessment of RV function. It is ideally suited to the sequential assessment of patients with RV pathology.

Chapter 2 The Right Ventricle Following Lung Resection - Review of the Literature

2.1 Introduction

As previously described (section 1.1.4, pg 23), during the course of the authors clinical work as an intensive care doctor in the cardiothoracic intensive care unit at the Golden Jubilee National Hospital, it became apparent that patients admitted for critical care following lung resection not only presented with respiratory failure (as may be expected following lung surgery) but frequently manifested with features of RV dysfunction/failure. The requirement for intensive care following lung resection, along with the incidence of RV dysfunction/failure in this population, is discussed in chapter 3.

This chapter reviews the studies that have examined changes in RV function in patients undergoing lung resection.

2.2 Methods

A database search was performed by the NHS Greater Glasgow and Clyde library network on 9th October 2014. The following strategy was utilised using the Ovid Medline (R) Database, 1946 to Present with Daily Update;

1. exp Ventricular Function, Left/ (28138)
2. exp Ventricular Function, Right/ (4247)
3. exp Ventricular Function/ (49943)
4. exp Ventricular Dysfunction, Left/ (23076)
5. exp Ventricular Dysfunction, Right/ (3776)
6. exp Ventricular Dysfunction/ (27594)
7. cardiac function.mp. (21293)
8. heart function.mp. (14797)
9. ejection fraction.mp. (41540)
10. ('pulmonary artery' adj2 pressure).mp. (9822)
11. exp Pneumonectomy/ (21595)
12. (lung adj2 resection).mp. (4035)
13. (wedge adj2 resection).mp. (2563)
14. (lobectomy adj4 lung).mp. (1131)
15. lung volume reduction surgery.mp. (876)
16.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (131135)
17. 11 or 12 or 13 or 14 or 15 (25941)
18. 16 and 17 (251)
19. limit 18 to English language (155)

Studies were included if they reported parameters related to RV or pulmonary artery function. Only studies examining the impact of lung resection surgery with pre-op and post-op measures were included. Articles examining lung volume reduction surgery alone were excluded (See below). References of all articles were reviewed for further relevant work, with eleven additional studies being identified. Of these final 166 articles, 62 were chosen for full text review. The search strategy was repeated in March 2017 with two additional studies being identified. Unless specified all data are reported as mean±SD.

2.2.1 Lung volume reduction surgery

Lung volume reduction surgery (LVRS) is a palliative treatment performed to treat severe emphysema. The least functional parts of the lung are identified and removed, with the intention of improving lung function, quality of life and exercise capacity. Careful patient selection is important for LVRS as benefits are limited and in selected groups it is even associated with an increased risk of death[164, 165].

There are very few LVRS procedures being performed in the UK, with 113 LVRS procedures performed during 2013-14, in contrast to 6361 lung resections performed for primary cancer[20, 166, 167]. For this reason, to allow application of any findings to real clinical practice, the work presented in this thesis has not included studies where patients have had LVRS unless they include subgroups having anatomical lung resection for non-emphysematous disease.

2.3 Results

For discussion, the studies have been divided in to three main groups; those utilising the ‘standard’ pulmonary artery catheter (PAC), those utilising the ‘volumetric’ PAC (section 2.3.2, pg 77) and those using echocardiography (section 2.3.3, pg 90).

Studies utilising PAC or vPAC are summarised in Table 3 below, with discussion beginning in section 2.3.1, pg 74.

Table 3. Studies using pulmonary artery catheters to examine right ventricular function following lung resection

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Rams et al.8 (1962)	61	*All Thoracotomy* 61 Pneumonectomy *Only 24 patients had post-op PAC.	Intra-op PAC	30 Days - 7 years	↑mPAP (exercise)	No association between follow-up PA pressures and clinical outcome. PA pressures intra-op were higher in those patients who died post-op ly and highest in those who died of *"cardiorespiratory complications."*	Retrospective study of factors associated with increased cardiorespiratory risk. PA pressures obtained by needle puncture intra-op before and after temporary ligation of the PA. Wide variation in follow-up time. The resting PA pressures at post-op follow-up were lower than those following intra-op occlusion of the PA.
Jezek et al.[168] (1970)	77	*All Thoracotomy* 43 Pneumonectomy 34 Lobectomy *Only 30 cases examined at 6 months	PAC	Pre-op 6 Months	*Age 60-64 yrs* ↑mPAP ↑TPR *Age >65yrs* ↑mPAP	No clinical outcomes associated with RV function.	Study of peri-operative changes in cardiopulmonary variables following lung resection. Main focus was association with age. Results presented in age groups.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Mlczoch et al.[169] (1975)	49	*All Thoracotomy* 14 Pneumonectomy 25 Lobectomy 6 Sub-lobar 2 Decortication 2 Thoracotomy * Only 28 cases examined at 6 months	PAC	Pre-op 6 Months	*Haemodynamics measured at rest and exercise* *All patients* ↑mPAP (rest and ex) ↑PVR (rest and ex)	No clinical outcomes associated with RV function.	Evaluation of pulmonary haemodynamics and lung function tests peri-operatively. Examined in relation to extent of resection; carcinoma or not. *"The extent of lung resection showed no influence on the pulmonary circulation."*
Reed et al.[170] (1992)	15	*All Thoracotomy* 13 Lobectomy 2 Pneumonectomy	VPAC	Intra-op 4-6 Hrs POD 1 POD 2	↔RVEDV ↓RVEF ↓PVR	*"Three patients had periods of sustained atrial arrhythmias on POD 1 or 2 and at that time had significant increases in RVEDV."*	RVEF decreased post-op and was lowest on POD 2. All despite a reduction in PVR. Decline in RVEF is independent of changes in PVR
Nishimura et al.[171] (1993)	9	*5 Lobectomy* *4 Bilobectomy* *18 patients recruited but only 9 were able to repeat follow-up examination.	PAC	Pre-op 4-6 months	↑mPAP with exercise ↑PVRI at rest and with exercise	No association between RV function and clinical outcomes	Same patients (+1 patient) as Miyazawa et al.[172] (1999) but followed up for less time. Conclusion that *"there is a deterioration in cardiopulmonary function after lobectomy" and "reduction in exercise tolerance appeared to be related mainly to the effects of pulmonary hypertension."*

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Reed et al.[173] (1993)	10	*All Thoracotomy* 9 Lobectomy 1 Biopsy* *Biopsy patient not included in post-op analysis	VPAC	Pre-op 1 Hr 4-6 Hrs POD 1	↔PRSW ↑RVEDVI ↑sPAP (↔mPAP) ↑RVESVI ↑RVSVI ↔RVEF ↓PVRI	No clinical outcomes associated with RV function.	Used PRSW relationship (RVSWI v RVEDVI) which has been described as a '*load independent index of RV contractility.*' No change in RVEF. No difference in PRSW at 4-6 hours and 24 hrs suggesting contractility was unaltered.
Lewis et al. [44] (1994)	20	*All Thoracotomy* 20 Pneumonectomy	VPAC	Pre-op Intubated OLV PA clamped Immediate post-op	*All Patients* ↓RVEF ↔mPAP ↔RVESVI ↔RVEDVI ↔PVR ↑PVR/RVEF	Association between late cardiorespiratory symptoms (higher NYHA classification) and lower RVEF at PA clamping.	Investigates the role of peri-operative RV assessment on post pneumonectomy morbidity and mortality. Develops a suggested algorithm for evaluation of a pneumonectomy patient using RVEF.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Okada et al.[174] (1994)	20	3 Pneumonectomy 2 Bilobectomy 15 Lobectomy *Same cohort of patients as Okada et al.[41]	VPAC	Pre-op Post-op hour 1 Post-op hour 6 POD 1 POD 2 Week 3	*All Patients* ↑RVEDVI ↑RVESVI ↓RVEF ↔PVRI *With Exercise(n=10)* ↑RVEDVI ↑RVESVI ↓RVEF ↑PVRI ↑mPAP	No clinical outcomes associated with RV function.	RVEF is depressed post-operatively and has only partially recovered by week 3 Elevations in mPAP and PVRI occur only during exercise, with the authors suggesting changes in afterload are the main determinant of RV performance and that RV function at rest compensates by increasing RV volume.
Boldt et al.[175] (1996)	50	*All Thoracotomy* 10 Pneumonectomy 40 Lobectomy	VPAC	Pre-op OLV Post-op 2hrs Post POD 1	*Pneumonectomy* ↓RVEF ↑RVEDVI ↑RVESVI ↑CVP ↑PAP (all OLV to POD 1) *Lobectomy* ↓RVEF (OLV)	No clinical outcomes associated with RV function.	Designed to assess different anaesthetic regimes in 2 lobectomy groups (n=20 in each). 10 pneumonectomy patients also included. In pneumonectomy, RV haemodynamics deteriorated at OLV and remained depressed until POD 1. No influence of anaesthetic regime on RV function

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Okada et al.[41] (1996)	18	*3 Pneumonectomy* *1 Bilobectomy* *14Lobectomy* *Same cohort of patients as Okada et al.[174] (1994).	VPAC	Pre-op Week 3	Same patients as Okada et al.[174]	No association between *pre-op* RVEF and *post-op* complications or length of stay. A decrease in RVEF with exercise was associated with a higher rate of complications and prolonged hospital stay.	Patients dichotomised according to severity of RV dysfunction, and whether RVEF increased or decreased with exercise. *"Evaluation of RV performance is useful in determining which patients are at risk for complications after lung resection. Exercise induced change in RVEF may be a better indicator of high risk."*
Reed et al.[163] (1996)	45	*All Thoracotomy* *Part one* 35 Lobectomy *or* Pneumonectomy (n not given) *Part two* 6 Lobectomy	VPAC	Pre-op POD 1 POD 2	*Part one* ↑RVEDVI ↓RVEF ↔PRSW ↔PVRI *Part two* ↑RVEDVI ↓RVEF ↓PVRI	No clinical outcomes associated with RV function.	Two part study. Part 1 assessing PRSW pre-op (n=35) and on POD 2 (n=6). No difference in PRSW with the authors concluding there was no change in RV contractility. Part 2 assessing reduction of afterload by continuous infusion of prostaglandin E_1. This reduced PVRI although RV dysfunction remained.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Backlund et al.[176] (1998)	24	*All Thoracotomy* 4 explorative 15 lobectomy 3 bilobectomy 2 pneumonectomy	TTE VPAC	Pre-op Recovery POD 1 POD 2 POD 3	*Both Groups* ↔RVSWI *Short O2 (S)* ↔RVEDVI ↓RVEDD ↑PVRI (POD 1-3) ↑mPAP (POD 1&2) ↓RVEF (POD 1&2) *Prolonged O2 (P)* ↓RVEDVI (POD 1) ↔RVEDD ↔PVRI	Patients developing AF had greater PVRI and a greater sRVP in the immediate post-op period	Complicated study designed to assess the effect of O_2 on post-op AF and RV function Patients allocated to FiO_2 35% until POD 3 (P, prolonged group) or POD 1 (S, short) RVP and PVRI increased in S-group compared with P-group. The authors conclude "*this may show evidence of RV strain without RV dysfunction*" in patients on short O_2 regimen. RVP tended to reduce following FiO2 0.6 in both groups (except in patients who developed AF) Conclusion that prolonged O2 therapy did not prevent occurrence of AF attributed to RV strain.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Miyazawa et al.[172] (1999)	8	*5 Lobectomy* *3 Bilobectomy*	PAC	Pre-op 4-6 months 42-48 months	↑mPAP at rest and with maximal effort exercise ↑PVRI at rest and with maximal effort exercise	No clinical outcomes associated with RV function.	Evaluation of post-op changes in cardiopulmonary function on exertion in patients with lung cancer surviving for more than 3 years. Conclusion that peak blood flow per unit of remaining lung during exercise becomes lower with time following lung resection, indicating deterioration of the pulmonary vascular bed.
Haniuda et al.[177] (2000)	8	*All Thoracotomy* 8 Lobectomy	PAC	Pre-op 6 Months	↑PAP (exercise) ↑PVRI (rest & exercise)	No clinical outcomes associated with RV function.	*Study was designed to clarify the effects of lung volume reduction surgery (LVRS) on the cardiopulmonary circulation. Studied 7 patients having LVRS but had 8 lobectomy patients included as a comparison group. Data for lobectomy group is shown.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
							Designed to determine whether lobectomy by VATS is also advantageous with respect to the RV performance in patients >70 yrs old.
Mikami et al.[178] (2001)	23	*All lobectomy* *13 VATS* *10 Thoracotomy*	VPAC	Pre-op 6 Hrs post-op 12 Hrs post-op POD 1 POD 2	*VATS* ↑RVEF No significant changes in other RV parameters	No clinical outcomes associated with RV function.	Values were reported as a percentage of pre-op values. Trends towards higher pulmonary resistance in thoracotomy group. There were minor changes in RV afterload following VATS compared with thoracotomy. *"Lobectomy using VATS offers beneficial effects of the right ventricular afterload."*

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Jorgensen et al.[179] (2003)	10	*All Thoracotomy* 10 Lobectomy	PAC TOE	Pre-op Immediate post-op	↔mPAP ↔PVRI	No clinical outcomes associated with RV function.	*Study designed to investigate the effect of LVRS on LV function, pulmonary haemodynamics and systemic haemodynamics. Ten lobectomy patients as a control group Although TOE imaging was performed it only examined LV function. Main focus of study is on LVRS group and beneficial effect of surgery on LV function. No changes in any parameter in the lobectomy group.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Mageed et al.[180] (2005)	30	*All Thoracotomy* All Lobectomy	VPAC	Pre-op Post-induction 2Hrs post-op	*All patients* ↓RVEF (2Hrs) ↔RVEDVI ↔PVRI ↔mPAP ↔RVSWI	No clinical outcomes associated with RV function.	Study designed to investigate the effect of lobectomy on pulmonary haemodynamic and gas exchange variables.

RV = right ventricular, PAC = pulmonary artery catheter, PA = pulmonary artery, mPAP = mean pulmonary artery pressure, TPR = total pulmonary resistance, PVR = pulmonary vascular resistance, VPAC = volumetric pulmonary artery catheter, RVEDV = right ventricular end diastolic volume, RVEF = right ventricular ejection fraction, POD = post-op day, PRSW = preload recruitable stroke work, sPAP = systolic pulmonary artery pressure, RVESV = right ventricular end systolic volume, RVSV = right ventricular stroke volume, OLV = one lung ventilation, RVSP = right ventricular systolic pressure, SVT = supraventricular tachycardia, CVP = central venous pressure, AF = atrial fibrillation, sRVP = systolic right ventricular pressure, FiO_2 = fraction of inspired oxygen, VATS = video assisted thoracoscopy, TOE = trans oesophageal echocardiography, LVRS = lung volume reduction surgery, LV = left ventricular, FVC = forced vital capacity, RVSW = right ventricular stroke work.

2.3.1 Studies utilising *'standard'* pulmonary artery catheters

The early studies evaluating pulmonary haemodynamics (pre 1990) exclusively involved the use of Pulmonary Artery Catheters (PAC)[168, 169, 181]. These three studies are of reasonable size (49-77 patients) and include a mixture of lobectomy and pneumonectomy patients. Although not stated explicitly, all appear to be retrospective, with the cohorts examined post-operatively all being smaller than the total number of patients examined pre-operatively. They are samples of convenience with only those undergoing investigations for other reasons included for analysis. For example, Rams et al. included 61 patients in his study but only performed follow-up PAC measurements on only 24 patients at follow-up (30 days to 7 years following surgery). This showed that mPAP was unchanged at rest but increased significantly with exercise.

These studies have significant selection bias as only those patients who survived the follow-up period were investigated. There is agreement from the 3 studies that mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) increase when compared to pre-op values. Those studies performing measurements on exercise, found a similar pattern with elevation in pressures also present on exertion[169, 181]. There was no association demonstrated between the extent of resection and changes in the pulmonary circulation.

There is limited information on clinical outcomes across these three studies. In addition to the longer term follow-up described above, Rams et al.[181] examined PA pressures intra-operatively (by direct needle puncture) prior to and following pulmonary artery ligation. This demonstrated mPAP prior to, and immediately following, occlusion of the pulmonary artery was lowest in those patients that survived post-operatively and highest in those who went on to have post-op cardiopulmonary deaths (Figure 14, pg 75)[181].

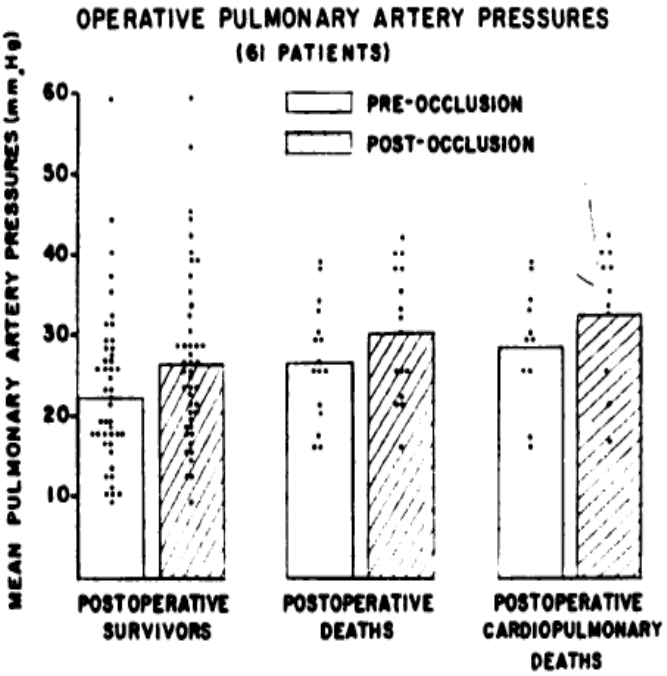

Figure 14. Operative mean pulmonary artery pressures prior to and following occlusion of the pulmonary artery
From Rams et al. (1962)[181]

Three studies after 1990 used exclusively PAC[171, 172, 177] and one used both PAC and trans-thoracic echocardiography (TTE)[179]. These prospective studies were smaller than the earlier PAC studies (8-10 patients) and contained exclusively lobectomy patients. There is limited information on clinical outcomes for all these studies and, where present there is no association with pulmonary circulation variables.

Nisihimura et al.[171] initially set out to examine 18 patients but only nine attended follow-up examination. The 9 patients were lost to follow-up "because of recurrence of carcinoma or poor general condition." The nine patients were examined pre-op and at six-months post-op; both at rest and during exercise (graded exercise on a bicycle ergometer). There was no change in mPAP at rest but an increase with exercise. Pulmonary vascular resistance index (PVRI)[F] increased at rest and on exercise. Miyazawa et al.[172] followed eight of these same patients up at 42-48 months. No information is given on the single patient lost to follow-up. At this stage there was an increase in mPAP at rest as well as with

[F] A number of studies describe variables indexed to body surface area; Pulmonary vascular resistance index (PVRI), RV end diastolic volume index (RVEDVI), RV end systolic volume index (RVESVI)

exercise (Figure 15). Again, PVRI was increased both at rest and with exercise. In a very similar study with many of the same authors, (8 patients examined at rest and with a graded exercise protocol) Haniuda et al.[177] demonstrated almost identical results with an increase in PVRI at rest and an increase in both, PVRI and mPAP with exercise.

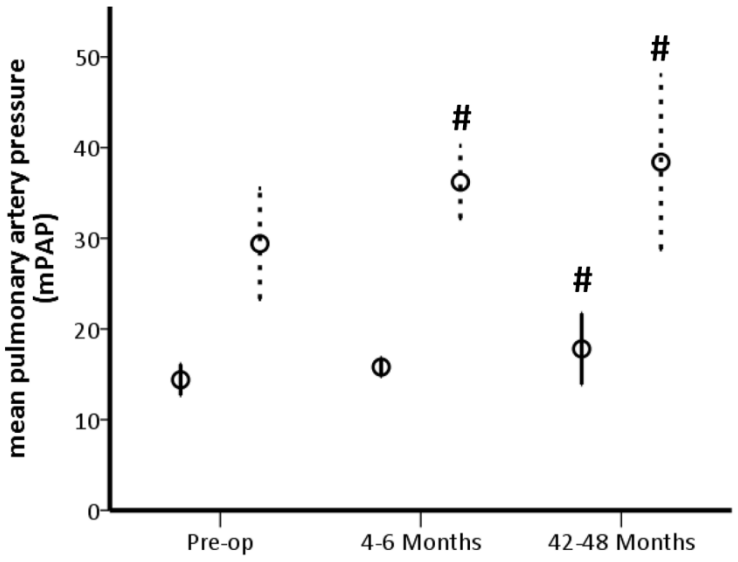

Figure 15. Changes in mPAP over time from Miyazawa et al.
Drawn from data presented by Miyazawa et al.[172]. Continuous lines = at rest. Dashed lines = exercise (50W bicycle ergometer). Value (error bars) = mean (SD), # = significant difference from pre-op values.

Jorgensen et al.[179] explored the effect of LVRS on pulmonary and systemic haemodynamics. They included ten patients undergoing lobectomy as a control group and also included TOE measures of LV function. There were no changes in PAC variables in the lobectomy subgroup.

The studies using standard PAC do not analyse changes in the immediate peri-operative period but they do suggest that pulmonary artery pressures are increased 6 months[168, 169, 171, 177] following surgery and that they continue to be increased on later follow-up[172] (3-4 years). There is an associated increase in PVR[168, 169, 171, 177] at this time and this is accentuated with exercise[169, 171, 177, 181]. Despite a paucity of clinical associations, there is a suggestion that elevated PA pressures at the time of PA clamping are associated with increased mortality.

2.3.2 Studies utilising '*volumetric*' pulmonary artery catheters

The development of fast response PACs allowing calculation of RV volumes (vPAC) were ideally suited to the investigation of the RV during lung resection with the majority of studies utilising this modality. The validity of this method has been questioned and is discussed following an initial review of the studies.

Reed et al.[163, 170, 173] performed a series of 3 studies (1992 - 1996) exploring RV dysfunction following lung resection and potential causative mechanisms. The first study demonstrated that RVEF fell from 45±2% pre-op to 36±3% on POD 2[170]. These changes occurred despite a reduction in afterload (from pre-op values) as measured by PVR. In the second of these studies they investigated preload recruitable stroke work (PRSW). PRSW is the relationship between RV Stroke Work Index (RVSWI, Equation 6) and RV End Diastolic Volume Index (RVEDVI) had previously been described as a load independent index of RV contractility[182].

$$RVSWI = \frac{(MPAP - CVP)x\ RVSV\ x\ 0.0136}{BSA}$$

Equation 6. Right ventricular stroke work index (RVSWI)
MPAP = mean pulmonary artery pressure, CVP = central venous pressure, RVSV = right ventricular stroke volume, 0.0136 = conversion factor for pressure to work, BSA = body Surface Area.

The PRSW relationship was initially calculated pre-operatively with the rapid infusion of crystalloid (250ml, 250ml and 500ml) and the relationship between RVSWI and RVEDVI plotted. A comparison was then made with the relationship between RVSWI and RVEDVI post-operatively, with no changes detected. Both RVEF and RVSWI were unchanged during the first post-op day and the authors conclude that *"changes in RV performance during the early post-op period were not due to inherent changes in the RV contractile state."* RVEDVI was increased in the first post-op day with PVR again reduced. The final study by Reed et al.[163] was a two part experiment; The first examined the PRSW pre-op and on post-op day two with the results showing that RVEF was reduced (43±1 % to 37±1%) and that contractility was unaltered. The second part assessed the haemodynamic response to a post-op reduction in afterload using an infusion of prostaglandin; this showed that despite a fall in PVRI, RVEF remained depressed suggesting changes in RVEF following lung resection are independent of changes in

afterload. The results of this final study would imply that changes in RV function following lung resection are not a result of changes in afterload or contractility with the authors suggesting *"better control of heart rate may enhance RV pump function."* The authors made no assessment of the matching of contractility and afterload (coupling). The changes in RVEF in this series of studies are summarised in Figure 16, showing a consistent decrease in RVEF on POD 2.

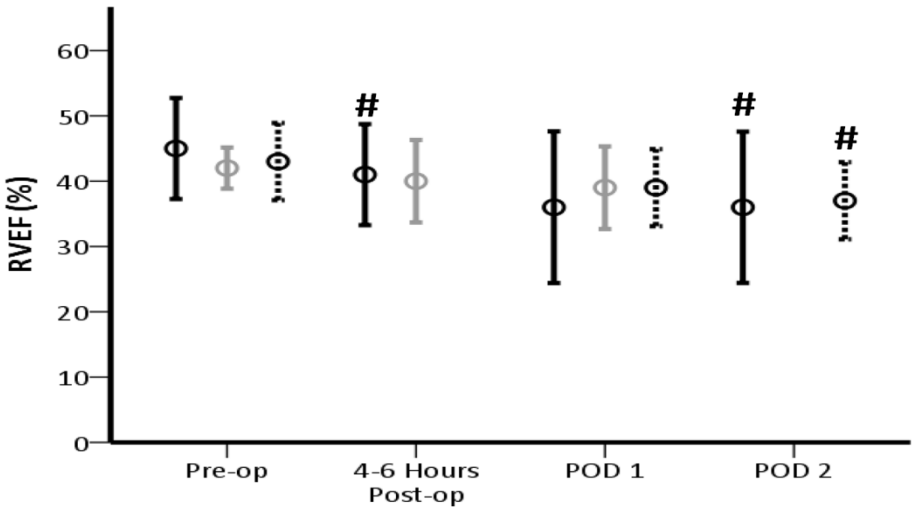

Figure 16. Changes in RVEF over time from studies by Reed et al.[163, 170, 173]
Drawn from data presented by Reed et al. Continuous lines = Reed (1992)[170]. Grey lines= Reed (1993)[173], Dashed lines = Reed (1996)[163]. Value (error bars) = mean (SD), # = significant difference from pre-op values, RVEF = right ventricular ejection fraction, POD = post-op day.

Lewis et al.[44] used the vPAC to assess changes in RV variables during the peri-operative period and their impact on post pneumonectomy morbidity and mortality. They showed a reduction in RVEF (45±10% to 39±8%) and an increase in the ratio of PVR and RVEF (3.2±2.3 to 4.4±3.1) during PA clamping, both of which returned to baseline in the post-op period. They highlighted that those patients with a RVEF <35% during PA clamping were more likely to develop cardiorespiratory symptoms (signified by New York Heart Association class III or IV), providing a link between peri-operative RV function and long-term functional outcome. In addition to this group who were more likely to develop late symptoms; those patients with pre-op RVEF >35%, a normal PVR (<200 $dyn \cdot s \cdot cm^{-5}$) or a PVR/RVEF ratio <5 were *less* likely to develop late cardiorespiratory morbidity.

Okada et al. published two studies[41, 174] from the same cohort of patients to examine the extent and duration of RV dysfunction following major pulmonary

resection. They also examined changes in RV haemodynamic variables with exercise. The first part of this first study was performed at rest and showed RVEF is reduced post-operatively (43±7% pre-op to 34±4% on POD 2), and that this has only partially recovered by 3-weeks post-op (to 37±6%). They also demonstrate increased RVEDVI, RVESVI and unaltered PVRI. The second part of this first study examined participants during exercise (a sub-maximal exercise protocol on a bicycle ergometer) pre-operatively and 3 weeks post-operatively. At 3-weeks post-op there were marked increases in pulmonary artery pressures and PVRI with exercise. The second study was a secondary analysis of the same patients and tried to identify associations between pre-op RV function and post-op morbidity. When comparing those who had a decreased RVEF with exercise, to those with an increased RVEF with exercise, there was a higher incidence of complications (not explicitly defined) in the former group (50% vs 0%). Those with a decrease in RVEF also had a longer hospital stay (37.5±15.9 vs 19.4±8.0 days).

Boldt et al. performed a study[175] to examine the impact of two different anaesthetic regimes on the cardiorespiratory system (Group 1A and 1B) and compared them to a pneumonectomy group (Group 2). The first author of this study, Joachim Boldt was later found guilty of research misconduct, including failure to acquire ethics and fabrication of study data. The majority of studies (nearly 100) he published since 1996 have been retracted from the medical literature[183]. Although this study has not been retracted, given the questions over work published by him, its findings will bear no impact on the work of thesis. It is presented here for completeness of the review.

Backlund et al.[176] conducted a complex prospective randomised study examining the effect of oxygen on post-op atrial fibrillation (AF) and its relationship to RV function. Patients were randomly[G] allocated to 35% oxygen until POD 1 (*short*) or until POD 3 (*prolonged*). In addition, the effect of 15 minutes of 60% oxygen on RV pressure at each post-op time-point (in both groups) was also examined. RVEF was unchanged from pre-op values in both groups. Post-operatively RV pressure and PVRI were increased in the short group compared with the prolonged group and the authors explain that this may show "RV *strain without RV dysfunction*". RV pressure was reduced following exposure to 60% oxygen in both groups, except in

[G] No details on randomisation provided

those developing AF. Risk factors for post-op AF were found to include intra-operative bleeding and high pre-op PVRI, with the prolonged administration of oxygen not preventing its development.

To determine if video assisted thoracoscopic surgery (VATS) lobectomy in comparison to thoracotomy was advantageous in terms of RV performance in patients >70 years old, Mikami et al.[178] examined a cohort of 23 patients. Absolute values of RV and pulmonary haemodynamic variables are not provided and are presented relative to baseline. In the VATS group RVEF was higher at 24 hours post-op than in the thoracotomy group (118±31% vs 90±31%) but with no change from baseline. There were no *significant* changes in markers of pulmonary resistance, although the study reports that *"pulmonary arteriolar resistance index*[H] *at 24hours post-op tended to be higher in the standard thoracotomy group than the VATS group."* Mageed et al.[180] performed a study to investigate the effects of lobectomy on pulmonary haemodynamics and gas exchange variables in 30 patients undergoing lobectomy. Values were obtained pre-op, intra-op and 2 hours post-op. At two-hours post-op, RVEF was reduced from pre-op values (37±6.6% to 27±12.7%) with no changes in any other measures of RV or pulmonary vascular function.

A summary of the changes with both, standard and volumetric pulmonary artery catheters is provided in

Table 4 (pg 81) and Table 5 (pg 82). The studies analysing the RV response to lung resection using vPAC give inconsistent results. Indeed, on POD 1 there are studies suggesting RVEF increases, decreases and remains unchanged[163, 173, 174, 178]. Although elevated afterload is the primary hypothesis for RV dysfunction following lung resection, there is no evidence of raised peri-operative PVR (a surrogate for afterload) with most studies showing it is unchanged or reduced[44, 163, 170, 173, 174, 178-180]. PA pressures in this same period are also unchanged[44, 163, 170, 173, 174, 179, 180]. Changes in the later post-op period (beyond 4 months) and with exercise (Table 5) are clearer, with pulmonary artery pressures and PVR more consistently elevated[168, 169, 171, 172, 177].

[H] Study refers to total pulmonary resistance index (TPRI) and pulmonary arteriolar resistance index (PARI) without defining either. Both have units of $dyn \cdot s \cdot cm^{-5} \cdot m^2$ which is the same unit as pulmonary vascular resistance index (PVRI).

	Time point						
Variable	**Post-op**	**2-6 hours**	**POD 1**	**POD 2**	**2-3 Weeks**	**4-6 Months**	**42-48 Months**
sPAP	↔ 44, 175 ↑ 173	↔ 71, 175 ↑ 173	↔ 163, 170, 174 ↑ 173	↔ 163, 170, 174	↔ 174	↑ 169	
dPAP			↔ 170	↔ 170	↔ 170	↑ 169	
mPAP	↔ 44, 173, 174, 179, 180	↔ 170, 173, 174	↔ 163, 170, 173, 174	↔ 163, 170, 174	↔ 174	↔ 171, 172, 177 ↑ 168, 169	↑ 172
PVR	↔ 44, 173, 174, 179, 180	↔ 174, 178 ↓ 170, 173	↔ 163, 174, 178 ↓ 170, 173	↔ 163, 170, 174, 178	↔ 174	↑ 168, 169, 171, 172, 177	↑ 172
RVEF	↔ 44, 173, 176 ↓ 174, 180	↔ 173, 178 ↓ 170, 174	↔ 163, 173, 176 ↓ 174 ↑ 178	↔ 176, 178 ↓ 163, 170, 174	↓ 174		
RVEDV	↔ 44, 174, 176, 180	↔ 170, 174	↔ 170, 174, 176 ↑ 163	↔ 170, 176 ↑ 163, 174	↔ 174		
RVESV	↔ 44, 174	↔ 174 ↑ 173	↑ 173, 174	↔ 174	↔ 174		

Table 4. Summary of change in pulmonary artery catheter variables following lung resection at rest
All changes are in comparison to pre-op levels with references. ↓= decreased in comparison to pre-op, ↑ = increased in comparison to pre-op, ↔ = unchanged in comparison to pre-op, POD = post-op day, sPAP = systolic pulmonary artery pressure, dPAP = diastolic pulmonary artery pressure, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, RVEF = RV ejection fraction, RVEDV = RV end diastolic volume, RVESV = RV end systolic volume.

	Time point		
Variable	**2-3 Weeks**	**4-6 Months**	**42-48 Months**
sPAP	↑ 174	↑ 169	
dPAP		↑ 169	
mPAP	↑ 174	↑ 170, 172, 173, 181	↑ 173, 181
PVR	↑ 174	↑ 170, 172, 173, 181	↑ 172
RVEF	↓ 174		
RVEDV	↑ 174		
RVESV	↑ 174		

Table 5. Summary of change in pulmonary artery catheter variables following lung resection on exercise
All changes are in comparison to pre-op levels with references. ↓= decreased in comparison to pre-op, ↑ = increased in comparison to pre-op, ↔ = unchanged in comparison to pre-op, sPAP = systolic pulmonary artery pressure, dPAP = diastolic pulmonary artery pressure, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, RVEF = RV ejection fraction, RVEDV = RV end diastolic volume, RVESV = RV end systolic volume.

The vPAC investigations in this section utilise *fast response* thermodilution techniques, based on methods described by Holt et al., to calculate RVEDV and by incorporation of SV (Cardiac Output/Heart Rate) the RVESV and RVEF[100]. These catheters were the subject of an editorial by Leibowitz in Critical Care Medicine in 2009 that questioned their validity, finding they were inaccurate in ventricles that were stable or undergoing pathophysiological changes[184]. They have been in use since the 1980's and a number of method comparison studies prior to this editorial had attempted to validate them against established methods for assessment of RV volumes. Prior to recognition of CMR and conductance catheterisation as the reference methods for assessment of RV volumes and function (see section 1.3, pg 41), angiography and radionuclide scanning were established methods for the in vivo assessment of RV function[108]. The methodology of these comparison studies is questioned in this section.

A common error in method comparison studies is to use correlation statistics to describe the strength of a relationship between two methods of measurement. Correlation coefficients are not best used in this setting as they measure association and not agreement, they do not determine if two different methods of measurement can be used interchangeably. If the two methods are interchangeable, with no error, when plotting the measurements on a scatter plot they should fall on the line of equality. Some of the difficulty with correlation coefficients is illustrated in Figure 17 (pg 84), which describes an artificial set of data (created by the author) for four novel methods of measurement compared with a gold standard.

All measurement methods described in this fictitious data set have a Pearson's correlation coefficient of 1. Although they all have perfect correlation and are associated, only measurement method A *may* be a useful alternative to the gold standard. There is evidence of systematic bias with method C with the new method providing a value consistently above that of the gold standard. Methods B and D illustrate there is perfect correlation if the measurements lie along *any* straight line but no evidence of agreement. It is clear from Figure 17 that even perfect correlation coefficients do not mean a new method of measurement is accurate. Correlation coefficients are also dependent on the range of the data provided, with coefficients more likely to be high with wider data ranges (Figure 18,

pg 85). In addition, although two methods of measurement may use different methodology, if they are originally designed to measure the same thing, then it would be likely that they would be inherently related so quantifying their association is irrelevant[185, 186]. The conclusion of Bland and Altman sums up the use of correlation in measurement studies:

> *"correlation is inappropriate for the study of agreement between methods. Despite this, people do it."*
>
> Bland & Altman (2003)[187]"

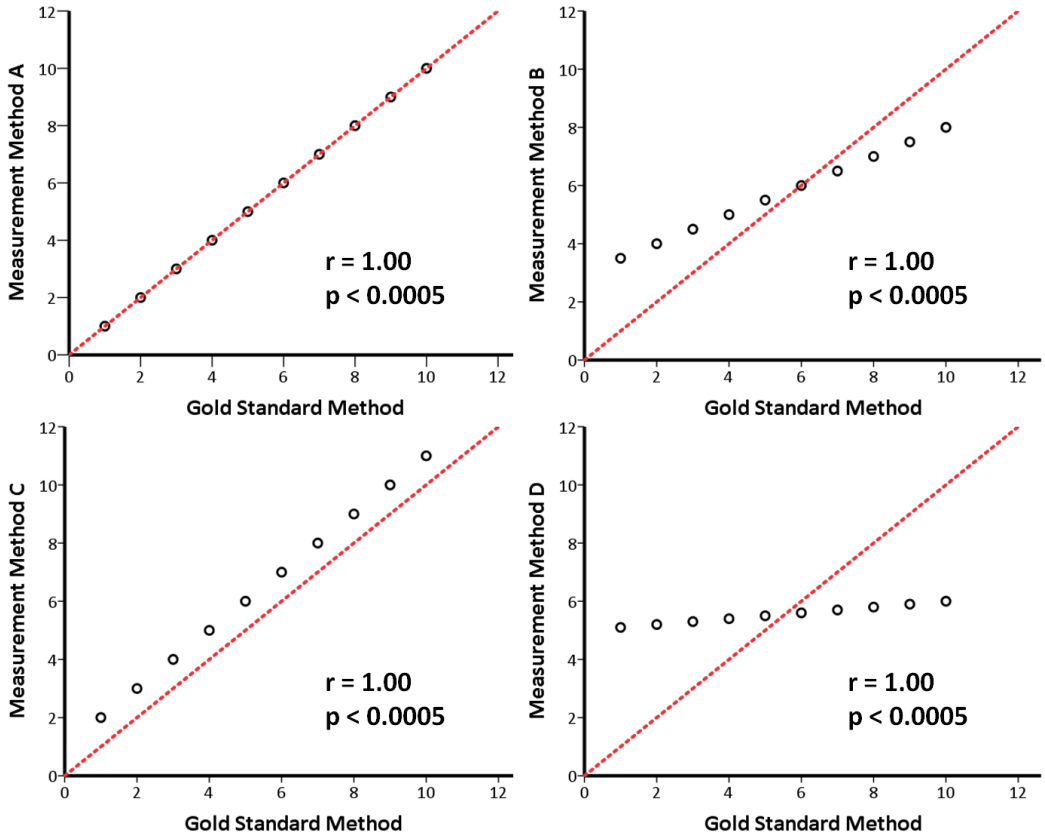

Figure 17. Correlation coefficients from artificial data of methods of measurement
Correlation coefficient (Pearson's) r = 1.00 for all plots. The dashed red line is the line of identity.

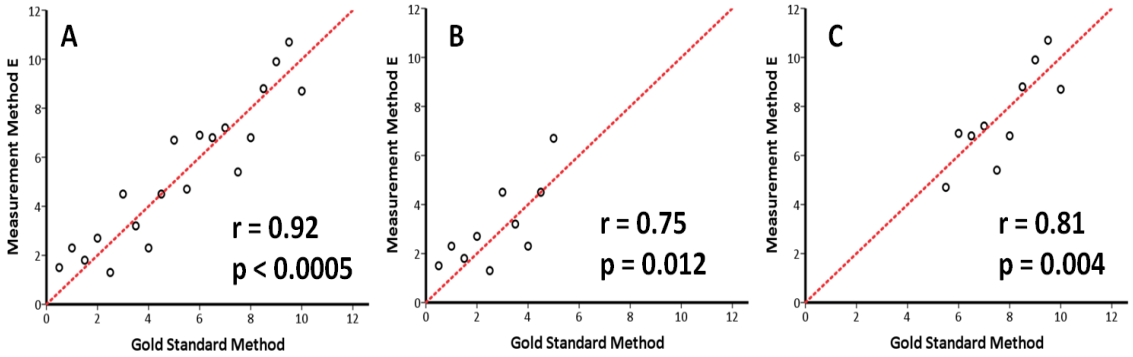

Figure 18. Correlation coefficients of artificial data for methods of measurement
A) All data with higher correlation coefficient than both B) which contains only lower values of same data and C) which contains higher values. The dashed red line is the line of identity.

Bland and Altman went on to offer a now famous analysis (plotting the difference against the mean of the two measurements, along with limits of agreement) which is considered a better method of assessing the inter-changeability of two measurement methods. It is the recognised statistical technique for validating new measurement methods against reference techniques[186, 188].

When vPAC was compared with *ventriculography*, there was evidence of association between the two methods. For RVEF, correlation coefficients ranged from 0.80 to 0.83 (although one study showed no significant association)[99, 189, 190]. As can be seen in Figure 19 (pg 86) and Figure 20 (pg 86), the two methods although associated, are not interchangeable. If the methods were interchangeable, values would lie along the line of equality. In Figure 19 and Figure 20 there is evidence of bias with the thermodilution method systematically providing lower values than angiographic determined RVEF. For assessment of RVEDV and RVESV, correlation coefficients were lower (0.71 and 0.64 respectively) with some studies again showing no significant association[99, 189, 190]. Bland Altman analysis was not performed.

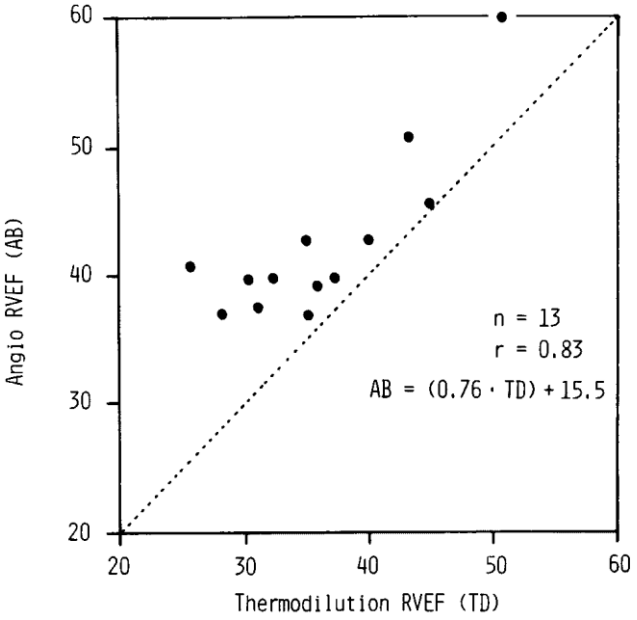

Figure 19. Comparison of angiography (Angio) and thermodilution RVEF measurements
Taken from Urban et al.[99] The dotted line is the line of identity.

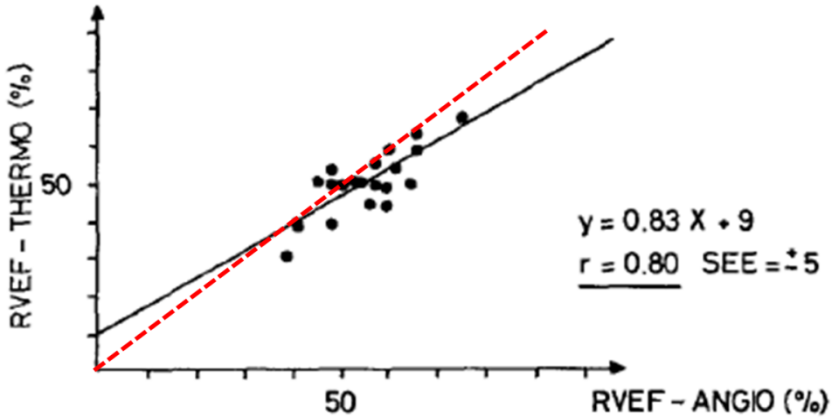

Figure 20. Relationship of RVEF determined by thermodilution (THERMO) and by angiography (ANGIO)
From Voelker et al.[189] The solid black line is the regression line. The dashed red line has been added and is the line of identity. Note different labelling of axes compared to Figure 19.

Spinale et al. compared RV volumes obtained from vPAC to those from biplane ventriculography in a swine model (n=10)[191]. This study also compared measurements in a number of different physiological states; at baseline, during infusion of isoproterenol (isoprenaline, a β_1 and β_2 receptor agonist), during hypovolaemia (haemorrhage to 50% baseline MAP) and with further infusion of isoproterenol following hypovolaemia. For all physiological parameters combined, there was association of RVEF (r=0.74) but with no evidence of agreement,

thermodilution tended to underestimate measurements with a mean difference of 9.6±1.5% on pooled analysis (Figure 21).

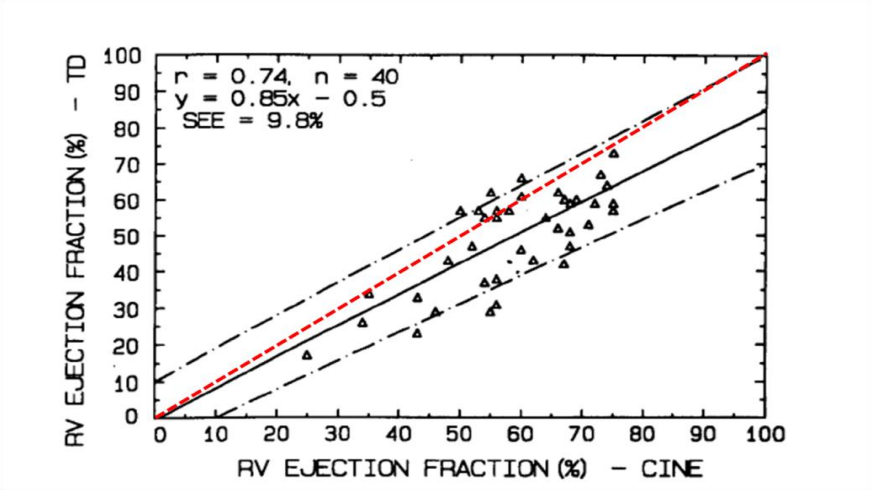

Figure 21. Comparison of RVEF measurements by cine-ventriculographic (CINE) and thermodilution (TD)measurements
From Spinale et al.[191] The solid black line is the regression line and the dashed black lines represent 90% confidence limits. The dashed red line has been added and is the line of identity.

There is no association testing presented for each of the individual physiological states but there was significant difference between the mean values of RVEF during the hypovolaemic and hypovolaemic with isoproterenol states (Figure 22). Although specific values are not given, extrapolating from this figure suggests this error is in the region of 10-15%.

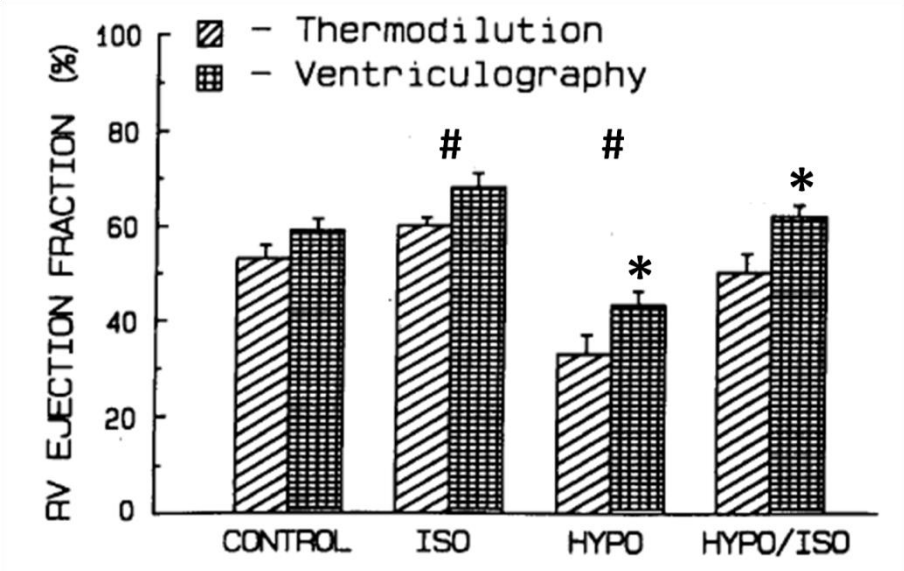

Figure 22. RVEF by ventriculography and thermodilution during pathophysiological states
ISO = During isoproterenol infusion, Hypo = Hypovolaemia, HYPO/ISO = Infusion of isoproterenol during hypovolaemia. # = Significant difference from control. * = significant difference from thermodilution measurements.

This study demonstrates the vPAC does not given reliable results on pooled analysis and that there is a deterioration in agreement in pathophysiological states. Bland Altman analysis was not performed.

Morrison et al. (in addition to comparing vPAC with angiography described above) compared vPAC obtained RVEF with both; gated first pass (GFP, n=36) and gated blood pool (GBP, n=40) radionuclide ventriculography[190]. Bland Altman analysis was not performed and this study only used correlation statistics (r=0.65 for GFP and r=0.69 for GBP). Based on this level of association and the lack of Bland Altman analysis, it is difficult not to agree with Morrison et als. conclusion that it *"does not support the use of vPAC determined RVEF*".

In 2001 Perings et al. attempted to validate vPAC RVEF against radionuclide RVEF at rest and during exercise[192]. The study showed significant association between the two methods at rest (r=0.73) and during exercise (r=0.74) but Bland Altman was not performed. Given the lack of robust assessment of the vPAC in this study the author would disagree with the authors conclusion, and believes the device is *not* useful for reliable and repetitive assessment of RVEF measurements at rest or during exercise.

Two studies have compared vPAC to CMR imaging (now established as the reference method for volumetric assessment of the RV) in cohorts with dilated cardiomyopathy and pulmonary hypertension[193, 194]. In the first study by Globits et al.[193] there was evidence of association between the two methods for RVEF (r=0.82). Despite this association, there were marked differences in the values obtained by each method with mean RVEF by vPAC 19±4.3% lower than RVEF by CMR. Additionally, vPAC overestimated RVEDVI and RVESVI by 58±41ml/m2 and 55±47ml/m2 (76% and 59% respectively). The study concluded that although vPAC was not suitable for assessment of absolute volume data, it may be more appropriate for assessment of serial measurements. Given that the study incorporated no repeat measures in different physiological circumstances, there is no evidence to support this statement. The second study by Hoeper et al. [194] demonstrated RVEDV assessed by vPAC was 231±165ml higher, and RVESV was 249±177ml higher than the corresponding CMR value. RVEF was measured as 12±8% by vPAC compared to 34±10% in the CMR group. As RVEDV and

RVESV were overestimated by 220% and 310% respectively, Hoeper et als. conclusion that vPAC provided *'invalid'* data seems an understatement.

Two studies in the same patients have compared transoesophageal echocardiographic variables with vPAC at three time points (pre-op, intra-op and post-op) in patients undergoing elective cardiac surgery. The first compared vPAC determined RVEF to fractional area change obtained from TOE[195]. Bland Altman analysis revealed a bias of -3.7% and a precision (±1.96SD) of 30.9%. The authors concluded that this was clinically acceptable, but also noted that the bias and precision deteriorated with tachycardia, pulmonary hypertension and low cardiac output. The second study made comparison with three-dimensional transoesophageal echocardiography (3D-TOE) determined RVEF[196]. This second study showed no association between the two measures of RVEDV and Bland-Altman analysis of RVEF showed an unacceptable bias of 15.6% for 3D-TOE.

In the article that was the focus of the editorial questioning the validity of vPAC measurements, Hein et al. used conductance catheterisation to attempt to validate vPAC in a swine model undergoing induced myocardial ischaemia by ligation of the right coronary artery (at baseline, during ischaemia and during reperfusion)[91, 184]. Bland Altman analysis indicated that vPAC underestimated RVEF, with a bias of -9.9% and limits of agreement of -26% to 6.1%. For RVEDV, vPAC overestimated with a bias of 31ml and limits of agreement from -25ml to 88ml. Area under the receiver operating characteristic curve (AUROCC) analysis was used to assess the ability of each method to diagnose ischaemia; The conductance catheter had an AUROCC of 0.98 with 100% sensitivity and 86% specificity for change in RVEF during ischaemia and an AUROCC of 0.92 (86% sensitivity and 100% specificity) for change in RVEDV. In contrast, the AUROCC curves for RVEF and RVEDV determined by vPAC failed to reach statistical significance (AUROCC for RVEF of 0.76, p=0.06 and AUROCC for RVEDV of 0.65, p=0.65).

As described above, Bland Altman analysis is the recommended investigation for method comparison studies and only three of the vPAC validation studies have utilised it[91, 195, 196]. Zink et al. (described on the previous page) was the only study that found an acceptable bias, but compared RVEF to fractional area change by TOE. The Bland Altman comparison of RVEF with FAC is flawed as one is a

measure of RVEF and the other is two-dimensional representation of RV function (i.e. they are not measuring the same thing). De Simone found an unacceptable bias when comparing 3D TOE derived RVEF (again, a method not yet validated for assessing RV volumes) to vPAC determined RVEF[196, 197]. In the only study using Bland Altman analysis and a recognised reference method (conductance catheter) there was unacceptable bias for RVEF and RVEDV.

The data examining RVEF by vPAC suggest that measurement using this method is unlikely to be accurate or precise. The majority of studies have not used the appropriate methods for validation and where they have, vPAC has been found to be inadequate. This is particularly true when comparison is made with established reference methods for assessment of RV function (CMR and the conduction catheter) where there is no evidence of agreement [91, 193, 194]. The author concludes that the findings of the Leibowitz editorial are valid. vPAC derived RVEF and RVEDV are inaccurate in ventricles that are stable and are unable to detect changes in ventricles that are undergoing pathophysiological changes[184].

For these reasons, questions remain over the results reported by these studies and suggest further work using *validated* techniques is required.

2.3.3 Studies utilising echocardiography

In the late 20th and early 21st century there was a shift towards non-invasive methods of assessing cardiovascular function. Echocardiographic assessment of the RV was becoming more common and published studies started to reflect this. The studies utilising echo for assessment of RV function following lung resection are summarised in Table 6 (below), followed by a discussion (pg 97).

Table 6. Studies using echocardiography to examine right ventricular function following lung resection

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & Time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Amar et al.[198] (1995)	100	*All Thoracotomy* 12 Wedge Resection 2 Pleural Resection 47 Lobectomy 39 Pneumonectomy *Same cohort of patients as Amar et al.[199] (1996)	TTE	Pre-op POD 1 POD 2-6	*SVT Group* ↑TRJ (POD 2-6)	Association between elevated tricuspid regurgitant jet velocity (not RVSP) on POD 2-6 and development of SVT	Designed to assess clinical and echo correlates of SVT. Patients dichotomised according to development of SVT or not. *"Suggests increased right heart pressure predisposes to clinically significant SVT after pulmonary resection."*
Amar et al.[199] (1996)	86	*All Thoracotomy* 47 Lobectomy 39 Pneumonectomy * Same cohort of patients as Amar et al.[198] (1995)	TTE	Pre-op POD 1 POD 2-6	*Pneumonectomy* ↑RVSP (POD 2-6) No changes in lobectomy group	*"the incidence of right ventricular enlargement by echocardiography was low in both groups and worsened in those patients in whom respiratory failure developed"*	Pneumonectomy associated with mild post-op pulmonary hypertension without associated RV systolic dysfunction. *"An early post-op increase in right heart pressure was more common after pneumonectomy than lobectomy but did not appear to adversely affect RV systolic function."*

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & Time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Amar et al.[200] (1997)	70	*All Thoracotomy* 70 Pneumonectomy	TTE	*"First Follow-up"*	*Diltiazem & Digoxin groups* ↔RAS ↔TRJ ↔RVSP	No clinical outcomes associated with RV function.	Study designed to determine if diltiazem or digoxin were superior for prophylaxis of supraventricular dysrhythmias. Assessed by serial Doppler echo for left and right heart function. Conclusion that diltiazem is safe and effective following pneumonectomy
Kowalewski et al.[45] (1999)	31	*All Thoracotomy* 22 Pneumonectomy 9 Lobectomy	TTE	Pre-op POD 2	*Pneumonectomy* ↑RVEDVI ↑RVESVI ↓RVEF No changes in the lobectomy group	In the pneumonectomy group, those patients that developed supraventricular arrhythmia were found to have ↓ post-op RVEF and ↑ post-op RVEDVI	Designed to investigate the effect of pulmonary resection on RV performance and it's possible contribution to mortality and morbidity. *"Pulmonary resection caused a significant dilatation and dysfunction of the RV in the early post-op period."*

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & Time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Foroulis et al.[201] (2004)	52	*All Thoracotomy* 35 Pneumonectomy 2 Bilobectomy 15 Lobectomy	TTE	Pre-op 6 Months	*Pneumonectomy* ↑PASP ↑RV dimensions (cf lobectomy group) *Lobectomy* ↑PASP	In the pneumonectomy group, patients with more debilitating dyspnoea at 6 months had higher PASP at this time	Prospective study using Doppler echocardiography assessment of RV parameters to detect the influence of pneumonectomy on right heart function. PASP elevation was higher in pneumonectomy group compared with lobectomy patients. Elevated PASP is associated with RV dilatation in both groups. *"Significant percent reduction of 6-month post-op FVC values is associated with increased PASP detecting that the amount of vascular bed resected plays an important role."*

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & Time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Venuta et al.[202] (2007)	51	36 Lobectomy 15 Pneumonectomy	TTE	Pre-op 1 Week 3 Months 6 Months 1 Year 4 Years	*Pneumonectomy* ↑TRJ ↑PASP ↑RVDD *Lobectomy* No statistically significant modification of any variable	No clinical outcomes associated with RV function.	Study of RV function with serial Doppler echocardiography. *"Right ventricle modifications are clearly evident after pneumonectomy."*
Colkesen et al.[203] (2009)	19	*All Thoracotomy* 16 Lobectomy 3 Pneumonectomy	TTE	Pre-op 2-4 weeks post-op	*All Patients* ↑Mitral A ↓Mitral E/A ratio ↑Tricuspid A ↓Tricuspid E dec ↓Mitral E'/A' ratio ↓Tricuspid E'	No clinical outcomes associated with RV function.	Study designed to evaluate the influence of lung resection on cardiac function by using Doppler echocardiography. Multiple Doppler and tissue Doppler measurements. Study determined that there were no systolic changes in function but that diastolic parameters may be affected.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & Time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Cumbo-Nacheli et al. [204] **(2013)**	67	*All Thoracotomy* 67 Pneumonectomy	TTE	Pre-op 24 (±29) months	*All Patients* ↔TRJ ↔RVSP ↑RV Size[#] ↓RV Function[#]	No clinical outcomes associated with RV function.	*Only 40 patients had pre and post-op TTE. 67 patients had post-op TTE. Retrospective study assessing changes in RV function in those patients who had TTE performed as part of clinical course. [#]RV size and function were qualitatively described as normal, mild, moderate or severe. Those patients with higher RVSP (≥40mmHg) had a higher proportion of patients with RV dilatation and dysfunction.
Kumbasar et al.[205] **(2013)**	20	*All Thoracotomy* 14 Lobectomy 6 Pneumonectomy	TTE	Pre-op POD 2 POD 7	*All Patients* ↓Tricuspid E ↑Tricuspid A ↓ Basal S'	No clinical outcomes associated with RV function.	Preliminary study assessing effect of lung resection on RV function using TDI. No comparison to other technique.

Study (Year)	(n)	Population / subgroup	Method of assessing RV function & Time points		Changes in RV function	Clinical outcome associated with RV function?	Comment
Wang et al.[206]	30	*Unknown approach* 10 Pneumonectomy 20 Lobectomy	TTE	Pre-op POD 7	*Pneumonectomy* ↑PAP ↓ Longitudinal Strain ↓Circumferential Strain ↓Radial Strain *Lobectomy* ↓ Longitudinal Strain ↓Circumferential Strain ↓Radial Strain	No clinical outcomes associated with RV function.	First study using speckle tracked echocardiography to assess the impact of lung resection on biventricular function.

RV = right ventricular, POD = post-op day, TTE = trans thoracic echocardiography, RVEF = right ventricular ejection fraction, RVSP = right ventricular systolic pressure, SVT = supraventricular tachycardia, RAS = right atrial size, TRJ = tricuspid regurgitant jet, RVEDD = right ventricular end diastolic diameter, AF = atrial fibrillation, FiO_2 = fraction of inspired oxygen, VATS = video assisted thoracoscopy, TOE = trans oesophageal echocardiography, FVC = forced vital capacity, RVDD = right ventricular diastolic diameter, TDI = tissue Doppler imaging.

Amar performed a series of studies[198-200] examining the incidence, risk factors and management of tachyarrhythmias following lung resection. As part of these studies, the role of RV function was investigated. His first study[198] was performed to examine the clinical and echocardiographic associations in those who developed supraventricular tachycardia (SVT) (mixed pneumonectomy, lobectomy, sub-lobar resections and pleural resections). Adequate echocardiographic images for measurement of Tricuspid Regurgitant Jet (TRJ) velocity were possible in 88% of participants pre-op, 74% on POD 1 and 82% on POD 2-6. There was no change in any values from pre-op to post-op, but in those patients who developed SVT, there was a higher TRJ velocity (TRJ; 2.7±0.6m/s vs 2.3±0.6m/s) on POD 2-6. Despite TRJ being used to calculate RVSP, there was no *significant* difference in RVSP between those patients who developed SVT and those who didn't. A logistic regression model demonstrated intra-operative blood loss ≥1L and elevated TRJ (≥2.7m/s) were independently associated with post-op SVT development. A secondary analysis of the same patients aimed to establish the effect of pneumonectomy and lobectomy on right heart echocardiographic parameters [199]. This demonstrated that by POD 2-6 those patients who had a pneumonectomy had a higher TRJ (2.5±0.6m/s vs 2.2±0.5m/s) compared to baseline and a larger RVSP (31±15mmHg vs 25±10mmHg) than those patients having a lobectomy. The study concluded that despite an early 'modest' post-op increase in RV pressure following pneumonectomy, there was no adverse effect on RV function.

Amars third study[200] was a prospective randomised[l] study to determine whether diltiazem is superior to digoxin for the prophylaxis of SVT after pneumonectomy and to assess the influence of these drugs on cardiac function. There was no change in RV echocardiographic parameters (right atrial size, Tricuspid regurgitation and RVSP) following pneumonectomy and no difference between the two groups (diltiazem or digoxin) at any time point. There was no significant difference in the incidence of SVD in either the diltiazem or digoxin group (14% vs 31%, p=0.09). In contrast to his first study, there is no comment on echocardiographic image availability at any time point.

[l] No details on randomisation provided

Backlunds 1998 study[176] using vPAC to assess RV function (section 2.3.2, pg 77) also performed TTE pre-op and on POD 1. RV end diastolic diameter (RVEDD) remained at pre-op levels in the group exposed to prolonged oxygen but decreased significantly in the group with short oxygen exposure (35±5mm to 27±4mm, $p<0.05$). There was a discrepancy between changes in RVEDD measured by TTE and RVEDVI measured by vPAC, this was attributed to the different measurement techniques and as described above, the accuracy of vPAC determined volumes has been questioned. Tricuspid regurgitant jets (TRJ's) were only seen in 8 (33.3%) patients pre-operatively and in only 4 (16.7%) on POD 1, irrespective of oxygen therapy. TRJ's are used to provided an estimation of RVSP (section 4.4.2.2.5, pg 154) but the inability to visualise them may result from imaging difficulties in this patient cohort that is exacerbated in the post-op period.

Kowalewski et al.[45] utilised TTE in a combined pneumonectomy and lobectomy group (pre-op and POD 2). They utilised the 'subtraction method' to assess RV volumes; "*RV volumes were calculated by subtracting the entire LV area on echo (including the left myocardium) from the entire heart area (including the RV area and the entire LV area)."* This method has previously been *validated* against volumetric PA catheter determined RVEF in a cohort with ARDS ($r=0.74$, $p<0.01$ for RVEF, no Bland Altman assessment)[207]. Imaging was available in all patients at both time points. In the pneumonectomy cohort there was an increase in the RVEDVI (66.2±5.2ml/m^2 to 80.0±7.2 ml/m^2, $p=0.004$), an increase in RVESVI (34.0±5.7 ml/m^2 to 48.5±6.8 ml/m^2, $p=0.003$) and a decrease in RVEF (48±5% to 39±4%, $p=0.017$). Those patients who developed post-op supraventricular arrhythmias following pneumonectomy (14/22, 63.6%) were found to have a lower post-op RVEF (37±3.9% compared with 42±4.5%, $p=0.021$) and higher RVEDVI (82.1±7.4 ml/m^2 compared with 76.3±6.4 ml/m^2, $p=0.031$), compared to those who didn't. There were no significant changes (RVEF, RVEDVI or RVESVI) in the cohort undergoing lobectomy and no association with those who developed post-op SVT.

Foroulis et al.[201]. assessed RV function in a pneumonectomy and lobectomy group pre-op and 6-months post-operatively. Tricuspid regurgitation was detectable pre-op in 9 (24.3%) patients within the pneumonectomy group and in 2 (11.8%) patients within the lobectomy group, with mean PASP ≤25mmHg ("normal") in both groups. Tricuspid regurgitation was found post-operatively in 31 (88.6%)

patients in the pneumonectomy group and 10 (58.8%) patients in the lobectomy group. This corresponded to an increase in PASP in both groups (≤25mmHg to 40.5±12.5mmHg in the pneumonectomy group and ≤25mmHg to 32.9±5.3mmHg in the lobectomy group, p=0.012 between groups). There was also the finding of higher PASP in those patients who had a right pneumonectomy in comparison to those who had a left sided procedure (48.3±10.6mmHg vs 35.3±10.8mmHg, p=0.002). There was a higher incidence of RV dilatation (defined as a diameter ≥25mm) post-operatively in the pneumonectomy group in comparison to the lobectomy group (60% vs 23.5%, p=0.03). Post-operatively there was an association with elevated PASP and RV dilatation in both groups with those patients with the largest RVEDD (>28mm)[J] having the highest PASP in both groups (48.5±11.3mmHg in the pneumonectomy group and 46.5±15.9 in the lobectomy group). In the pneumonectomy group those patients with post-op class IV dyspnoea (dyspnoea with minimal exertion, or at rest - incapacitating) had significantly higher PASP (65.0±7.1mmHg, p=0.016) than those with less severe post-op dyspnoea (Class I; 35.4±8.6mmHg, Class II; 39.8±10.4mmHg or Class III; 41.6±13.9mmHg). In the lobectomy group there was no association between PASP and class of dyspnoea.

Venuta at al.[202] and Cumbo-nacheli et al.[204] performed longer term echocardiographic follow-up (2-4 years) following lung resection. The first study[202] by Venuta et al. prospectively assessed RV function up to 4 years following lobectomy or pneumonectomy. Only one patient from each group was lost to follow-up as a result of death. In the lobectomy group there was no change in any of the measured variables (TVI; Tricuspid valve insufficiency measured by a subjective scale of 0 = normal valve and competent to 3 = high grade insufficiency, PASP, RVEDD[J] and TRJ velocity). In the pneumonectomy group there was an increase in the all the measured variables from pre-op values; TVI (0.9±0.7 to 1.3±0.5, p=0.05), PASP (26.1±2.8mmHg to 34.3±7.6mmHg, p<0.00001), RVEDD (26.4±2.3mm to 31.4±3mm, p<0.001) and TRJ velocity (2.3±0.1m/s to 2.6±0.1m/s, p<0.0001). There were no clinical changes associated with RV function in either group. The second study by Cumbo-nacheli et al. was retrospective with a sample of convenience of 67 patients who had TTE performed 2 years following pneumonectomy. Only 40 patients had pre-op TTE and comparison is made

[J] Level of measurement of dimension is not provided. This level (basal or mid-cavity) can impact on size and is important for reproducibility of measurement.

between these groups. There were no changes in post-op TRJ velocity and RVSP. RV size was described qualitatively as normal or mild, moderate or severe dilatation. Likewise function was described qualitatively as normal or mild, moderate or severe dysfunction. Post-operatively there was an increase in the proportion of patients with dilatation (0% to 20%) and dysfunction (0% to 17%). Those patients with a higher RVSP (≥40mmHg) had a higher proportion of patients with RV dilatation (40% vs 8%) and RV dysfunction (40% vs 11%) than those with a lower RVSP (<40mmHg). There was no association between RV parameters and clinical outcomes.

Two studies incorporated tissue Doppler (TDI) measurements to examine changes following lung resection. The first study by Colkesen et al.[203] examined changes 2-4 weeks following lobectomy (16 patients) and pneumonectomy (3 patients). There were no changes in volume parameters, but when examining the tissue Doppler velocities of the tricuspid valve, changes were evident. The tricuspid A velocity increased (65±19cm/s to 80±30 cm/s, p=0.006) and tricuspid E deceleration time decreased (327±68msec to 274±51msec, p=0.01) with an associated decrease in tricuspid E' (9±2cm/sec to 8±2cm/sec, p=0.03). This pattern would suggest impaired RV relaxation and filling. Caution must be taken when interpreting Doppler values as they can be heavily influenced by heart rate which increased significantly (78±13bpm to 90±12bpm, p=0.001) during the study[128]. There were no clinical outcomes associated with RV function in this study.

The second study by Kumbasar et al.[205] (14 lobectomy and 6 pneumonectomy) examined TDI measurements of the tricuspid valve and RV pre-op, and on POD 2 & POD 7. There was a decrease in tricuspid E by POD 7 in comparison to POD 2. There was an increase in tricuspid A from pre-op to post-op (POD 2 and POD 7). The E/A ratio drops from 0.94 pre-operatively to 0.78 on POD 2 and 0.61 on POD 7. This pattern suggests impaired RV relaxation in the post-op period. In addition, there was a decrease in ventricular basal S' on POD 2 which had recovered to pre-op levels by POD 7. Those patients who had pneumonectomy had a lower ventricular basal S' on POD 2 in comparison to those who had a lobectomy (10.7±2.4cm/s vs 14.4±3.3cm/s, p=0.04). This pattern suggests a decrease in systolic function that has recovered by POD 7 and that those patients who have a pneumonectomy had more systolic dysfunction on POD 2 than those undergoing a lobectomy. The authors conclude that there is significant systolic dysfunction

(more following pneumonectomy) following lung resection which largely recovers by POD 7. Alongside the systolic dysfunction, there is ongoing diastolic dysfunction with evidence of impaired RV relaxation one week following surgery. Both of these studies are small in numbers and in addition; diastolic function following lung resection is still being explored and the role of TDI assessment of the RV and tricuspid valve for assessment of diastolic function needs validated[128].

In the most recent study and one that incorporates a novel echocardiographic parameter, Wang et al.[206] performed a prospective study using speckle tracked echocardiography (STE) in patients undergoing pneumonectomy (n=10) or lobectomy (n=20). Results show that following pneumonectomy there is an increase in PASP and that PASP is higher in the pneumonectomy group compared with the lobectomy group. Following both pneumonectomy and lobectomy there was a deterioration in all RV strain values (longitudinal, circumferential and radial strain) in all RV regions (free wall, septal and global) with the effect larger in the group undergoing pneumonectomy (Figure 23). There was no association made with clinical parameters. Radial strain of the RV is difficult given the thin RV free wall with limited thickening during systole. The main component of RV contraction is longitudinal shortening and the majority of values reported in the broader literature for strain assessment of the RV are for longitudinal strain (free-wall or global).

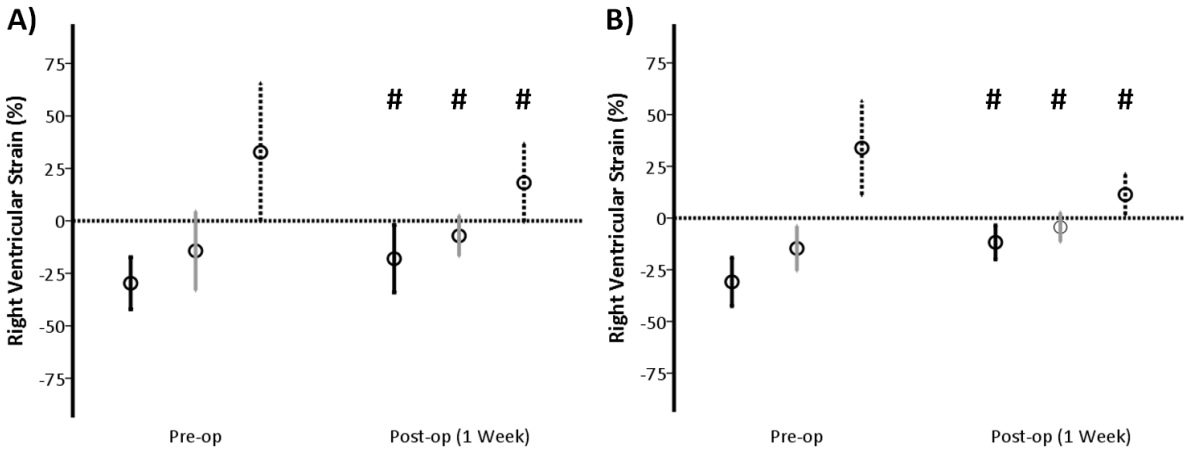

Figure 23. Changes in strain from Wang et al.
Drawn from data presented by Wang et al.[206]. A) = Lobectomy, B) = Pneumonectomy. Continuous black lines = longitudinal strain. Grey line = circumferential strain, Dashed lines = radial strain. Value (error bars) = mean (SD), # = significant difference from pre-op values. Radial strain represents myocardial thickening and is a positive value. Longitudinal and circumferential strain represent myocardial shortening and are negative values.

The majority of studies utilising echocardiography demonstrate an elevation in TRJ velocity measured by continuous wave Doppler (used to determined PASP, see section 4.4.2.2.5, pg 154)[198, 201, 202, 206]. This is particularly true in the pneumonectomy group[199, 201, 206, 208]. Only two studies (both following pneumonectomy however) showed *no change* in TRJ/PASP[200, 204]. Although not every study reported availability of imaging, TRJ were not visible in all patients with Amar reporting 74-82% availability in the post-op period (up to POD 6). This is consistent with previous work in other populations which has shown TRJ are visible in 80% of patients with PASP >35mmHg and 95% of patients with PASP >50mmHg[137].

Caution must be used when analysing those echo studies with volumetric or area changes[45, 176, 201, 202, 204, 208]. RV dimensions are very difficult to measure and are highly probe position dependent[128]. ASE guidelines for echo analysis of the right heart recommend that 2D estimates of RVEF should not be performed given the numerous geometric assumptions[45]. None of these methods have been validated in this particular sub-group.

There was also evidence of dysfunction using less established echocardiographic parameters such as tissue Doppler analysis and speckle tracked strain measurements[203, 205, 206]. The two tissue Doppler studies highlight diastolic dysfunction and a minimal (or transient) effect on systolic function. Strain echocardiography demonstrated post-op RV dysfunction in both pneumonectomy and lobectomy patients.

2.3.4 Additional studies

A number of additional studies contribute to the picture of what happens to RV function following lung resection but do not fit the original search criteria of having pre-op and post-op values. Two studies examined changes intra-operatively at the time of one lung ventilation (OLV) and pulmonary artery clamping.

Wink et al.[85] performed a study using the conductance catheter in patients undergoing lung resection. Measurements were taken during OLV, before and after clamping of the (right or left) pulmonary artery, with and without thoracic epidural analgesia. The study showed that at clamping, afterload increased (as

signified by increased effective arterial elastance [Ea]; 0.49mmHg/ml to 0.75mmHg/ml, described in section 1.2.3.4.2, pg 34), contractility increased (measured by end systolic elastance [Ees]; 0.30mmHg/ml to 0.33mmHg/ml), ejection fraction fell (48.3% to 44.3%) and RV-PA coupling deteriorated (Ees/Ea; 0.64 to 0.48). This was a homeometric response (increased contractility) to increased afterload (see section 1.2.3.9, pg 39). Although epidural analgesia reduced baseline contractility, it did not impair the homeometric response to increased afterload. This study utilised the reference method for assessment of RV function and demonstrated an increase in afterload, an increase in contractility and a deterioration in coupling (Figure 24) at the time of PA clamping. Clamping of the pulmonary artery is an analogous situation to pneumonectomy, where the pulmonary artery is *ligated* at the time of resection. A lobectomy would result in ligation of a branch pulmonary artery and may result in less pronounced physiological changes.

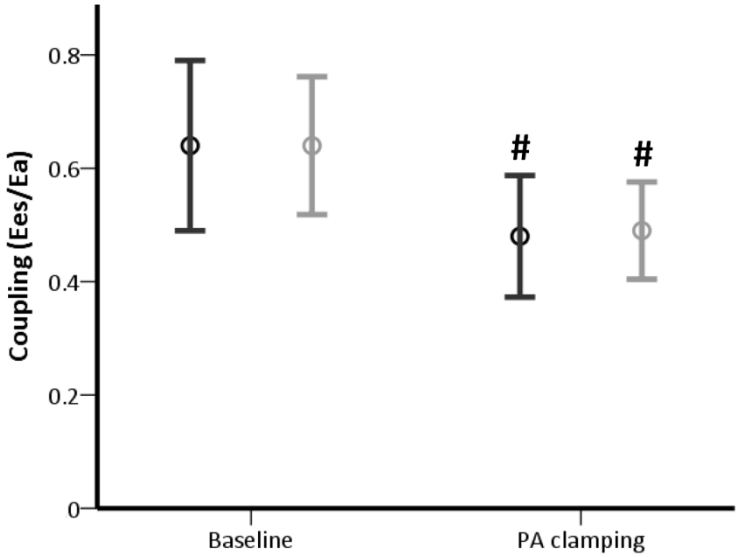

Figure 24. Change in RV-PA coupling at time of PA clamping
Drawn from data presented by Wink et al.[85]. Black lines = Control patients. Grey lines = Patients with thoracic epidural. Value (error bars) = mean (95% CI), # = significant difference from baseline values. PA = pulmonary artery.

Matyal et al.[43] used trans oesophageal echo (TOE) to examine the RV myocardial performance index (RV-MPI) in patients undergoing lung resection. RV-MPI was measured prior to one lung ventilation (OLV) and 10 mins after being established on OLV. There was no change in RV-MPI following OLV however there was a complex association between RV-MPI and those patients who developed SVT

post-op. Those patients with a normal RV-MPI (<0.4) prior to OLV were more likely to develop SVT (42%) than those with an abnormal RV-MPI (≥0.4, 10%). Additionally, in those patients who had a normal RV-MPI at baseline, if their RV-MPI deteriorated on OLV they were more likely to develop SVT (8/14 patients, 57%) than those patients whose RV-MPI remained unchanged (0/4 patients, p=0.045).

In the only study using CMR to assess cardiac function following lung resection, Smulders et al.[209] reviewed 15 patients more than 5 years following initial pneumonectomy and made comparison with 25 normal controls. They showed that pneumonectomy is associated with alterations in cardiac function (higher HR, lower stroke volume and lower LVEF). RV ejection fraction was not assessed and there were no changes in RV volumes or RV mass. The study demonstrated that there are marked intra-thoracic anatomical changes following lung resection; this was characterised by rotation following left sided pneumonectomy (at times to such an extent it resulted in the cardiac apex being directed *posteriorly*) and lateral movement following right-sided pneumonectomy. The authors feel these anatomical changes may explain the deterioration in LV function they observed following pneumonectomy. It is hard to see how such dramatic changes in cardiac position would *not* have an effect on cardiac function.

2.4 Conclusion

Although there are concerns about the methodology used, the literature in totality suggests that lung resection has a significant impact on the right ventricular-pulmonary vascular unit, with changes evident in the immediate post-op period and continuing to be present at long-term follow-up.

There appears to be a difference in those undergoing pneumonectomy in contrast to lobectomy; where studies report outcomes for both groups, there is increased *frequency*[45, 199, 201, 202, 206] and *magnitude*[201, 205, 206] of changes in RV parameters in those undergoing pneumonectomy.

Although clinical outcomes were not measured for all studies there does appear to be an association between peri-operative changes in RV parameters and both, short and long-term morbidity. Those patients with higher PASP at 6 months had

more debilitating dyspnoea[201]. Those patients developing post-op arrhythmias had higher RV pressures, increased PVR, RV dilatation and decreased RVEF[45, 176]. Amar et al. showed those patients developing SVT had elevated TRJ velocity[198]. The group with a deterioration in RVEF with exercise, had a higher rate of complications (although complication type not specifically described)[41]. This was also true with the two studies that showed complex association between intra-operative changes in RV parameters and post-op morbidity. The first demonstrated that those patients who had a deterioration in the RV-MPI from a normal level, were more likely to develop post-op SVT[43]. In the second, those patients who had a lower RVEF at the time of PA clamping were more likely to have poor functional status (as signified by NYHA class III or IV) at long-term follow-up (10 months)[44]. These studies suggest that peri-operative events continue to have an impact long in to the recovery period.

The most commonly hypothesised mechanism of RV dysfunction following lung resection is elevated afterload, but this has *not* been consistently demonstrated in these studies[43, 44, 174]. PVR is often measured as a surrogate of afterload but there is no consistent change in the post-op period (up to POD 2), with most studies showing it unchanged or even reduced[44, 163, 170, 173, 174, 178-180]. PVR is commonly measured in clinical practice but is a measure of opposition to mean flow and ignores the pulsatile component of afterload[70]. True afterload is the RV input impedance and is a composite of both static and pulsatile components[46, 70]. Wink et al.[85]. used the conductance catheter in patients undergoing lung resection and were able to demonstrated an elevation in E_a (Effective arterial elastance, a more complete measure of afterload, see section 1.2.3.4.2, pg 34) at the time of pulmonary artery clamping but no studies have been able to demonstrate a consistent increase in the immediate post-op period despite evidence of RV dysfunction at this time.

Given the methodological concerns regarding the techniques used in the majority of studies to date, further work using validated methods is required to fully understand the RV response to lung resection. As described in chapter 1, CMR is considered the reference method for non-invasive evaluation of RV function and being free from acoustic windows, it would be ideally suited to the assessment of the RV following lung resection. Validation of further non-invasive methods in this

population, potentially utilising trans thoracic echocardiography (with its portability and widespread availability) would have utility in this population.

Chapter 3 Critical Care and Right Ventricular Function Following Lung Resection

3.1 Introduction

As described in Chapter 1, the best opportunity of cure following a diagnosis of lung cancer is with surgery. Although operative mortality is low (1.7%), lung resection is associated with significant peri-operative morbidity and high rates of complications, including; bleeding, respiratory failure, cardiac arrhythmia, myocardial infarction, cerebrovascular accident (CVA) and renal failure[20, 210-214]. Many of these complications will require management and interventions that can only be provided in an intensive care unit (ICU). Such treatments include invasive ventilation, inotropic support and renal replacement therapy (RRT)[215]. Prolonged ICU admission may also require tracheostomy to aid ventilator weaning[212]. Data regarding morbidity following lung resection is plentiful but usually focused on specific individual complications e.g. atrial fibrillation (AF) or acute lung injury (ALI). Comparatively little data exists on the need for intensive care; whilst the data that is available can be difficult to interpret due to regional variation in patient selection and resource availability influencing outcomes and provision of critical care[214].

Existing studies indicate that 6.3% to 18.0% of patients undergoing lung resection require unplanned intensive care post-operatively, with high in-hospital mortality of between 16.6% and 46% in this group[212, 215-220]. Extrapolating these figures to UK resection rates indicate that between 535 and 1530 patients annually may require unplanned ICU admission following their surgery.

As discussed in Chapter 1, lung resection numbers are increasing, with older and sicker patients with more comorbidities presenting for surgery with an increased risk of ICU admission post-operatively. ICU care has significant patient and financial costs and in this context, understanding the factors influencing the need for ICU admission not only has clinical importance but also has implications for resource consumption as the costs of health care rise[213].

It is known that RV function is affected by conditions that require critical care management; acute respiratory distress syndrome (ARDS),[221, 222], sepsis[223], pulmonary embolism[58] and pulmonary hypertension. It is also known that

interventions provided in ICU, such as positive pressure ventilation, are known to negatively affect RV function[224]. No previous work has specifically examined RV function in those patients admitted to ICU following lung resection and as described in Chapter 1, it was the authors anecdotal experience that patients admitted to ICU following lung resection frequently had evidence of RV dysfunction / failure.

This investigation was performed to provide an estimate of the number of patients requiring unplanned intensive care support following lung resection at our institution. It also aims to provide information on who is admitted, their resource requirement, mortality and to investigate the factors associated with their admission, including the incidence of RV dysfunction / failure.

The work in this investigation was performed by the author as pilot data to be used for a competitive proposal for the Association of Cardiothoracic Anaesthetists and Critical Care (ACTACC) national collaborative audit 2015[225]. The proposal was titled "Critical Care After Lung Resection (CALoR) and was successfully adopted, resulting in a multi-centre retrospective project (CALoR 2), which commenced in 2015. The original pilot data was published in *Anaesthesia* in 2015 and is expanded on here[226]. The published manuscript is provided as Appendix 1. The original article was written by the author with review by co-authors: Dr Alistair Macfie, Professor John Kinsella and Dr Ben Shelley.

3.2 Methods

The study was registered with the hospital's clinical governance department and approval was obtained from the hospitals Caldicott guardian (personal communication, 31st July 2015). Research ethics committee approval was not sought as this study was judged to be service evaluation[227]. A retrospective review of consecutive patients undergoing lung resection at the Golden Jubilee National Hospital over a 2-year period (1st Jan 2013 to 31st Dec 2014) was performed. Individual patient data was collated from a prospectively collated surgical database (Cardiac, Cardiology and Thoracic Health Information System; CaTHI, Amor Group, Renfrew, Scotland). Lung resections within this database were categorised as "pneumonectomy"; "lobectomy/bilobectomy" and "sublobar resection (segmentectomy/wedge/biopsy)." Consequently all resections not involving anatomic lobectomy, including metastasectomy, wedge resections and wedge

biopsies were all included in the same ‘sublobar resection' group. The primary anaesthetic technique, namely total intravenous anaesthesia (TIVA) or volatile based, was obtained from the Recall AIMS electronic anaesthetic charting system (Informatics Clinical Information Systems Limited, Glasgow). For this study, any patients exposed to volatile anaesthetic agents (even for short periods e.g. for blood pressure control) were allocated to the volatile anaesthetic group. Data for ICU patients were obtained from patient notes, the hospitals ICU clinical information system (Centricity CIS; GE Healthcare®, Buckinghamshire, UK) and from the Scottish ICU audit database (Ward Watcher; Critical Care Audit Ltd, Yorkshire, UK).

To investigate the incidence of RV dysfunction in the cohort admitted to ICU, a case note review was performed. Complete clinical notes for each ICU admission was provided as Rich Text Format (RTF, Microsoft, Washington, USA) documents. To ensure all episodes of RV dysfunction were captured, a search procedure was performed in each document (Microsoft Word, Microsoft, Washington, USA) for the following terms; *right, ventricle, RV, ventricular, TTE, Echo, TOE, nitric oxide, iNO, pulmonary hypertension and pulmonary artery pressure.* Additionally, the clinical portal system (NHS Scotland) was searched for additional information, including imaging reports for this group. The echocardiography system (EchoPAC, GE Healthcare) within the hospital was searched for any imaging performed. RV dysfunction was defined as; a TAPSE <1.6cm, mid RV diameter >3.5cm or a verbal description of dysfunction or dilatation *without* clinical features consistent with low cardiac output or hypoperfusion. RV failure was defined as evidence of RV dysfunction with signs of reduced cardiac output and/or hypoperfusion including; cardiac index <2.2L/min/m^2 on cardiac output monitoring, requirement for inotropic support, evidence of renal failure, acidaemia, hyperlactaemia, or a verbal description of 'failure'.

The Golden Jubilee National Hospital is a tertiary referral cardiothoracic surgery centre and is the one of the largest thoracic surgery units in the UK[12]. Pre-op assessment, broadly in keeping with the British Thoracic Society guidelines, occurs at clinic prior to admission[228]. Admission is typically the day before operation and surgery is performed by a team of five consultant thoracic surgeons. Unless otherwise indicated all patients are routinely extubated in the operating theatre at the completion of surgery and are transferred to the theatre recovery

unit. After a period of observation they are then transferred to a high dependency unit (HDU, level 2 care as per Intensive Care Society "*levels of critical care*")[229] where invasive monitoring, vasopressor infusions, high flow nasal oxygen and non-invasive ventilation can all be provided.

For this study, ICU admissions (level 3 care)[229] were defined as those patients requiring intubation for invasive ventilation and/or requirement for renal replacement therapy (RRT). In our institution patients requiring these interventions must be transferred to the intensive care unit where care is shared between the surgical team and cardiothoracic intensivists. Those patients with immediate post-op respiratory failure who were unable to be extubated at the end of their operation were included as unplanned ICU admissions if ventilated for more than 12 hours.

Categorical data are presented as frequency (%) and continuous data are presented as mean (SD) or median (IQR) as appropriate to data distribution. Categorical variables were compared using the Chi-squared or Fisher's exact tests and continuous variables were compared using the Student t or Mann-Whitney U tests as appropriate. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS for windows, version 22 (IBM Corp, Armonk, NY, USA). Logistic regression was performed to assess the role of potential explanatory anaesthetic and surgical variables on the need for ITU admission. To allow adjustment for patient co-morbidity and surgical complexity, these analyses were adjusted for Thoracoscore[230]. Thoracoscore was chosen as it reflects a composite of patient and surgical risk factors. Logistic regression models were created to ascertain the effects of anaesthetic technique (TIVA or Volatile), regional anaesthetic choice (epidural or paravertebral block) and surgical approach (video assisted thoracoscopy (VATS) or open).

3.3 Results

3.3.1 Critical care following lung resection

One thousand, one hundred and sixty nine patients underwent lung resection during the study period. Seventy eight (6.7% of *all* resections) pneumonectomies were performed, 775 (66.3%) lobectomy/bilobectomies and 316 (27.0%) sublobar procedures. Thirty patients (2.6% of all resections) required unplanned intensive

care following their surgery. One patient (1.3% of *all* pneumonectomies) following pneumonectomy; 27 patients (3.5%) following lobectomy/bilobectomy and 2 patients (0.6%) following a sublobar resection. Overall hospital mortality was 0.9%. In the ICU cohort mortality was 26.7%, in contrast to 0.2% for the group not requiring ICU ($p<0.001$, Fisher's exact test). Those patients admitted to ICU were older, had worse baseline lung function and a higher pre-op Thoracoscore (Table 7, pg 112). Patients surviving following an admission to ICU had a longer length of hospital stay (Median 7.0 and 25.5 days, $p<0.001$, Mann Whitney U-Test).

Patients admitted to ICU within a week of their surgery had a lower mortality (8.7% of 23 patients) than those patients admitted beyond post-op day 7 (85.7% of 7 patients) ($p<0.001$, Fisher's exact test, Figure 25).

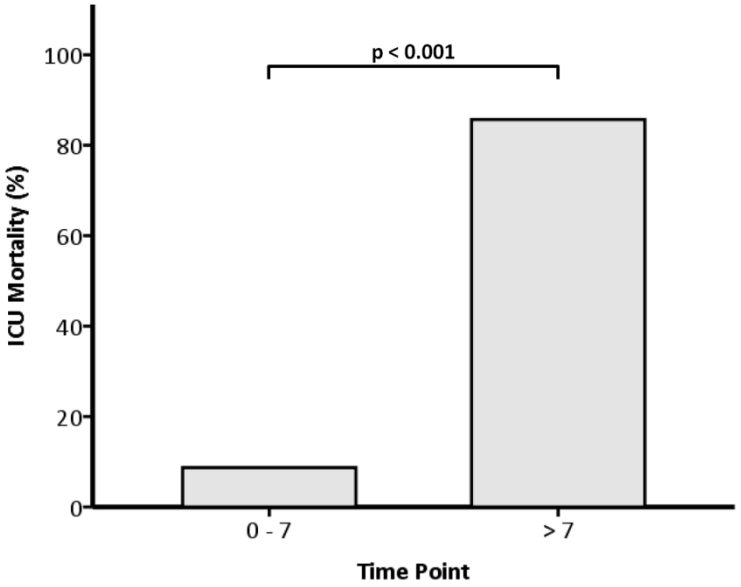

Figure 25. Intensive care unit mortality for admission time period
Mortality in those admitted from day 0-7 = 8.7%, Mortality in those admitted beyond day 7 = 85.7%, Fisher's exact test.

Characteristic	No ICU admission (n=1139)	ICU admission (n=30)	p value
Age (yrs)	67.0 (59.0, 73.0)	71.0 (64.5, 74.3)	0.02*
Female Sex	624 (55%)	15 (50%)	0.60§
FEV_1%	88.2 (21.4) *n=539*	80.1 (19.3) *n=30*	0.043†
TLCO%	70.9 (18.8) *n=476*	60.8 (16.1) *n=30*	0.004†
APACHE II	-	17 (14.8, 23.3)	-
Thoracoscore	0.8 (0.4, 2.0) *n=941*	2.2 (1.2, 2.7) *n=30*	<0.001*
Resection type			
Pneumonectomy	77 (6.8%)	1 (3.3%)	0.478‡
Lobectomy / Bilobectomy	748 (65.7%)	27 (90.0%)	0.007§
Sublobar Resection	314 (27.6%)	2 (6.7%)	0.011§
Right Sided	686 (60.2%)	18 (60.0%)	0.980§
Approach (c.f. VATS)			
Open	782 (68.7%)	28 (93.3%)	<0.01‡
In-hospital mortality	2 (0.2%)	8 (26.7%)	<0.001‡
Post-op stay, survivors (days)	7.0 (5.0, 9.0) *n=1137*	25.5 (13.0, 44.8) *n=22*	<0.001*
Duration of ventilation (days)	-	5.5 (2.0, 19.5)	-
ICU stay (days)	-	8.5 (2.8, 19.5)	-

Table 7. Characteristics of those patients not admitted to ICU and those admitted to ICU following lung resection at the Golden Jubilee National Hospital between Jan 2013 and Dec 2014

Values are number (%) and median (IQR). Where the dataset was incomplete,*(n)* represents the number of patients with data available. FEV_1% = percent predicted forced expiratory volume in 1 second; TLCO% = percent predicted transfer factor for carbon monoxide; APACHEII = acute physiology and chronic health evaluation II; VATS = video assisted thoracoscopy; § = chi-squared test, * = Mann Whitney U-Test; † = students t-test; ‡ = Fisher's exact test.

Twenty three patients (76.7%) were admitted to ICU with respiratory failure. Admission diagnosis was categorised as documented in patient notes, some patients had more than one cause of respiratory failure (e.g. lobar collapse with ARDS and respiratory infection) (Table 8). Mechanical ventilation was required in 28 (93.3%) patients and median duration of ventilation was 5.5 days (Table 9).

Diagnosis	ICU admission (n=30)	ICU Deaths (n=8)
Respiratory failure	23 (76.7%)	6 (75.0%)
- Respiratory infection*	15 (65.2%)	
- ARDS*	8 (34.8%)	
- Lobar collapse*	6 (26.1%)	
- Pulmonary embolism*	1 (4.3%)	
- Cardiac failure*	4 (17.4%)	
Renal failure	1 (3.3%)	0 (0%)
Cardiac arrest	3 (10.0%)	1 (12.5%)
Bleeding	3 (10.0%)	1 (12.5%)

Table 8. Admission diagnosis in patients admitted to ICU following lung resection.
Values are number (%). *Reflects the number of patients admitted with each diagnosis, some patients had multiple diagnoses. ARDS = acute respiratory distress syndrome.

Intervention	ICU Admission (n=30)	ICU Deaths (n=8)
IPPV	22 (73.3%)	5 (22.7%)
CVVH	2 (6.7%)	0 (0%)
CVVH & IPPV	6 (20.0%)	3 (50.0%)
Tracheostomy	11 (36.7%)	1 (9.1%)
Duration of Ventilation (days)	5.5 (2.0, 19.5)	-
ICU Stay (days)	8.5 (2.8, 19.5)	-

Table 9. Interventions, mortality, duration of ventilation and length of stay in patients admitted to ICU following lung resection
Values are number (%) or median (IQR). IPPV = Intermittent positive-pressure ventilation; CVVH = continuous veno-venous haemofiltration.

Data were complete for the group admitted to ICU. The databases for the group not admitted to ICU were incomplete. Pulmonary function tests, Thoracoscore,

primary anaesthetic technique and primary analgesic technique were all missing some data points (Table 7, pg 112 and Table 10).

Anaesthetic and surgical Technique		No ICU admission (n=1139)	ICU Admission (n=30)	p value
Approach	**Open**	782 (68.7%)	28 (93.3%)	<0.01†
	VATS	357 (31.3%)	2 (6.7%)	
Primary Anaesthetic	**TIVA**	583 (51.9%)	11 (36.7%)	0.10*
	Volatile	540 (48.1%)	19 (63.3%)	
Primary Analgesia	**Epidural**	418 (47.6%)	13 (43.3%)	0.77*
	PVB	461 (52.4%)	16 (56.7%)	

Table 10. The influence of anaesthetic and surgical technique on need for ICU admission following lung resection
Values are number (%); † = Fisher's exact test; * = Chi-squared test; VATS = video assisted thoracoscopic surgery; TIVA = total intravenous anaesthesia; PVB = paravertebral blockade.

When assessing the influence of surgical and anaesthetic factors, VATS procedures accounted for 30.7% of all lung resections but represented only 6.7% of those patients requiring intensive care (p<0.01, Fisher's exact test). Total intravenous anaesthesia was the sole primary anaesthetic technique for 51.5% of all procedures but only 36.7% of patients admitted to ICU (p=0.10, chi-squared test). There was no apparent association between paravertebral or epidural anaesthesia and requirement for ICU, with proportions similar in both the ICU admission group and the no ICU admission group (Table 10).

As there were a small number of patients admitted to ICU (n=30), we created three separate logistic regression models to assess for any association between the surgical and anaesthetic factors listed in Table 10 and the need for ITU admission (following adjustment for Thoracoscore). Due to the extreme skewed distribution of the data, Thoracoscore was log transformed to normality (Log_{10} Thoracoscore) and inputted along with approach, primary anaesthetic type and primary analgesic type. The three logistic regression models were statistically significant (p≤0.001) and accounted for between 8% and 10% (Nagelkerke R^2) of the variance in ICU admission (Table 11, pg 115).

	Odds Ratio	95% CI	P-value
Log_{10} Thoracoscore	4.05	(1.76, 9.33)	0.001
Surgical Approach	5.25	(1.23, 22.43)	0.025
Note: Approach is for open procedure compared with VATS			
Log_{10} Thoracoscore	5.26	(2.31, 11.96)	<0.001
Primary Anaesthetic	2.08	(0.97, 4.47)	0.061
Note: Primary anaesthetic is for volatile compared with TIVA			
Log_{10} Thoracoscore	5.17	(2.15, 12.47)	<0.001
Secondary analgesia	1.08	(0.50, 2.30)	0.847
Note: Secondary analgesia is for PVB compared with epidural			

Table 11. Logistic Regression models predicting ICU admission following lung resection.
VATS = video Assisted thoracoscopic surgery, TIVA = total intravenous anaesthesia, PVB = paravertebral Blockade.

Log_{10} Thoracoscore was a significant predictor variable in all three models (p≤0.001) however the only independently significant predictor was surgical approach, with the use of an open procedure associated with 5.25 (p=0.025, 95% CI 1.23, 22.4) times higher odds of ICU admission. There was a trend towards increased ICU admission in patients undergoing volatile anaesthesia (p=0.061, OR 2.08, 95% CI 0.97, 4.47). There was no association between ICU admission and regional anaesthetic choice (p=0.847).

3.3.2 Right ventricular function in critical care following lung resection

Of the patients admitted to ICU, nine (30%) had evidence of RV dysfunction/failure at some point during their critical care admission. A description of the basic demographics and clinical course of these patients is given in Table 13 (pg 119). Of these nine patients, two (patient no. 8 and 9) had evidence of alternative pathologies that may have significantly contributed to RV dysfunction; one had evidence of saddle pulmonary embolism and the other had severe RV impairment pre-operatively. As this investigation was to determine the incidence of RV dysfunction *resulting from lung resection* and given the confounding nature of the pathologies in these two patients, they have not been included in the analysis. Therefore, seven patients (25.0%) had evidence of RV dysfunction in the ICU cohort following lung resection (six with evidence of RV failure) and they are

compared with the 21 patients admitted to ICU with no evidence of RV dysfunction. The characteristics of these two groups are provided in Table 12. Given the small numbers and the retrospective nature of the study, no statistical comparison has been made and this review is of a descriptive nature only.

Characteristic	RV Dysfunction (n=7)	No RV Dysfunction (n=21)
Age (yrs)	69.0 (63.0, 73.0)	73.0 (63.5, 75.5)
Female Sex	4 (57.1%)	11 (52.4%)
FEV_1%	71.0 (60.0, 102.0)	82.0 (72.0, 93.5)
TLCO%	56.0 (43.0, 73.0)	57.0 (46.0, 74.0)
APACHE II	17.0 (12.0, 24.0)	17.0 (14.5, 23.0)
Thoracoscore	2.7 (1.0, 5.0)	2.0 (1.2, 2.6)
Day of admission	8.0 (2.0, 12.0)	2.0 (1.0, 5.5)
Resection type		
Pneumonectomy	0 (0%)	1 (4.8%)
Lobectomy / Bilobectomy	7 (100%)	19 (90.5%)
Sublobar Resection	0 (0%)	1 (4.8%)
Right Sided Procedure	5 (71.4%)	13 (61.9%)
Approach (c.f. VATS)		
Open	7 (100%)	20 (95.2%)
In-hospital mortality	5 (71.4%)	3 (14.3%)

Table 12. Characteristics of patients admitted to ICU with evidence of RV dysfunction and those without evidence of RV dysfunction.
Values are number (%) and median(IQR). FEV_1% = percent predicted forced expiratory volume in 1 second, TLCO% = percent predicted transfer factor for carbon monoxide, APACHEII = acute physiology and chronic health evaluation II, VATS = video assisted thoracoscopy.

Of the seven patients, all had evidence of RV dysfunction on echocardiography, four with trans thoracic echocardiography (TTE) and three with trans oesophageal echocardiography (TOE). Of the 30 patients admitted to ICU, 19 (63.3%) had

echocardiography (TTE or TOE) during their admission. As part of their assessment, two patients had pulmonary artery catheters (PAC) inserted which demonstrated evidence of pulmonary hypertension. All seven patients had evidence of RV dilatation on echocardiography. Five patients had evidence of dilatation and functional impairment which was described from "*moderate*" to "*severe*". The other two patients had evidence of ventricular dilatation but function was described as "*satisfactory*" or "*coping*". Echocardiographic images of a patient admitted to ICU with RV failure following lung resection are provided (Figure 26 and Figure 27, pg 118).

Five patients (71.4%) with evidence of RV dysfunction died in ICU, in contrast to three (14.3%) in the cohort without evidence of RV dysfunction. The two patients who survived had evidence of dilatation but function was described on echo as not being impaired, whereas the patients that died all had evidence of functional impairment. All patients with evidence of RV dysfunction had respiratory failure on admission to ICU and all required intermittent positive pressure ventilation (IPPV). Six patients (85.7%) had evidence of RV failure with haemodynamic compromise, and all of these patients were on multiple vasoactive infusions (including adrenaline, nor-adrenaline, dobutamine, vasopressin and milirinone). Five of the six patients (83.3%) with haemodynamic compromise received pulmonary vasodilator therapy; all five had inhaled nitric oxide (iNO) administered and one patient received epoprostenol (Flolan) in addition to iNO. No patients had extracorporeal support. Two patients required RRT in the form of continuous veno-venous haemofiltration, although it is not clear from the review if this was as a focused intervention for RV failure or part of management of multi-organ failure.

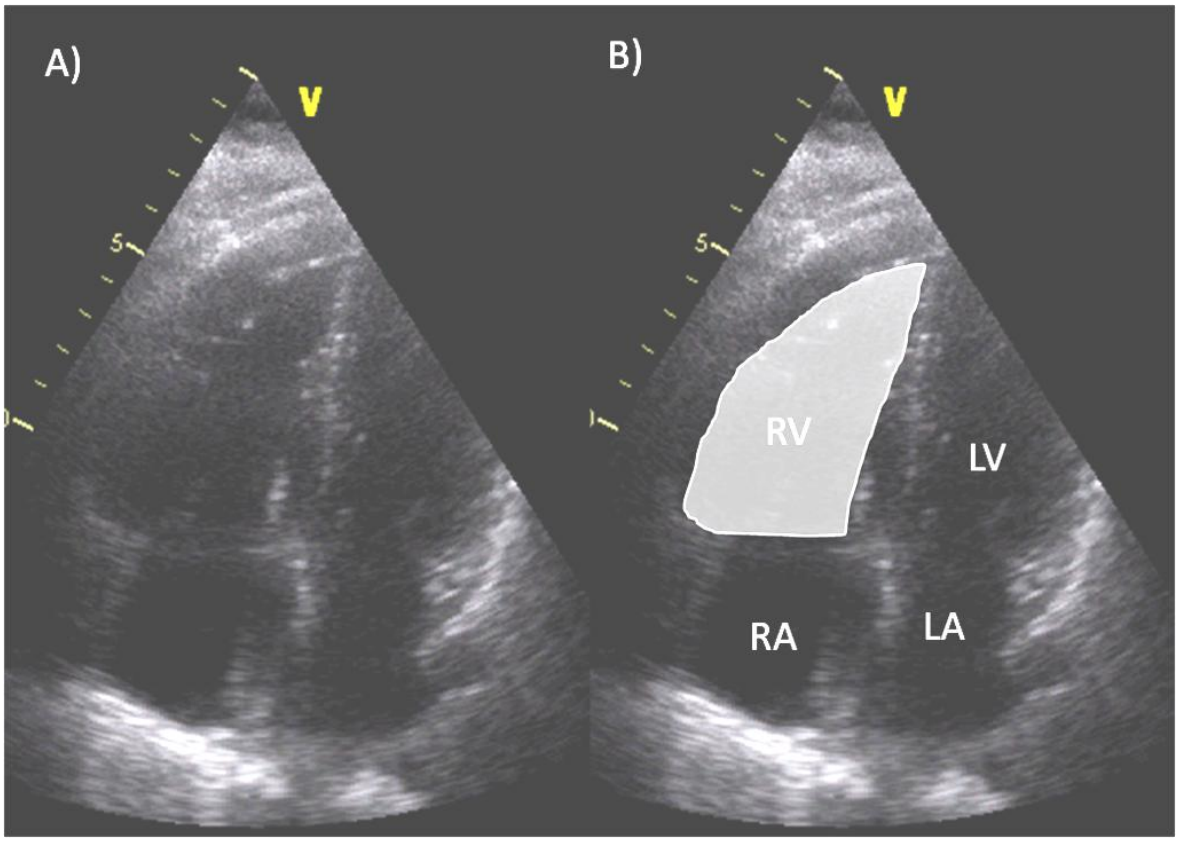

Figure 26. Trans thoracic echocardiography of patient admitted to ICU with RV failure following lung resection (Apical 4-chamber view)
A) Plain image B) Annotated image. Area in white is the right ventricle and is dilated (similar size to the left ventricle). RV = right ventricle, LV = left ventricle, RA = right atrium, LA = left atrium.

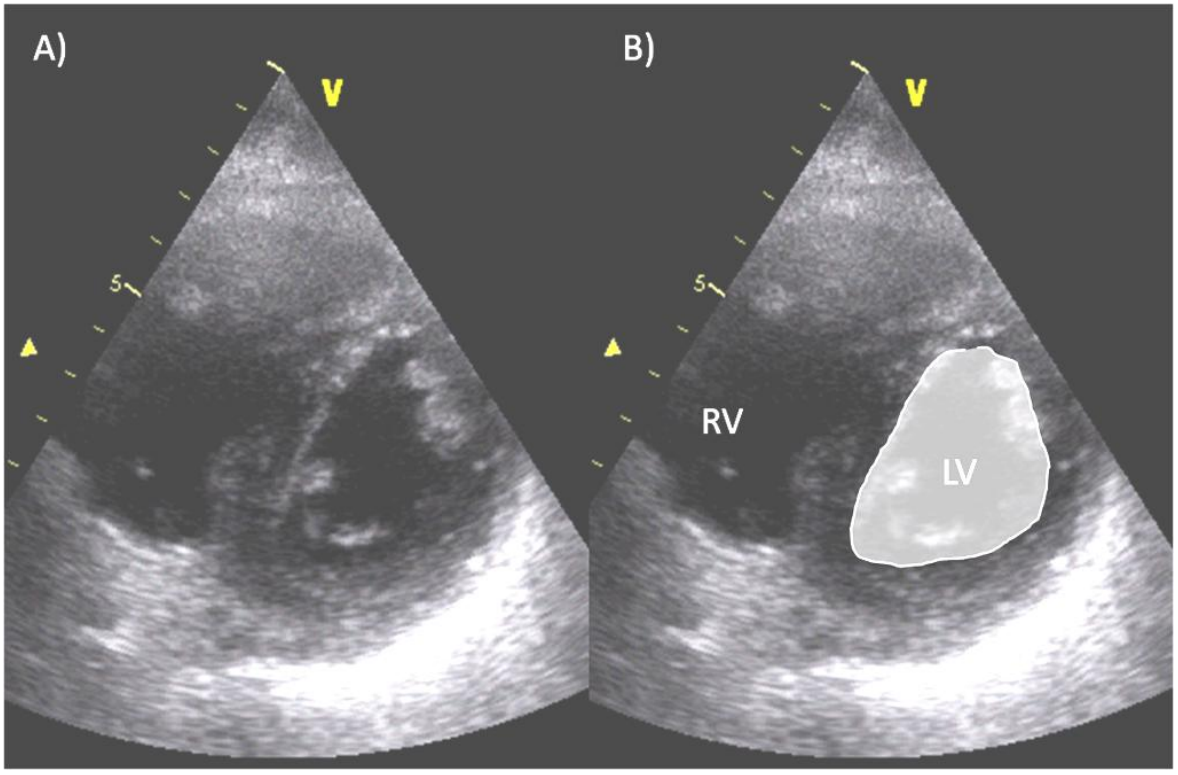

Figure 27. Trans thoracic echocardiography of patient admitted to ICU with RV failure following lung resection (Para-sternal short axis view)
A) Plain image B) Annotated image. Area in white is the left ventricle and is compressed during systole ("D-shaped") suggesting RV pressure overload. RV = right ventricle, LV = left ventricle.

Table 13. Intensive care unit (ICU) patients with right ventricular dysfunction

No.	Age sex	Approach resection type	PMHx	Clinical course	RV dysfunction/failure identified	ICU outcome
1	70 ♀	Thoracotomy RLL & upper wedge	Obesity Type 2 DM PVD Previous PE HTN COPD OA Ex-smoker	Progressive respiratory failure with Increasing FiO2 requirement from POD 3. Required NIV from POD 7. Acute deterioration POD 9 requiring ventilation. Persistently hypotensive with low cardiac output state requiring high doses of vasoactive medications (NA, adrenaline, vasopressin and dobutamine) and iNO.	POD 10 TOE RV severely dilated and impaired	Died POD 10
2	75 ♂	Thoracotomy RLL and RML	COPD IHD Kidney Ca with previous nephrectomy	Oliguria/anuria post-op Admitted to ICU for CVVH POD 2. Respiratory failure and cardiovascular collapse POD 3 TOE-> RV dysfunction. Managed with iNO, dobutamine, NA, vasopressin and CVVH.	POD 2 TOE Dilated dyskinetic RV "only just coping"	Discharged POD 10

No.	Age sex	Approach resection type	PMHx	Clinical course	RV dysfunction/failure identified	ICU outcome
3	63 ♀	VATS to thoracotomy LUL	CVA ALD (oesophageal varices) COPD Hypertension	Intra-op bleeding requiring transfusion. Extubated post-op. , Admitted from HDU with cardiovascular collapse POD 3. Managed with NA, dobutamine, adrenaline, vasopresin, milirinone, iNO and Flolan. TTE and PAC at that time.	POD 3 TTE RV dilated, moderate impairment of systolic function PAC showed PA pressures of 93/43mmHg	Died POD 3
4	60♂	Thoracotomy RUL	AF - warfarin IHD Ex-smoker	For aspergilloma. Intra-op bleeding requiring transfusion. Initially managed in HDU. Admitted ICU POD 8 with respiratory failure and sepsis. On POD 9 noted to have RV dysfunction which was managed with dobutamine, adrenaline and iNO. Parameters improved but developed MOF and died.	POD 9 TTE RV dilated and moderately impaired	Died POD 19
5	74 ♀	VATS to thoracotomy RUL	Pulmonary fibrosis IHD	Initially good post-op progress, slowly deteriorated from respiratory dysfunction. Admitted ICU POD 17 with respiratory failure requiring ventilation. Developed cardiovascular collapse and RV dysfunction with persistent pulmonary hypertension. Required CVVH for renal failure. Managed with iNO, dobutamine and NA.	POD 18 TOE showed dilated RV POD 18 PAC PAP 80/40	Died POD 24

No.	Age sex	Approach resection type	PMHx	Clinical course	RV dysfunction/failure identified	ICU outcome
6	66♀	Thoracotomy LUL	Pulmonary fibrosis	Admitted with respiratory failure POD 2, treated as post-op ARDS. No significant haemodynamic compromise evident although TTE performed.	TTE POD 4 - RV mildly dilated with satisfactory function RVSP moderately elevated (57mmHg)	Discharged POD 18
7	69♂	Thoracotomy RUL and RML	Ex smoker IHD AF on warfarin	Admitted POD 12 with respiratory failure and sepsis, initially made good progress and was extubated. Re-ventilated for respiratory failure on POD 26 with significant haemodynamic compromise and RV dysfunction on TTE. Managed with NA and dobutamine.	TTE poorly functioning. Dilated RV with septal shift, severe TR, increased PAP	Died POD 28
8	72♂	Thoracotomy LLL	AF COPD IHD	Uneventful immediate peri-operative period. Developed respiratory failure POD 7. POD 12 found to have bilateral PE's. TTE at that time demonstrated dilatation but preserved function. RVSP reduced as clinical picture improved. Developed respiratory failure (?ARDS), required ventilation. No significant haemodynamic instability.	TTE POD 12 showed a large 'serpentine' thrombus. Moderate dilatation, normal systolic function and severely elevated RVSP (67mmHg)	Discharged POD 50

No.	Age sex	Approach resection type	PMHx	Clinical course	RV dysfunction/failure identified	ICU outcome
9	51♂	Thoracotomy L Wedge resection	Ex-smoker HTN Rheumatic valvular disease AF	Pre-op rheumatic valvular disease with right heart dilatation and severe systolic impairment. Deterioration immediately post-operatively with poor respiratory function and hypotension. Requirement for ventilation and vasoactive medication for management of haemodynamic instability; NA and dobutamine.	TTE immediately post-op showed torrential tricuspid regurgitation, dilated RV and RA with severely impaired function	Discharged POD 5

PMHx = past medical history, RLL = right lower lobectomy, RML = right middle lobectomy, LUL = left upper lobectomy, RUL = right upper lobectomy, LLL = left lower lobectomy, DM = diabetes mellitus, PVD = peripheral vascular disease, PE = pulmonary embolus, HTN = hypertension, COPD = chronic obstructive pulmonary disease, OA = osteoarthritis, IHD = ischaemic heart disease, Ca = cancer, CVA = cerebrovascular accident, ALD = alcoholic liver disease, AF = atrial fibrillation, FiO_2 = fraction of inspired oxygen, NIV = non invasive ventilation, NA = nor-adrenaline, POD = post-op day, iNO = inhaled nitric oxide, CVVH = continuous veno-venous haemofiltration, TTE = trans thoracic echocardiogram, TOE = trans oesophageal echocardiogram, HDU = high dependency unit, ARDS = acute respiratory distress syndrome, RVSP = right ventricular systolic pressure, PAP = pulmonary artery pressure, RA = right atrium.

3.4 Discussion

The main finding of this study is an unplanned ICU admission rate of 2.6% following lung resection. ICU admission was associated with increased mortality, prolonged duration of ventilation, requirement for tracheostomy and prolonged hospital stay. An incidence of RV dysfunction in ICU following lung resection of at least 25% was also discovered. RV dysfunction in this group is associated with high mortality (71.4%) and appears to have a large resource burden. Of the eight patients who died in the ICU cohort, five (62.5%) had evidence of RV dysfunction.

Both patient factors and surgical factors are known to influence the need for ICU admission following lung resection. Patient factors include; increasing age >65 years old, poor respiratory function including; Forced Expiratory Volume in 1 second (FEV_1) <45% predicted, Diffusion Limitation of Carbon Monoxide (TLCO) <50% predicted and medical co-morbidities[213-215]. Consistent with previous work, patients admitted to ICU for support in this study were older and had worse lung function when compared to the patients not requiring ICU.

In other reported series, respiratory failure was the primary reason for admission in 50% to 77% of patients[212, 215, 218]. There were similar findings in this cohort with 23 patients (76.7%) admitted with a diagnosis of respiratory failure and 28 patients (93.3%) requiring ventilatory support. Mean ventilation time was just under two weeks and a third of patients further required tracheostomy for prolonged ventilator wean. In the 22 patients requiring respiratory support alone (i.e. without RRT), mortality was 28.6%. Of the two patients requiring RRT alone, both survived. Six patients required both RRT and ventilation, with a survival of 50%, this is in contrast to previous work which reported poor outcomes in this patient group.

> *"The combination of mechanical ventilation and haemofiltration was universally fatal in our patients."*
>
> Pilling et al. (2004)[212]

The marked difference in mortality between those patients requiring ICU early (post-op days 0 to 7) and late (after post-op day 7) is interesting. The author theorises that the group of patients admitted late are a different population and

have continued to deteriorate despite maximal ward or high dependency unit treatment and are 'self selecting' themselves to do poorly. Qualitative review indicates that the patients admitted early were more likely to have diagnoses amenable to immediate intervention such as lobar collapse or bleeding and those admitted later had a higher incidence of consequential secondary pathologies such as ARDS or bronchopneumonia. This early and late phenomenon is analogous to primary and secondary lung injury as described by Licker et al.[231] (Figure 28).

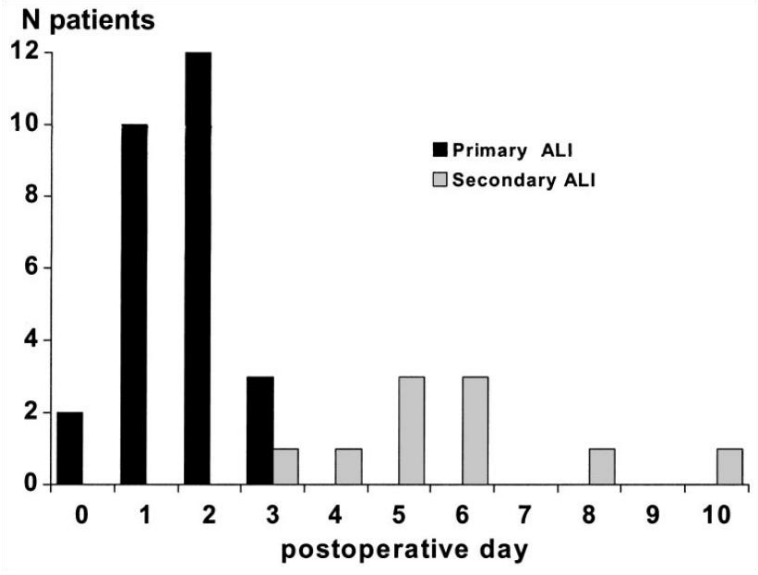

Figure 28. Time related distribution of acute lung injury following thoracic surgery
From Licker et al.[231].

The choice of a TIVA or volatile anaesthetic for thoracic procedures has been the subject of much debate. In this investigation, following adjustment for Thoracoscore, there is a trend towards decreased risk of ITU admission in patients anaesthetised using a TIVA technique (p=0.061). Though volatile agents have been described as having theoretical, physiological and laboratory advantages over TIVA for thoracic anaesthesia, there is a lack of data looking at patient outcomes[232-234]. Importantly, in this study we included all patients with any *exposure* to a volatile agent, no matter what the duration. We therefore may be over estimating the proportion having a volatile anaesthetic in the group not admitted to ICU**.** In contrast to the potential benefits offered by volatile agents, there is a body of evidence demonstrating a theoretically advantageous free radical scavenging and antioxidant effect of Propofol[235, 236]. There is no strong

clinical evidence in favour of either volatile or TIVA in lung resection and a 2013 Cochrane review update concluded;

> *"no evidence indicated that the drug used to maintain anaesthesia during one-lung ventilation affected participant outcomes"*
>
> Modolo et al. (2013)[232]

Furthermore, it is not yet clear if there is a cumulative effect from use of these agents or if any effect (beneficial or detrimental) is as a result of all or nothing exposure.

Pneumonectomy has previously been reported as an important surgical factor in determining the need for ICU admission[215]. In this cohort only one patient was admitted following pneumonectomy, the small number means that any in-depth analysis of the factors associated with ICU admission in this specific group would be underpowered and meaningless. This also needs to be considered in the wider context of a decline in the number of pneumonectomies performed over the last 30 years and a shift in national guidelines[K].

> *"avoid pneumonectomy where possible by performing bronchoangioplastic resection or non-anatomical resection"*
>
> *Lim et al.(2010)[228]*

There has been no published work looking at the importance of surgical approach (open or VATS) on the need for unplanned ICU admission. In this cohort, the logistic regression model incorporating surgical approach demonstrated a significant effect on the need for ICU care, with the use of an open procedure associated with a *five times* higher odds of ICU admission. There are several confounders to this as there will be cases where a VATS procedure will not be possible due to relative contraindications such as; pneumonectomy, previous thoracic surgery and central tumours. Also, if there is intra-operative difficulty during a VATS procedure, the default will be to progress to an open procedure. Peri-operative difficulties requiring conversion could influence the need for ICU

[K] Joint guidelines by the British Thoracic Society and Society for Cardiothoracic Surgery in Great Britain and Ireland.

admission. In our cohort, two of the patients admitted to ICU following an open procedure were conversions from a VATS technique.

Though anecdotally, it appears as if there has been more widespread adoption of a paravertebral analgesic technique for patients undergoing lung resection, historically UK practice has been significantly in favour of the use of thoracic epidural blockade[237]. Current evidence is conflicting with several large systematic reviews and meta-analyses showing no difference in the techniques or favouring paravertebral blockade[238-240]. This investigation demonstrated no difference in the need for ITU admission between patients undergoing thoracic epidural versus paravertebral analgesia.

Brunelli et al. developed a scoring tool designed to predict the need for emergency ICU admission following lung resection. Increasing score was associated with an incremental increase in the need for ICU admission, although this was shown to only have moderate discriminative ability (signified by an area under the receiver operating characteristic curve (AUROCC) of 0.66) in an external validation study[215, 219]. Thoracoscore is a scoring system incorporating both patient and surgical risk factors and is used to evaluate the risk of in-hospital mortality following thoracic surgery (Table 14 and Equation 7, pg 127)[230]. Although not previously reported as important in determining the need for ICU care, it would seem intuitive that those patients at higher risk of mortality would be at higher risk of unplanned ICU admission. This is consistent with mortality scoring tools predicting ICU requirements in other surgical groups, for example, following cardiac surgery[241]. In our study, as might be anticipated, patients admitted to ICU had a higher Thoracoscore compared to those not requiring ICU admission and although not previously validated to predict ICU requirement, Thoracoscore had good predictive power with an AUROCC of 0.74 (95% CI 0.68, 0.80, $p<0.001$) (Figure 29, pg 128)[242]. A Thoracoscore of 0.89 had 93.3% sensitivity and 54.2% specificity with a positive predictive value of 6% but with a negative predictive value of 99.6%. Thoracoscore could therefore be used to highlight patients at *lower* risk of ICU admission, potentially identifying those suitable for enhanced recovery programmes or same day admission.

Variable	Value	β-coefficient
Age (Yrs)	<55	-
	55-65	0.7679
	>65	1.0073
Gender	Female	-
	Male	0.4505
ASA scale[243]	≤2	-
	≥3	0.6057
MRC dyspnoea scale	≤2	-
	≥3	0.9075
WHO Performance status	≤2	-
	≥3	0.689
Comorbidities	0	-
	1-2	0.7447
	≥3	0.9065
Priority of surgery	Elective	-
	Emergency	0.8443
Procedure class	Other	-
	Pneumonectomy	1.2176
Diagnosis group	Benign	-
	Malignant	1.2423

Table 14. Variables used to calculate Thoracoscore
Adapted from Falcoz et al.[230]. MRC = Medical Research Council; WHO = World Health Organisation. Values for MRC dyspnoea scale and WHO performance status are detailed in appendix 3. Comorbidities included: smoking addiction, history of cancer, chronic obstructive pulmonary disease, arterial hypertension, heart disease, diabetes mellitus, peripheral vascular disease, obesity and alcoholism.

$$Logit = -7.3737 + Sum\ (beta)$$

$$Predicted\ in\text{-}hospital\ death\ rate = \frac{e^{(Logit)}}{(1 + e^{(Logit)})}$$

Equation 7. Logistic regression equation used to calculate Thoracoscore
-7.3737 is constant from Falcoz et al.[230]. Beta is calculated from values obtained from Table 14.

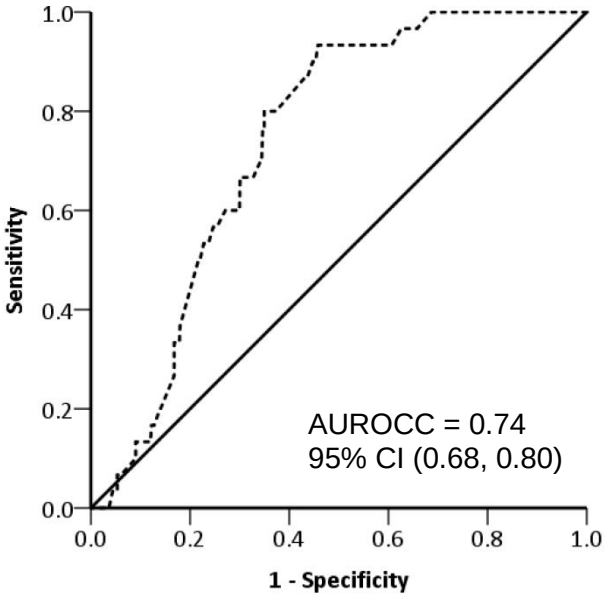

Figure 29. Receiver operating characteristic curve for prediction of ICU admission following lung resection using Thoracoscore
Dashed line AUROCC = 0.74 (95% CI 0.68-0.80, p<0.001). Solid line AUROCC = 0.5 (line of no effect).

Although 'thoracic surgery' is often thought of as 'high risk' for complications when compared with other 'non-thoracic procedures', these results demonstrate that not all lung-resection procedures are equal. In this cohort, sub-lobar resections were less likely to require ICU than lobectomy patients. Likewise, VATS procedures were less likely to require ICU than those requiring open resections. This is consistent with Thoracoscore where pneumonectomy patients are at higher risk of in-hospital death than those undergoing lesser resections.

The cause of RV failure in all settings can be divided in to three main categories; excessive preload, excessive afterload and insufficient contractility. In most cases, acute RV failure is multi-factorial and results from a combination of established disease, complicated by acute derangements in one or more of these three factors[158, 244]. In the patient undergoing lung resection, the multi factorial elements could include both patient and surgical factors. The patient factors may include diseases resulting from the common aetiological factor as their lung cancer, namely cigarette smoking. Pulmonary hypertension (PH) is common in patients with advanced COPD and some patients have 'out of proportion' PH with only mild COPD[245, 246]. Patients presenting for lung resection are also prone to atherosclerotic disease with ischaemic heart disease being common[27, 247]. These factors may make this group of patients *susceptible* to RV dysfunction.

Surgical factors such as one lung ventilation and surgical handling of the lung, may result in post-op lung injury[248]. Post-op sepsis, respiratory failure and myocardial ischaemia are also common complications following lung resection[17, 249, 250]. All of these may result in disruption of preload, afterload or contractility, and contribute to RV dysfunction and failure. In addition the commonly hypothesised increase in afterload following lung resection, may significantly contribute.

Consistent with the idea that patient factors contribute to development of RV dysfunction in the ICU, all patients with evidence of RV dysfunction had a history of significant cardiovascular and/or respiratory disease. All of the patients with RV dysfunction presented with respiratory failure requiring ventilation (which can contribute to RV dysfunction in its own right)[251] and the majority had cardiovascular instability requiring vasoactive medications. None of the patients in this cohort were admitted *immediately post-operatively* with evidence of RV dysfunction. This suggests the hypothesised increase in afterload that occurs following lung resection was not the *only* factor associated with the development of post-op RV dysfunction.

3.4.1 Strengths and limitations

A strength of this study is that it is one of the largest reported data sets looking at critical care requirement following lung resection with complete information on the patients admitted to ICU. It is also the first time the incidence of RV dysfunction in ICU following lung resection has been examined.

The investigation has limitations, primarily it is retrospective and will demonstrate association not causation. There are also confounders; though reflecting data from a large number of patients (n=1169), as the incidence of ITU admission was only 2.6%, there were insufficient ‘positive’ outcomes (ICU admissions) to allow for comprehensive multi-variable assessment of predictive variables. Despite the dataset for the cohort admitted to ICU being complete, some variables for the group not requiring ICU were missing. To account for this missing data, the number of analyses performed for any variable less than 80% complete was limited. Finally, as data on the presence of cardiac comorbidities was not recorded in our database, we were unable to calculate and compare Brunelli score for risk of ICU admission.

Despite the large denominator (of non-ICU patients and ICU patients without RV dysfunction), only seven patients had evidence of RV dysfunction in the ICU cohort, meaning detailed statistical analysis would be meaningless. It is also difficult to unpick exactly the cause of RV dysfunction. As already described, RV dysfunction is common in ICU patients without lung resection. It is therefore unknown whether the RV dysfunction observed in this cohort would have happened independently of lung resection.

As the data was reviewed retrospectively, there was a reliance on the fidelity of documentation. Many of the echocardiograms in ITU were performed on portable machines with imaging not stored and not available for further analysis. In many situations no formal report was issued. This means diagnosis of RV dysfunction was often based on the written comments of the echocardiographer. This introduced a degree of subjectivity to identification of patients with RV dysfunction.

The investigation will have been subject to selection bias. Although there was a high incidence of RV dysfunction in the group who died, these patients are more likely to have required investigations as they deteriorated. In addition, only 19 (63.3%) of all the patients admitted to ICU had echocardiography performed meaning RV function of one third of the patients is unknown. Although the remaining patients would have had low clinical suspicion, this means the incidence of RV dysfunction in ICU patients may be higher than reported here. Although it would not have been possible with the methodology employed, we have no data on RV function in the cohort not admitted to ICU. There may been patients who developed RV dysfunction, not requiring ICU interventions (ventilation and renal replacement therapy in this cohort), who were managed in the HDU or ward environment.

3.5 Conclusion

This review provides single centre data for those patients requiring unplanned ICU care following lung resection. It gives an indication of the factors that may be important in influencing the need for admission and demonstrates a favourable ICU admission and survival rate when compared to existing data. Future work should focus on the comprehensive assessment of potentially modifiable risk factors associated with unplanned ICU admission.

RV dysfunction is common in patients admitted to ICU following lung resection and is associated with a high mortality. Patients following lung resection may be at increased risk of RV dysfunction (and failure) as a result of their underlying medical history and the surgical intervention. Work is required to prospectively identify the incidence of RV dysfunction following lung resection and its impact on those patients requiring critical care support.

Chapter 4 Materials and Methods and Generic Results

4.1 Introduction

This chapter details the methods common to the imaging and biomarker studies presented in this thesis (chapters 5, 6, 7 and 8) as they were carried out on the same population.

Results common to this population, such as demographics and post-op change in functional status, are also described in this chapter.

4.2 Generic methods

4.2.1 Ethical approval

The study received ethical approval from the West of Scotland Research Ethics Committee (REC Ref: 134/WS/0055, Approval Date 16th April 2013).

4.2.2 Study setting

The study was performed at the Golden Jubilee National Hospital / West of Scotland heart and Lung Centre, Clydebank. The details of this hospital are described in section 3.2, pg 108.

4.2.3 Patient population

Patients meeting inclusion criteria were highlighted from the Wednesday elective list of the lead surgeon (Mr Alan Kirk, consultant thoracic surgeon) and were initially approached on the Friday prior to their admission when they attended the pre-op assessment clinic. Those patients not meeting any of the exclusion criteria were provided with information about the study and given written details to review prior to their admission on the Tuesday morning, the day before their surgery. Those participants providing informed consent went on to participate in the study. Inclusion criteria were; the provision of informed consent, age >16 years and planned elective lobectomy by thoracotomy. Exclusion criteria were; Pregnancy, on-going participation in any investigational research which could undermine the

scientific basis of the study, contraindications to magnetic resonance imaging[L], wedge/segmental/sub-lobar lung resection, pneumonectomy, isolated middle lobectomy and video assisted thoracoscopic surgery (VATS)/minimal access lung resection.

4.2.3.1 Justification of inclusion/exclusion criteria

Greater physiological disruption may be expected following pneumonectomy, however the numbers of this more invasive procedure are reducing and accounted for only 5.3% of the lung resections performed in the UK in 2014-15[252]. To make any findings applicable to practice we have excluded those undergoing pneumonectomy. Conversely lesser resections may involve less physiological disruption and have less of an impact on the right ventricular-pulmonary vascular unit meaning any deterioration may be more subtle. To allow any changes to be confirmed within a reasonable sample size, these patients have also been excluded. Additionally, these lesser resections (segmentectomy/wedge/sub-lobar/isolated middle lobectomy) made up only 19.7% of the lung resections performed in the UK in 2014-15, meaning lobectomy/bilobectomy accounted for the vast majority (73.5%) of lung resections performed[252].

VATS resections have increased significantly in recent years. Although VATS accounted for 16.9% of all UK lobectomies in 2011-12, by 2013-14 this had increased to 30.5%[252]. The decision to exclude VATS results from two factors. Firstly, at the time of this studies conception, the majority of lung resections were performed by thoracotomy and to ensure adequate recruitment, this type of approach was preferable. The second reason relates to the inflammatory response to lung resection; the inflammatory response is attenuated with VATS resections in contrast to thoracotomy[253]. The inflammatory response may be implicated in post-op RV dysfunction (further discussed in future work, section 10.3.1, pg 289) and although not examined in this thesis, to allow this mechanism to be explored, VATS procedures are excluded[254].

[L] i) Cardiac pacemaker, artificial heart valve, neurotransmitter, cochlear implant, ii) Aneurysm clips, iii) Metal injuries to the eye and iv) Loose metal in any part of the body.

4.2.4 Anaesthetic protocol

The intention of the study was not to alter anaesthetic, surgical or post-op management. In an attempt to standardise care as much as possible, a protocol based on the practice of the lead anaesthetist (Dr Mark Steven, consultant cardiothoracic anaesthetist) and lead surgeon (Mr Alan Kirk) was developed. This reflected the practice of the majority of the clinicians working in the Golden Jubilee National Hospital.

This involved intravenous induction and volatile maintenance of anaesthesia. For analgesia, a thoracic epidural was sited pre-operatively and maintained post-operatively with continuous infusion. Where insertion was unsuccessful, paravertebral catheters were sited intra-operatively by the operating surgeon and augmented with patient controlled analgesia (PCA) with morphine boluses. Lung isolation was achieved using a double lumen endo-tracheal tube. Ventilation was with a lung protective protocol[M]; tidal volume <8ml/kg, positive end expiratory pressure (PEEP) 0-5cm H_2O, Maximum Airway Pressure (P_{max}) limited to 30cm H_2O, Fraction of inspired oxygen (FiO_2) was titrated to maintain oxygen saturation (SaO_2) 92% to 98% along with a generally permissive approach to hypercapnia.

4.2.5 Data collection

Data were collected by the author and research nursing staff during the patients hospital admission and at 2-month clinic follow-up. Postal questionnaire was performed one year following surgery. All anonymised data were collated and stored in a password protected database created using proprietary database software (Microsoft Access® 2007, Microsoft, Washington, USA) by a research nurse (Miss Christine Groundwater) assisting with the study.

4.2.5.1 Baseline demographic data

Routine patient demographics were collected prospectively at the time of recruitment. Data were extracted from patient records and from face to face

[M] Although the protocol would not be considered 'lung protective' in the conventional sense, it was setting protocolised limits for the intra-operative care of the patient and reflected the broad practice within our institution.

interview. Information was recorded in dedicated case report forms (Appendix 2 and 3).

As part of their routine work-up for lung resection, Pulmonary Function Tests (PFT's) were performed in all patients prior to attending the Golden Jubilee National Hospital for lung resection. Where these had not been performed prior to attendance, they were performed at the GJNH by respiratory physiologists according to standardised guidelines. These are reported as absolute values and as percent predicted, this compares the participant to values obtained from population studies of healthy subjects with values matched for age, height, sex and ethnicity[255]. Parameters were collected to allow calculation of Thoracoscore[230]. This score is described in section 3.4, pg 127.

4.2.5.2 Self report of exercise tolerance and function status

Self report of functional status was collected by completion of a written questionnaire encompassing; New York Heart Association (NYHA) functional classification[256], World Health Organisation (WHO) performance status classification[257], Medical Research Council (MRC) Dyspnoea Scale[258] and the EuroQOL 5 Dimension (EQ-5D) score. Permission was obtained from EuroQOL for use of the EQ-5D score (personal communication, September 2012). These were all completed pre-operatively (pre-op), at 2-month clinic follow-up and by postal questionnaire at 1 year. Three attempts were made at postal follow-up and if no response was received then this was abandoned. The individual domains of each of these scores is provided in case report form 2 in Appendix 3.

4.2.5.3 Six minute walk testing

Six minute walk testing (6 MWT) was completed on a 30 metre flat, straight course as per American Thoracic Society (ATS) Guidelines[259]. Six MWT was completed pre-op and where the participant was able to complete the test, at 2-month follow-up. As per ATS guidelines, pulse oximetry was performed for the duration of the study and emergency medical equipment was immediately available.

Small changes in 6MWT distance can be attributed to the inherent source of variation within the test itself, such as participant motivation and a training effect from having previously performed the test. To include those patients with

significant *clinical* changes in functional status, we chose to use the minimal clinically important distance (MICD) for patients with severe COPD, 26±2m. Although normally utilised to measure *improvement*, the MID is the change in 6MWT distance where patients sense an actual change in their functional status and is essential for determining the effectiveness of interventions in clinical trials[260]. A MID has not been validated for patients following lung resection.

4.2.5.4 Imaging

Non-contrast cardiovascular magnetic resonance (CMR) and Trans-thoracic Echocardiographic (TTE) imaging were performed contemporaneously. Imaging took place pre-operatively (pre-op), on post-op day (POD) 2 and at 2-month clinic follow-up. Full details of CMR imaging, including protocol and analysis are described in section 4.3. Full details of echocardiographic imaging, including protocol and analysis are described in sections 4.4 and 4.5.

4.2.5.5 Laboratory sampling

Blood sampling was performed pre-op (prior to induction of anaesthesia), immediately post-op (once extubated in recovery area) and then on the mornings of POD 1 and 2, and at 2-month follow-up. The analysis of B-Type Natriuretic Peptide (BNP) and Highly Sensitive Troponin-T (HS TnT) is described in section 4.6, pg 160.

4.2.5.6 Intra-operative clinical data

Intra-operative data were collected continuously and automatically for the duration of the anaesthetic by the 'RECALL Anaesthetic Intra-operative Management System' (AIMS) electronic charting system (Informatics Clinical Information Systems Limited, Glasgow). Duration of surgery was taken as the duration of the end tidal carbon dioxide ($ETCO_2$) trace. The appearance of CO_2 represents intubation and it's disappearance, represents extubation. Duration of one lung ventilation (OLV) was prospectively recorded in the RECALL AIMS electronic anaesthetic charting system by the primary anaesthetist or where this did not happen, from manual inspection of the airway pressure and tidal volume vs. time curves.

4.2.5.7 Post-operative clinical data

Post-op clinical data was collected as described above (exercise tolerance, 6MWT, CMR imaging, echocardiography and laboratory sampling) along with data describing the patients critical care and hospital stay.

Critical care stay parameters were continuously and automatically recorded (at approximately 2 minute intervals) by the ICU clinical information system (Centricity CIS; GE Healthcare©, Buckinghamshire, UK). This systems allows accurate recording of multiple parameters combined with electronic patient notes. Haemodynamic variables included; heart rate, cardiac rhythm (manually inputted by nursing staff), blood pressure and central venous pressure. Respiratory variables included; continuous oxygen saturations (SaO_2), respiratory rate, supplemental oxygen administered, ventilator settings and arterial blood gas results. Other data collected by this system included; fluid administration (type and volume), urine output, cumulative fluid balance and medication prescriptions (dose and / or infusion rate). This system automatically calculates fluid balance and cumulative totals are reset at 07:59 in the morning, meaning fluid balance is for the 24 hours prior to this point. Requirement for vasoconstrictor (typically nor-adrenaline) during critical care stay was documented. Arrhythmia was recorded as per patient notes (CIS or paper copy) and where possible, confirmed with a 12 lead electrocardiogram (ECG).

Length of high dependency unit (HDU) stay was calculated as the time from the first recorded oxygen saturation on CIS to the end of *continuous* recording of oxygen saturations. This was chosen as a pragmatic solution to the problem of defining exact discharge time from HDU. Discharge from any critical care environment can vary from the time the patient is actually *ready* to leave. This is often for logistical reasons, including the time of day (patients tend not to be discharged overnight) and the availability of ward beds. The change of continuous to intermittent measurement is believed to reflect the time of stepping down the care requirement of the patient (from HDU/level 2 care, to ward/level 1 care[229]).

Also for pragmatic reasons, hospital stay for the purpose of this study was calculated as *post-op* hospital stay. Although the majority of patients are admitted to the Golden Jubilee National hospital the day before their surgery, some are

admitted earlier for logistical reasons e.g. as the hospital is a referral centre for the West of Scotland (including rural and island communities), some patients have significant distances to travel and are admitted earlier.

4.2.6 Data synthesis and statistics

Data are presented as mean (SD) or median (IQR) as appropriate to distribution. Normality was assessed with visual inspection of the data and the Shapiro-Wilk test ($p>0.05$). Where possible, transformations were made as appropriate for data distribution, where it was not possible to transform to a normal distribution, a non-parametric test was used. Inter and intra-observer variability (reproducibility and repeatability) were assessed with the intraclass correlation coefficient (ICC) for both absolute agreement and consistency, and the coefficient of variation (COV). Coefficient of variation is a measure of variability and was defined as the ratio of the standard deviation to the mean (Equation 8)[261].

$$Coefficient\ of\ Variation\ (\%) = \frac{Standard\ Deviation}{Mean} x\ 100$$

Equation 8. Coefficient of Variation

The ICC and COV were interpreted as described in Table 15. Bland Altman plots were created to assess bias and any systematic differences between observers or measures[186].

Coefficient of Variation	Intraclass correlation coefficient	Interpretation
>15%	<0.5	*"poor"*
10-15%	0.5-0.75	*"moderate/acceptable"*
<10%	0.75-0.90	*"good"*
	>0.90	*"excellent"*

Table 15. Quantitative interpretation of the intraclass correlation coefficient and coefficient of variation
From Holm et al.[262] and Koo et al.[263].

Changes over time for normally distributed data were assessed using one-way repeated measures analysis of variance (ANOVA) with post-hoc comparisons using the paired t-test. Changes over time for non-parametric data were assessed using Friedman's test with post-hoc pairwise comparisons using the Wilcoxon rank sum test. Comparisons of parametrically distributed data between unpaired groups was using an independent-samples t-test or one way analysis of variance as appropriate. Comparisons of non-parametrically distributed data between unpaired groups was using the Mann-Whitney U-test or Kruskal-Wallis test as appropriate. Categorical variables were compared using the Chi-squared or Fisher's exact tests. The McNemar test was used to determine difference between paired dichotomous variables.

All associations were visually inspected and assessed using Pearson's correlation coefficient or Spearman's correlation coefficient as appropriate. The ability of continuous variables to predict binary outcomes was assessed using the area under the Receiver Operating Characteristic curve (AUROCC). The optimal cut-off of a continuous variable was defined by the point at which the sum of sensitivity and specificity was maximal (Youden's index). Positive and negative predictive values (PPV and NPV respectively) were also calculated as shown in Equation 9 and Equation 10 .

$$PPV = \frac{number\ of\ true\ positives}{number\ of\ true\ positives + number\ of\ false\ positives}$$

Equation 9. Positive predictive value (PPV)

$$NPV = \frac{number\ of\ true\ negatives}{number\ of\ true\ negatives + number\ of\ false\ negatives}$$

Equation 10. Negative predictive value (NPV)

For assessment of association between variables with repeated measures made in the same patients at multiple time points, analysis of covariance (ANCOVA) was performed allowing within-subject correlation to be partitioned out[264]. The strength of association between variables obtained from correlation coefficients (Pearson's or Spearman's) are interpreted as described in Table 16, pg 140.

Correlation coefficient (r)	Interpretation
0-0.19	*"very weak"*
0.20-0.39	*"weak"*
0.40-0.59	*"moderate"*
0.60-0.79	*"strong"*
0.80-1	*"very strong"*

Table 16. Interpretation of strength of association by correlation coefficients
From BMJ.com[265].

Statistical analyses were performed using SPSS for Windows, version 22 (IBM Corp, Armonk, NY, USA). A p-value <0.05 was considered statistically significant and absolute p values are reported. When SPSS produced an output of p=0.000, the p-values is presented as p<0.0005. No adjustments were made for multiple comparisons.

4.3 Cardiovascular magnetic resonance assessment of right ventricular function

4.3.1 Introduction

Given the methodological concerns regarding the techniques used to assess RV function in previous studies and ongoing uncertainty about mechanism of RV dysfunction (section 2.4, pg 104), further work using validated techniques was required to understand the RV response to lung resection. As described in chapter 1, cardiovascular magnetic resonance (CMR) is the non-invasive reference method for assessment of RV structure and function and has not yet been used to sequentially assess RV function in a lung resection cohort[46, 266]. The aim of this investigation is to provide a comprehensive understanding of the volumetric changes in the RV following lung resection. By using a volumetric estimate of RV-PA coupling (1.2.3.7. pg 38) the matching of ventricular performance and arterial load following lung resection was assessed.

The role of patient and surgical factors on post-op changes in RV function was explored and the potential impact of RV dysfunction in terms of short and long term (up to one year) morbidity will be investigated.

4.3.2 Methods

CMR imaging was performed pre-op, on POD 2 and at 2-month follow up. Where possible, pre-op CMR imaging was performed the day before surgery but in a proportion of cases, due to MRI unavailability, imaging was only possible on the morning of the operative day. In these situations the case was scheduled as part of an afternoon list. Following surgery, CMR imaging took place on the afternoon of POD 2 and when the patient returned for 2-month clinic follow-up.

4.3.2.1 Power analysis

The primary outcome of the study was to determine a change in RVEF from pre-op to POD 2 using CMR. POD 2 was chosen as the time for post-op CMR imaging as previous work (using alternative methodology) consistently suggested a decrease in RVEF on POD 2[163, 170, 174]. Although the validity of this work has been questioned, these studies describe an *absolute* fall in RVEF of 6-9% by POD 2[163, 176]. It was prudent therefore that this study was powered to detect a change of at least this magnitude.

Power calculation was carried out in consultation with the Robertson Centre for Biostatistics (University of Glasgow). Based on a 2-sided, paired t-test with a significance level of 5%, a study of 19 patients would have 80% power to detect a deterioration in RVEF of 6%. Allowing a margin of 30% for withdrawals, 28 patients were to be recruited.

4.3.2.2 Image acquisition

All CMR imaging was performed at the Golden Jubilee National Hospital using a 1.5 Tesla Siemens Avanto (Siemens, Germany) whole body scanner by band 7 Health and Care Professionals Council (HCPC) accredited advanced practitioner radiographers according to a standardised protocol. All patients completed a short safety questionnaire about suitability for CMR imaging prior to study recruitment and consent, however before entry in to the CMR scanning room, patients were asked to complete and sign a departmental safety questionnaire to ensure there were no absolute contraindications to CMR imaging. Patients were dressed in a hospital gown or their own pyjamas and were asked to lie on the examination table which was remotely removed from the bore of the scanner to an accessible

position. Adhesive pads for continuous 3-lead ECG monitoring were placed on the patient's chest and a pulse oximeter was positioned on the patient's finger allowing continuous oxygen saturation monitoring. The patient was provided with an emergency buzzer and protective ear defenders. The scanning table was then positioned within the bore of the magnet and staff retreated to the CMR control room. Proper functioning of the microphone and headphones, that allow direct communication between patient and operator, was verified prior to the commencement of image acquisition. There were no deviations from this methodology for both the pre-op and two-month post-op scans.

Imaging on POD 2 followed a similar pattern except for a few differences as a result of recent surgery. During the procedure of thoracotomy and lung resection, surgical clips and linear stapling devices are required. To ensure that all implanted equipment was suitable for immediate MR imaging, a record of all equipment used intra-op was collected by the surgical team so that CMR safety could be verified with the manufacturer. All equipment confirmed by the manufacturer as being safe was 'signed off' by a radiologist with an interest in MR imaging (Dr Des Alcorn, consultant radiologist). The majority of cases used similar equipment and a list of 'confirmed MR safe' equipment was developed. In the event of new equipment being used, MR safety was confirmed with the manufacturer, signed-off by Dr Alcorn and added to the confirmed MR safe list. As the patients had been safely scanned on POD 2, there were no concerns with scanning at 2-months, unless the patient had undergone an additional procedure in the interim.

Chest drainage is required following lung resection to remove any air and liquid that may have collected in the thoracic cavity as a result of surgery. At the Golden Jubilee National Hospital, chest drainage is usually performed using the Thopaz (Mendela, Switzerland) thoracic drainage system. This is an electronic drainage system that is *not* MR safe. In those patients where chest drainage was still required at the time of scanning, the drain was changed to an underwater seal chest drain shortly before the scan and changed back immediately after. The chest drain was secured to the side of the MR examination table while in the scanner.

Where feasible, all infusions were discontinued for the short duration of CMR scanning. This was to minimise the number of patient connections whilst in the scanner. If possible, for example in the case of epidural infusions, this was

discontinued immediately before scanning and reinstituted immediately after scanning. In the specific case of an epidural infusion, this was often with an additional 'top up' dose post scan. Where it was not possible to discontinue infusions, for example when the patient required inotropes or vasoconstrictors, MR safe syringe pumps were available. All patients scanned on post-op day 2 were escorted throughout by a member of the research team. This was either the author or a research nurse with experience in critical care. All POD 2 imaging was completed 'in hours' with immediate availability of a consultant thoracic surgeon for management of potential complications.

ECG-gated fast imaging steady state free precision cines (TrueFISP, Siemens) were utilised throughout. Methodological details of particular importance include standardised imaging parameters of repetition time, echo time, flip angle, voxel size, field of view = 4.3ms, 1.2ms, 60^{o}, 1.4 x 1.4 x 6mm, 340mm respectively; 6mm imaging slices were used with a 4mm interslice gap. Short axis imaging was performed during breath holds and initiated at the atrioventricular valve plane, identified from a horizontal long-axis views, and propagated sequentially to the cardiac apex to provide complete coverage of both ventricles.

On completion of each scan, the images were saved to the hard-drive of the scanner and backed up to the hospitals clinical imaging network. At completion of the study, all images were randomised and anonymised by a member of the radiography staff (Miss Vanessa Orchard) according to a random number sequence generated using the 'RAND' function of proprietary spreadsheet software (Microsoft Excel® 2007, Microsoft, Washington, USA). Images were stored on CD's (10 per disc) for batch analysis. Two copies of the protocol to allow identification were stored in sealed envelopes, one in the radiography department and another in a locked drawer within the anaesthetic research office, both at the Golden Jubilee National Hospital.

4.3.2.3 Image analysis

To ensure no incidental findings of clinical importance were missed, safety reporting of all anonymised CMR imaging was performed by Dr John Payne (consultant cardiologist and lead for cardiac imaging at the GJNH), with a report generated and placed in the patient record. Post-processing software using

manual planimetry was utilised to determine left ventricular and RV volumes. Randomised and anonymised images were dual reported by the author and by his co-investigator Dr Alex Arthur (a clinical research fellow in cardiothoracic anaesthesia). Initial training in assessment was performed by Dr David Corcoran (Clinical Research Fellow in CMR imaging, with level 3 European Association of Cardiovascular Imaging certification in CMR imaging)[N] [267] who also assisted with ongoing scan analysis and held the deciding vote in any disagreements over RV contours. All analyses were performed using proprietary software (Argus, Siemens, Erlangen, Germany).

For assessment of intra-observer variability, ten of the randomised and anonymised scans were selected for repeat analysis by Dr Alex Arthur. This was performed more than one month after first analysis.

The images making up the 'short axis stack' from each anonymised patient were loaded on to the Argus program from the CD copy of each file. At the time of image acquisition, if there are concerns about the image quality or there is evidence of artefact, duplicate scans are performed. Any duplicate 'slices' from the stack were identified and removed. An example of the analysis screen from the software is provided in Figure 30, pg 145.

[N] Level 3 competency is required for individuals wishing to perform, interpret, and report CMR studies fully independently, to lead a CMR laboratory and to supervise CMR training programmes in an accredited CMR training centre.

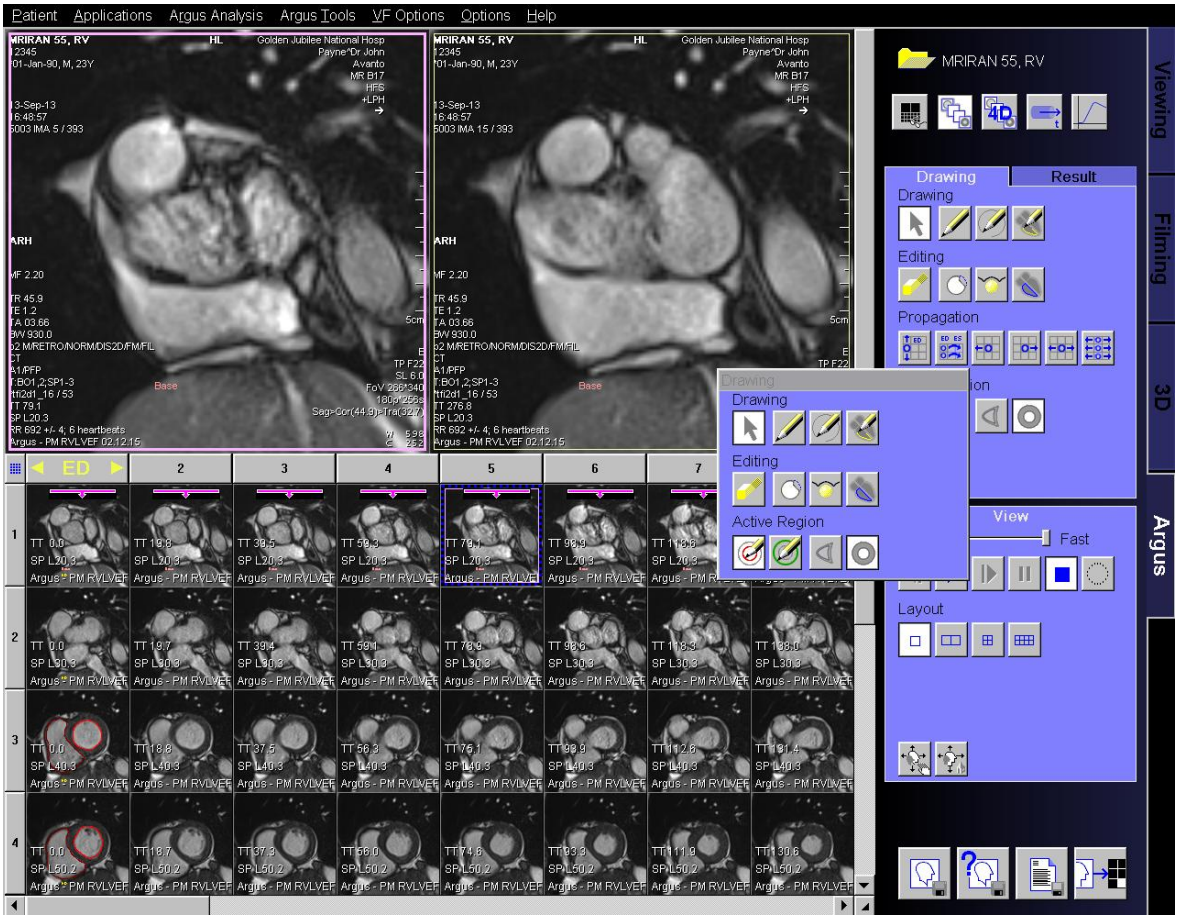

Figure 30. Screen shot from Argus analysis software
Each row of images represents a loop of cine images acquired during one cardiac cycle at consecutive slice positions. This begins at the base of the heart (top of screen) and moves apically to the bottom of the heart (bottom of screen). The first image on each row is the end-diastolic image (indicated by yellow ED at top of left hand column).

Image acquisition is triggered by R-wave deflection on the ECG, so the end diastolic image was determined automatically by the software as the first image within each loop of cine images. The full image stack was assessed and the end systolic image was determined manually as the point where the LV blood pool was smallest. The same images were used for determination of both LV and RV volumes at end diastole and end systole.

The methods for assessment of LV and RV volumes are standard in clinical MR practice[114]. Following identification of the end systolic and end diastolic images, the endocardial border of the RV was contoured in both diastole and systole. The RV outflow tract up to the pulmonary valve (where it was visible) was included in the analysis. As per convention, to improve reader reproducibility, the trabeculations of the RV were ignored and a smooth endocardial border drawn (Figure 31, pg 146)[114].

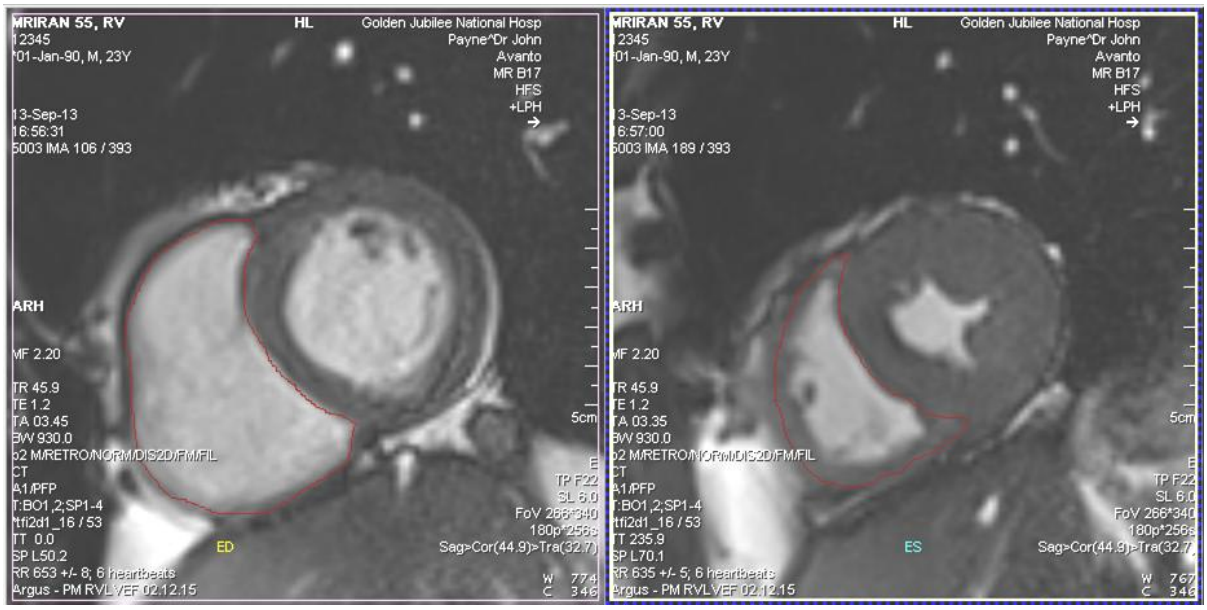

Figure 31. Defining endocardial borders of the right ventricle
The endocardial surface of the right ventricle at end diastole and end systole. End diastole (identified by the yellow 'ED') is on the left with the smooth endocardial border identified by the red line. End systole (identified by the blue 'ES') is on the right with the endocardial border identified by the red line.

Definition of the basal ventricular slice can prove difficult, with large volumes erroneously included or excluded, leading to errors in analysis. To overcome this problem, once the basal slice was identified, it was cross-referenced with the horizontal long axis view to ensure the slice was not atrial in origin (Figure 32).

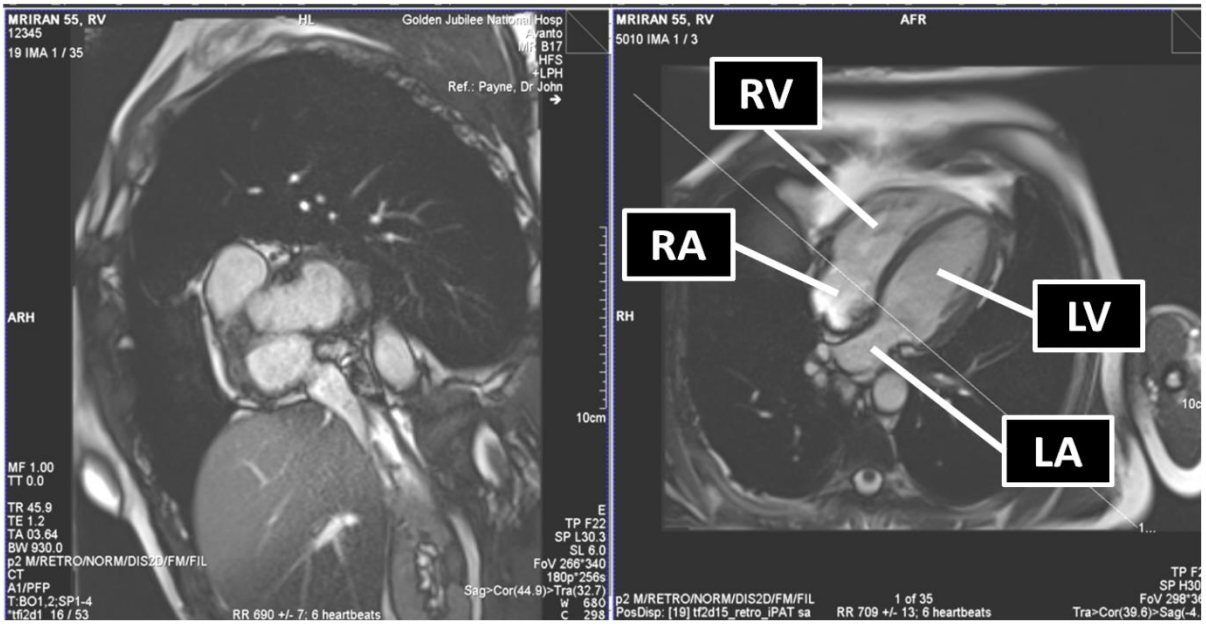

Figure 32. Cross referencing of right ventricular basal slice
Comparison of a short axis image (left) with the horizontal long axis image (right) to determine if the image is ventricular in origin. In this example the structures are not right ventricular in origin and would not be included. RA = right atrium, RV = right ventricle, LV = left ventricle, LA = left atrium.

A similar process took place for determination of LV volumes with the endocardial border of the LV being determined in both systole and diastole. The papillary muscles were included as part of the myocardial blood pool (Figure 33); this is accepted practice as long as reference values using the same approach are used[114]. The basal slice for the LV was determined as the most basal slice surrounded by 50% or more of ventricular myocardium. Where there was any difficulty in defining the LV basal slice a similar process as described for the RV was used where the slice was cross referenced against the horizontal long axis image.

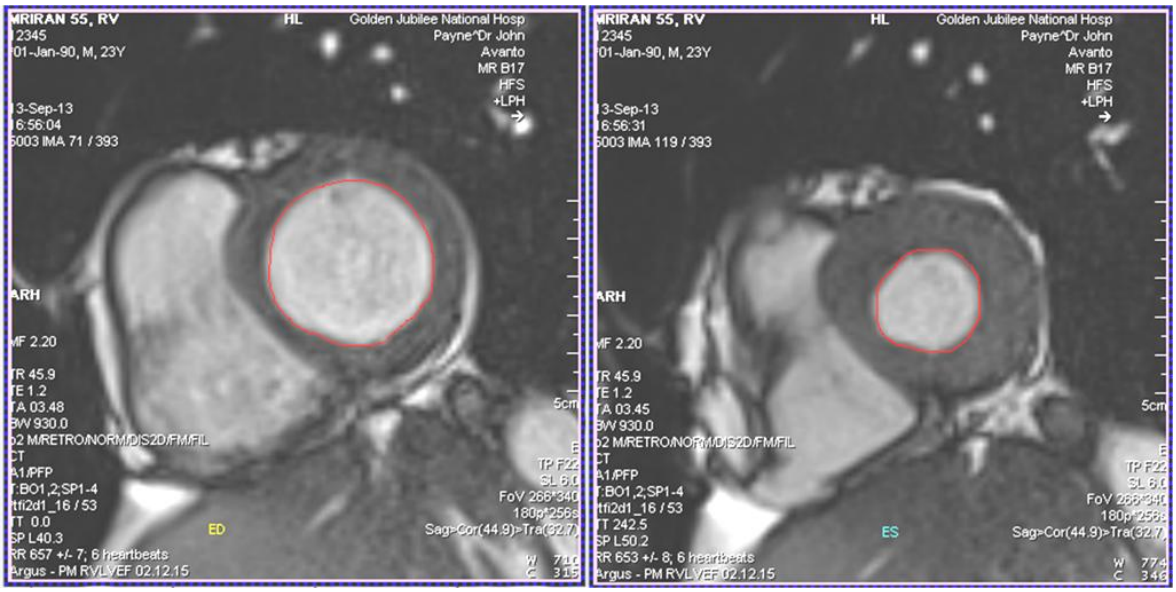

Figure 33. Defining endocardial borders of the left ventricle
The endocardial surface of the left ventricle at end diastole and end systole. End diastole (identified by the yellow 'ED') is on the left with the endocardial border identified by the red line. End systole (identified by the blue 'ES') is on the right with the endocardial border identified by the red line.

Following tracing of the myocardial borders for each slice, an automated calculation was carried out, using the sum of discs method, to obtain; Right and left end systolic volume (ESV) and end diastolic volume (EDV). From these, Right and left stroke volume (SV) and ejection fraction (EF) are automatically calculated (Equation 11 and Equation 12, pg 148).

$$Stroke\ Volume\ (ml) = End\ Diastolic\ Volume\ (ml) - End\ Systolic\ Volume\ (ml)$$

Equation 11. Stroke Volume

$$Ejection\ Fraction\ (\%) = \left(\frac{Stroke\ Volume\ (ml)}{End\ Diastolic\ Volume\ (ml)}\right) x\ 100$$

Equation 12. Ejection Fraction

4.4 Echocardiographic assessment of right ventricular function following lung resection

4.4.1 Introduction

Although the non-invasive reference method for assessment of RV function is CMR, the most commonly used tool in clinical practice is trans-thoracic echocardiography (section 1.3.2.2, pg 46). This investigation will describe changes in commonly used echocardiographic parameters for assessment of RV systolic function following lung resection and will also attempt to validate these methods in this population by comparing them to contemporaneously obtained CMR results

In the American Society of Echocardiography guideline for assessment of the right heart in adults, Rudski et al.[128] recommends using a number of measures for assessment of RV systolic function, including; Fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and S' wave velocity at the tricuspid annulus (S'Wave). This guideline also recommends measurement of pulmonary artery systolic pressure (PASP) and an estimation of right atrial pressure from inferior vena cava (IVC) size and collapse. Additional measures depend on clinical scenario but as pulmonary artery acceleration time (PAAT) can be used to estimate mean pulmonary artery pressure (MPAP), it is measured here.

4.4.2 Methods

Trans thoracic echocardiography (TTE) was performed contemporaneously to CMR imaging (pre-op, POD 2 and at 2-month clinic follow-up). Effort was taken to ensure TTE was performed as close in time to CMR as possible. This was often on the same transfer from the ward or high dependency unit. e.g. patients went from the ward to CMR imaging, then to TTE imaging (or vice versa) and then back to the ward.

4.4.2.1 Image acquisition

All TTE imaging was performed at the Golden Jubilee National Hospital on a Vivid E9 cardiovascular ultrasound system (GE Healthcare, Chicago, Illinois, USA) using a M5Sc-D transducer with a frequency of 1.5 to 4.6 MHz. All studies were performed by band 7 British Society of Echocardiography (BSE) accredited cardiac physiologists according to a standardised protocol[268]. Two-dimensional recordings were collected with frame rates ranging from 60 to 80 frames per second. Four consecutive cardiac cycles were recorded for further analysis. Three lead ECG analysis took place simultaneously.

Where possible, allowing for recent surgery and chest drain placement, imaging took place in the lateral decubitus position. Two dimensional images were obtained from the standard parasternal and apical 4-chamber (A4C) views. Additional focussed RV imaging was obtained from the A4C view. A sub costal view was utilised to obtain images of the inferior vena cava. Colour Doppler imaging was performed of all valves. Continuous wave Doppler was performed of tricuspid valve (TV) regurgitation in all available views. Pulsed wave Doppler analysis of the RV outflow tract and TV inflow was performed. Pulsed tissue Doppler imaging was performed of the TV annulus and RV free wall. M-mode analysis could be obtained offline from 2D scans. The full protocol incorporated all aspects required for a comprehensive echocardiogram as recommended by the British Society of Echocardiographers[269]. There were no deviations from this methodology for any of the scanning time points.

4.4.2.2 Image analysis

At completion of the study, all images were randomised and anonymised by the author according to a random number sequence generated using the 'RAND' function of proprietary spreadsheet software (Microsoft Excel® 2007, Microsoft, Washington, USA). More than one month following randomisation and anonymisation, all images were dual reported by the author and by a band 7, BSE accredited cardiac physiologist. All image analysis was performed offline using proprietary software (EchoPAC, GE Healthcare, Chicago, United States). Where appropriate, end diastole was determined as the peak of the R-wave and end-systole as the end of the T-wave. All analyses were performed as described in international consensus guidelines referred to above[128]. Only analysis of those

parameters examined as part of this thesis are described in this chapter. For assessment of intra-observer variation, 10 scans were chosen for repeat analysis by the author. This happened more than one month following their first analysis.

4.4.2.2.1 Fractional area change

Fractional area change (FAC) was calculated from a standard apical 4-chamber (A4C) TTE view. The RV endocardium was traced from the annulus, along the free wall to the apex, and then along the interventricular septum back to the annulus. Care was taken to trace the free wall beneath trabeculations (Equation 13 and Figure 34).

$$Fractional\ area\ change\ (\%) = 100\ x \left(\frac{End\ diastolic\ area - End\ systolic\ area(cm^2)}{End\ diastolic\ area\ (cm^2)} \right)$$

Equation 13. Fractional area change

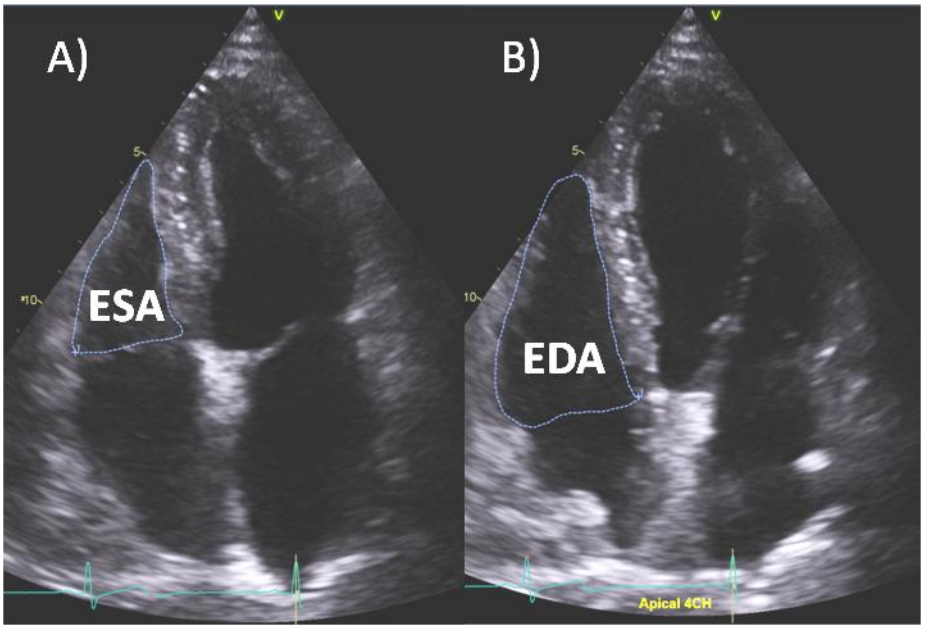

Figure 34. Right ventricular fractional area change (FAC)
Contouring of right ventricle during A) End-systolic area (ESA) and B) End-diastolic area (EDA). Area in A) = 8.8cm^2 Area in B) = 17.2cm^2 giving FAC of 48.8%.

4.4.2.2.2 Tricuspid annular plane systolic excursion

Tricuspid annular plane systolic excursion (TAPSE) was obtained from a standard A4C TTE view by placing an M-mode cursor across the lateral tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole (Figure 35).

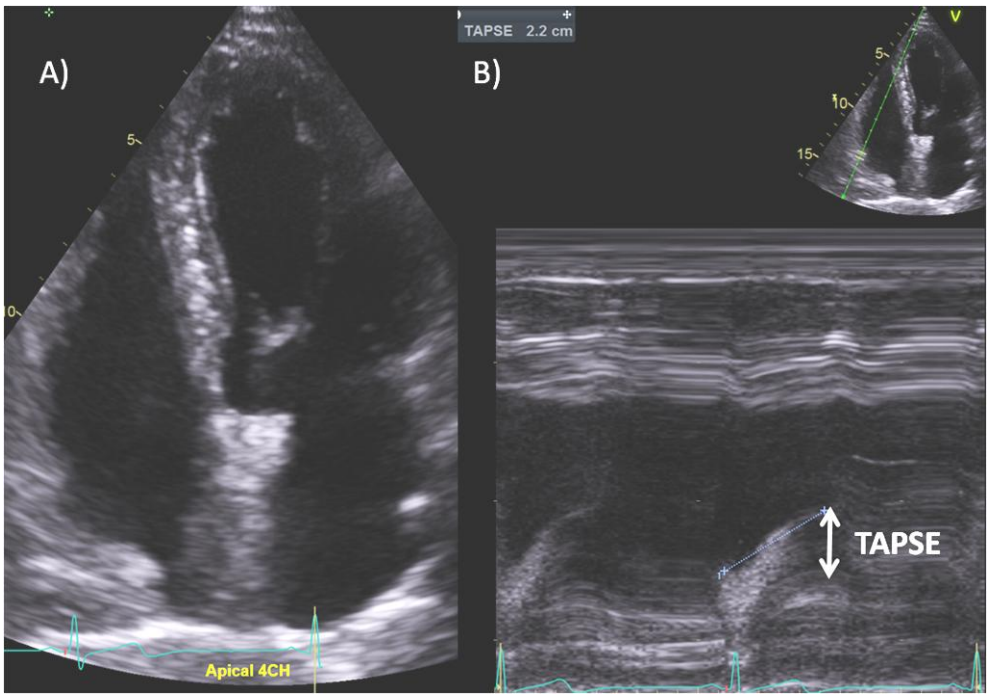

Figure 35. Tricuspid annular plane systolic excursion (TAPSE)
A) Apical 4-chamber view B) M-mode cursor placed across lateral tricuspid annulus with TAPSE of 2.2cm.

4.4.2.2.3 S' wave velocity at the tricuspid annulus (S' wave)

S' wave was obtained by pulsed Doppler analysis of the tricuspid annulus or basal segment of the RV free wall from an A4C TTE view (Figure 36A). Velocity profiles were produced for the whole cardiac cycle and S' taken as the highest systolic velocity (Figure 36B). Care was taken not to over gain the Doppler envelope.

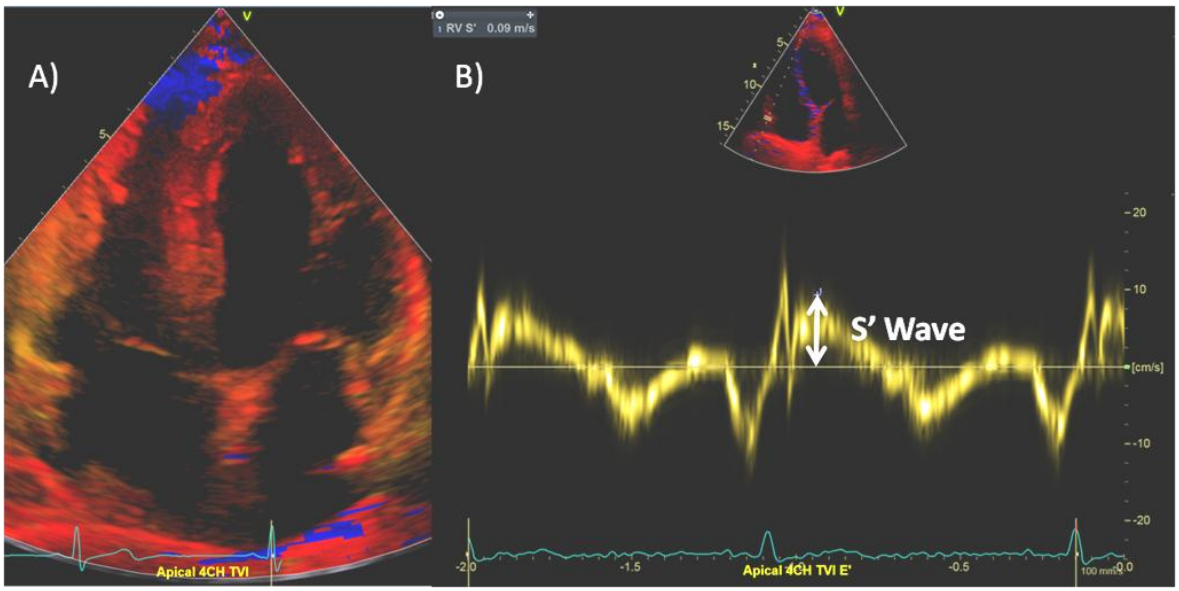

Figure 36. S' wave velocity of the tricuspid annulus (S' wave)
A)Pulsed tissue Doppler of apical 4-chamber view B) Velocity profile with region of interest placed at lateral tricuspid annulus. S' wave of 9cm/s.

4.4.2.2.4 Inferior vena cava diameter

Right atrial pressure was estimated from inferior vena cava (IVC) diameter and collapse (Figure 37A). An M-mode cursor was placed across the IVC with diameter measured at end expiration and following a 'sniff' (Figure 37B). Care was taken to ensure that any change in diameter was not the IVC translating in to another plane. An IVC diameter of ≤2.1cm that collapses >50% with a sniff was interpreted as reflecting a RAP of 3mmHg. An IVC diameter of ≥2.1cm that collapses >50% with a sniff, or an IVC diameter of ≤2.1cm that collapses <50% with a sniff, was interpreted as of 8mmHg. An IVC diameter of >2.1cm that collapses <50% with a sniff was interpreted as 15mmHg[128].

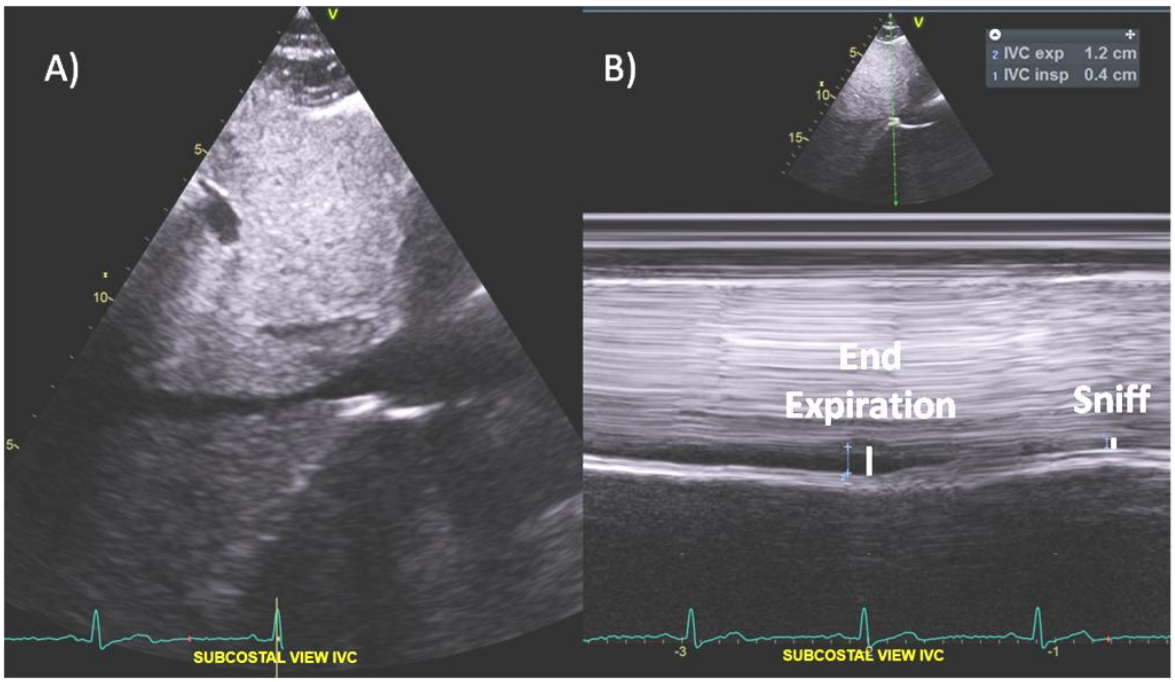

Figure 37. Inferior vena cava (IVC) diameter and collapse
A) Sub-costal view with IVC B) M-mode cursor placed across IVC with measurement during end expiration and during sniff. IVC diameter at end expiration = 1.2cm, IVC diameter during sniff = 0.4cm (collapse of >50%) giving a right atrial pressure of 3mmHg.

4.4.2.2.5 Pulmonary artery systolic pressure (PASP)

Continuous wave Doppler was used to assess the tricuspid regurgitant jet (TRJ) velocity. The TRJ was interrogated from all available views and measurements taken from the signal with the highest velocity (Figure 38A & B). Pressure gradient across the tricuspid valve was estimated with the simplified Bernoulli equation (Equation 14). With the addition of estimated right atrial pressure (as estimated from Inferior Vena Cava diameter), RVSP was determined (Equation 14). In the absence of RV outflow tract or pulmonary valve obstruction, this is widely considered an estimate of pulmonary artery systolic pressure (PASP).

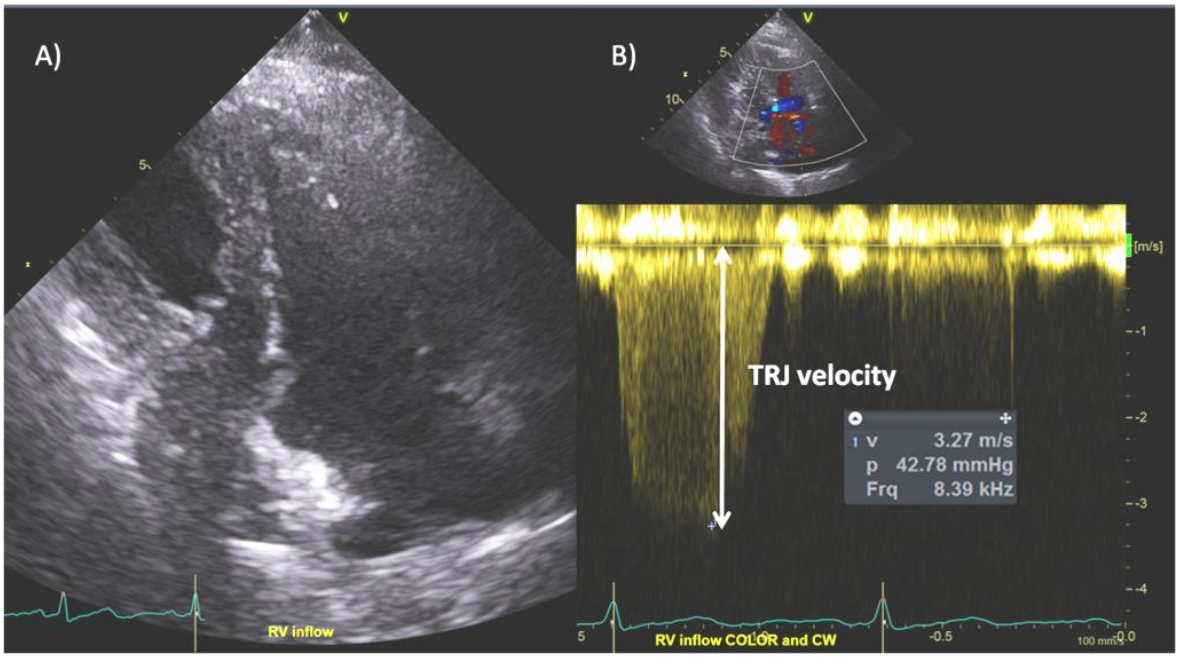

Figure 38. Tricuspid regurgitant jet (TRJ)
A) RV inflow view (right ventricle at top right of image and right atrium at bottom right of image with tricuspid valve in middle) B) Continuous wave Doppler interrogation of tricuspid valve. Peak TRJ velocity = 3.27m/s giving a gradient of 42.8mmHg.

$$Right\ ventricular\ systolic\ pressure\ (mmHg) = 4(peak\ TRJ\ velocity)^2 + RAP$$

Equation 14. Right Ventricular Systolic Pressure/ Pulmonary artery systolic pressure (PASP)
TRJ = Tricuspid regurgitant jet, RAP = Right Atrial Pressure.

4.4.2.2.6 Pulmonary artery acceleration time (PAAT)

Pulmonary artery acceleration time (PAAT) was obtained from pulsed Doppler analysis of the pulmonary artery. PAAT was quantified as the interval between onset of flow and peak flow (Figure 39A & B).

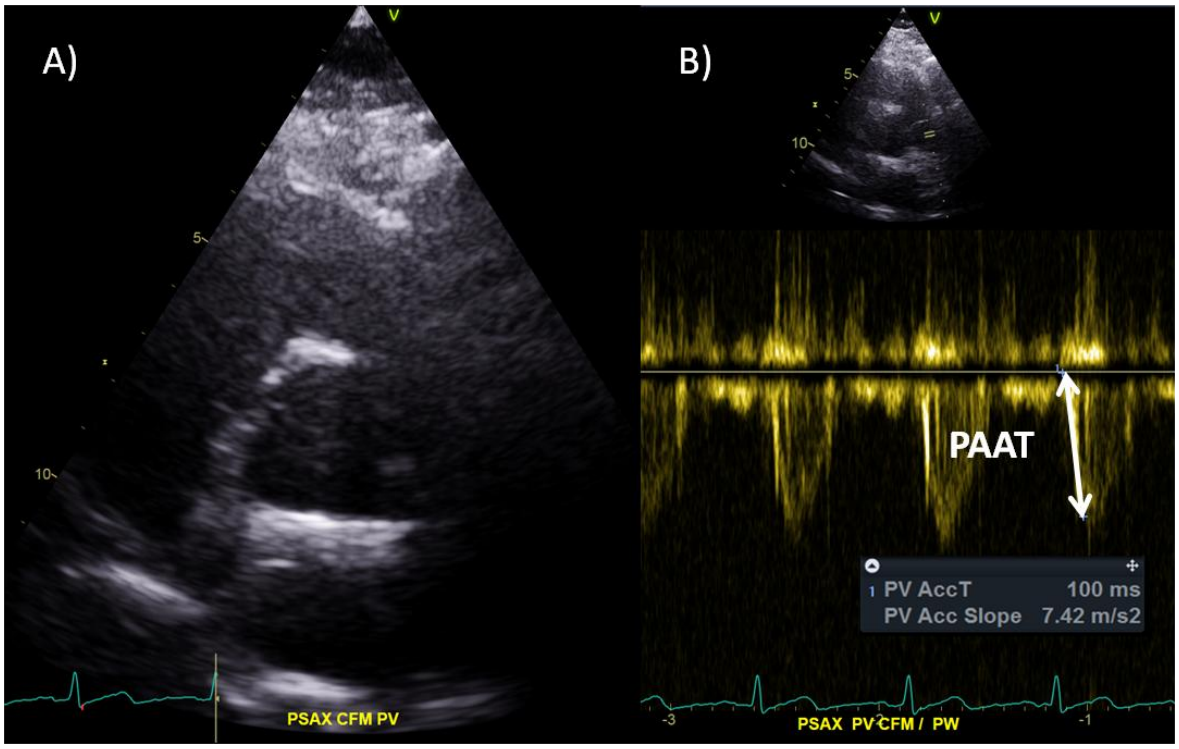

Figure 39. Pulmonary artery acceleration time (PAAT)
A) Parasternal short axis view of right ventricular outflow track, pulmonary valve and pulmonary artery B) Velocity profile with PAAT measurement of 100ms. White arrow indicates the gradient from onset of flow to peak flow with PAAT measured as the time (x-axis) between the points.

4.5 Two dimensional speckle tracked strain assessment of right ventricular function

4.5.1 Introduction

As described in section 1.3.2.3.5, pg 56, speckled tracked strain echocardiography allows for angle independent assessment of RV deformation parameters and has been shown to overcome some of the difficulties associated with other echocardiographic measures of RV function. RV strain has been advocated as a less load-dependent method of assessing RV function and may yield further information regarding contractility following lung resection[270]. This investigation will describe the changes in RV *global* peak longitudinal strain (RV-GPLS, incorporating the free wall and the septum) and RV *free wall* peak longitudinal strain (RV-FWPLS) following lung resection.

Previous work in other populations has shown these two parameters have a strong association with $RVEF_{CMR}$ and that they have excellent predictive capability for poor RV function. This study will seek association of RV-GPLS and RV-FWPLS with $RVEF_{CMR}$ in this population and if evident, assess their predictive capability for poor RV function as determined by $RVEF_{CMR}$.

4.5.2 Methods

4.5.2.1 Image acquisition

As described in section 4.4.2.1, pg 149, apical four-chamber views were obtained using conventional two-dimensional grey scale echocardiography at a frame rate of 60-80 frames per second. Four consecutive cardiac cycles were recorded and care was taken to ensure the best visualisation of the RV, allowing accurate delineation of the endocardial border.

4.5.2.2 Image analysis

Off-line analysis of speckle tracked strain of the RV was performed on randomised and anonymised images using semi-automated, proprietary analysis software (EchoPAC, GE Healthcare, Chicago, United States). Analysis of all images was performed by the author. For assessment of inter-observer variability, Dr Piotr Sonecki (Consultant cardiologist with a special interest in imaging), agreed to the

dual reporting of eight randomised and anonymised scans. For assessment of intra-observer variability, 19 (one quarter of the total performed) randomised and anonymised scans were selected for repeat analysis more than one month following their first analysis. Where there was any discrepancy in results of imaging (different strain results or inability to obtain global and/or free wall strain due to image quality), these scans were reviewed by both the author and Dr Sonecki to assess potential causative factors. Where there was an ongoing disagreement, Dr Sonecki had the casting vote.

From A4C echocardiographic video loops, the software automatically stops at end systole by automatic identification of the end of the T-wave. The region of interest (ROI) of the RV was defined by tracking the endocardial border of the free wall and septum (Figure 40A, pg 158). The ROI of the RV consists of six segments and the width was adjusted to fit the wall thickness. Appropriate tracking was signified by the software (Figure 40B) and segments with insufficient tracking were excluded. The endocardial border was re-drawn if there were concerns about contouring and it looked as though the segment had been inappropriately excluded. The process was then repeated for the RV free wall only (Figure 41A & B, pg 159). Following this process and approval of each of the segments, a strain output with strain curves was produced by the software (Figure 40C and Figure 41C). RV-GPLS was obtained by averaging values for six segments and RV-FWPLS was obtained by averaging values for the three free wall segments. In the case of segment exclusion due to inability to achieve adequate tracking, values were averages of the remaining segments.

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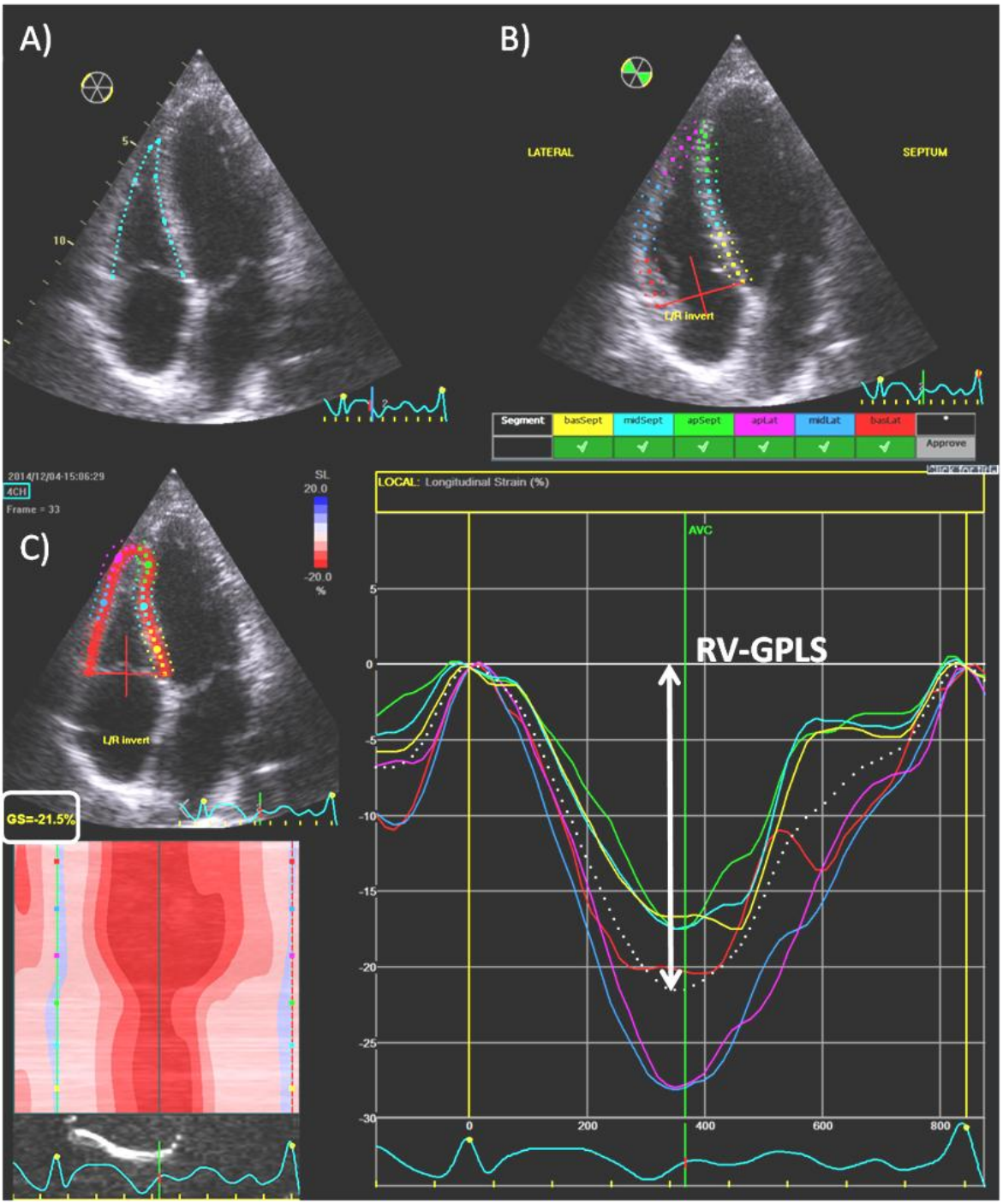


Figure 40. Two dimensional right ventricular global peak longitudinal strain (RV-GPLS) analysis

A) Contouring of RV endocardial border B) Region of interest with approval of segment tracking C) Strain output with longitudinal strain curves. RV-GPLS value of -21.5%. Curves illustrate strain in each segment (coloured lines) and globally (dashed line).

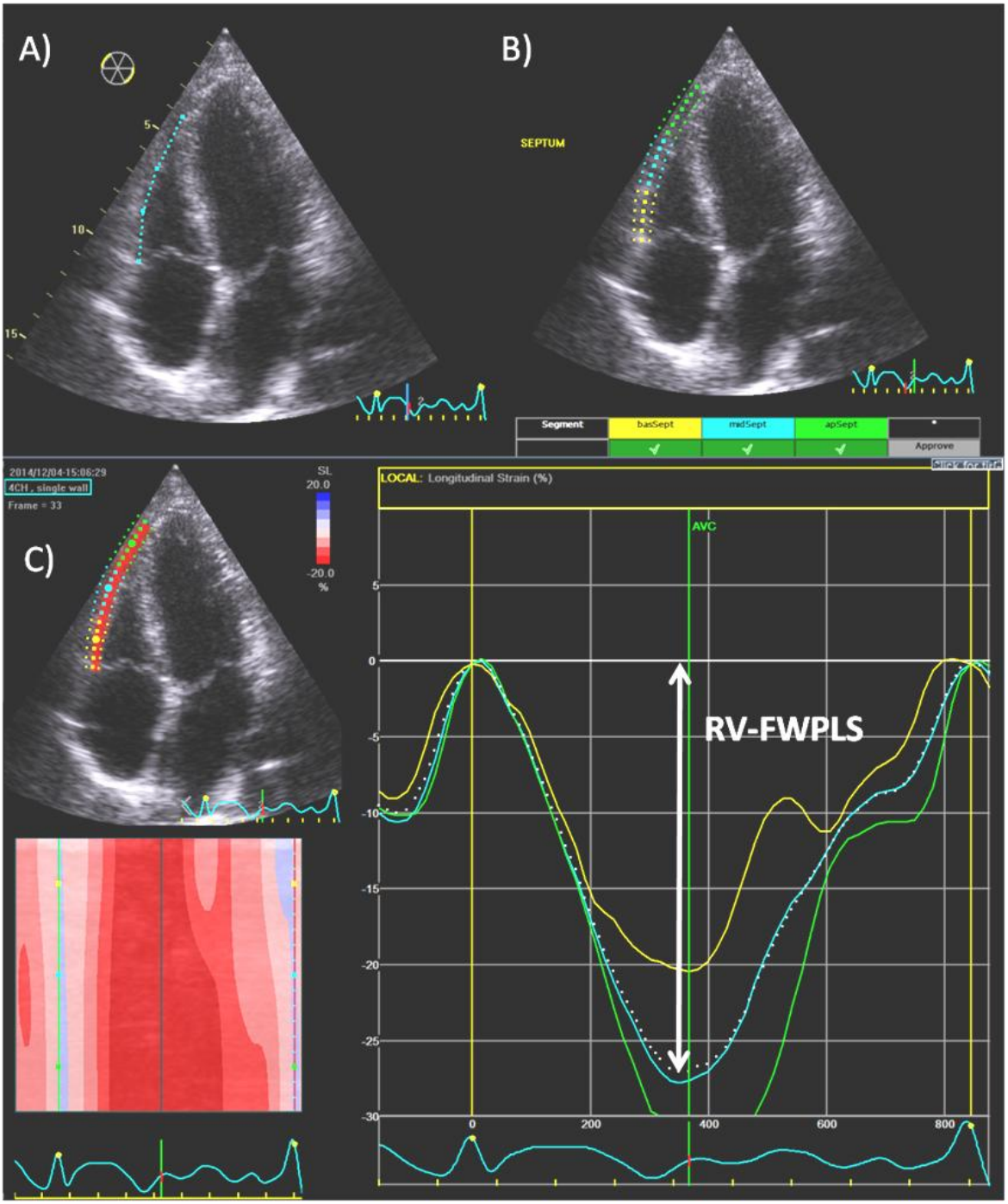


Figure 41. Two dimensional right ventricular free wall peak longitudinal strain (RV-FWPLS) analysis

A) Contouring of RV free wall endocardial border B) Region of interest with approval of segment tracking C) Strain output with longitudinal strain curves. RV-FWPLS value of -27.3%. Curves illustrate strain in each segment (coloured lines) and for entire free wall (dashed line).

4.6 Biomarkers of myocardial dysfunction

4.6.1 Introduction

B-type natriuretic peptide (BNP) is released in response to myocardial stretch and high-sensitivity troponin T (hsTnT) is released in response to cardiac myocyte necrosis. Elevation of BNP and hsTnT has been demonstrated in a number of clinical conditions with RV dysfunction and failure[154, 155, 271-273]. Following lung resection, peri-operative BNP elevation is associated with the extent of resection and post-op complications, including atrial fibrillation (AF)[274-278]. Furthermore, troponin rise is associated with early mortality in the same population[279]. In an non-cardiac surgery setting, peri-operative BNP and troponin are associated with post-op complications and long-term mortality[152, 275, 280-284].

BNP and hsTnT reflect myocardial injury although not specific to the RV. The author hypothesises that elevation of BNP and hsTnT following lung resection, in the absence of LV disease, would signal RV dysfunction.

4.6.2 Methods

4.6.2.1 Biomarker sample handling

Routine care for patients undergoing lung resection involves placement of an arterial cannula; this allows continuous assessment of haemodynamic variables and sampling without need for further venepuncture. Where possible blood for biomarker analysis was sampled from this arterial cannula along with bloods required for normal clinical care. When the arterial cannula had been removed as part of the patients care, a peripheral venous sample was obtained. Blood sampling was performed pre-op (prior to induction of anaesthesia), immediately post-op (once extubated in recovery area) and then on the mornings of POD 1 and 2, and at 2-month follow-up. Twenty millilitres (ml) of blood were collected using BD Vacutainer® blood collection tubes with 2x 4ml Lithium Heparin (green top) tube, 1x3.5ml Serum Sep Clot Activator (yellow top) tube, 1x4ml EDTA (purple top) tube and 1 x 1.8ml Citrate (Blue top) tube. BNP and hsTnT were measured as described below, the remaining samples were immediately centrifuged at room temperature and stored at -80^{o}C in the research laboratory of the Golden Jubilee National Hospital.

4.6.2.2 B-type natriuretic peptide measurement

BNP was measured immediately using the Alere Triage® system (Alere, Stockport, UK)[285]. This is a point of care fluorescence-based immunoassay system. The Alere CardioRenal® panel was used which allows rapid measurement of BNP and neutrophil gelatinase-associated lipocalin (NGAL). Prior to commencing recruitment, training for all members of the research team was provided by Ms Janice McIvor (Alere specialist support team). The provided transfer pipette was used to place a sample of EDTA plasma in to the test device and the manufacturers guidelines were followed throughout. BNP was expressed as ng/ml and coefficient of variation was assessed seven times during the study by using high and low reference frozen controls for every batch (25) of test devices.

4.6.2.3 High sensitivity Troponin T measurement

hsTnT assays were processed with routine clinical samples in the biochemistry laboratories at the Golden Jubilee National Hospital under the supervision of Dr Frank Findlay (consultant clinical scientist, biochemistry). hsTnT was determined by enhanced immunoturbidimetric assay run on a Roche Cobas 6000e analyser (Roche, Basel, Switzerland).

4.7 Generic results

The results described here apply to the cohort recruited for the imaging and biomarker studies described above. Results for the specific imaging and biomarker studies are detailed in chapters 5, 6, 7 and 8.

4.7.1 Patient demographics and operative characteristics

From September 2013 to September 2014 28 patients were recruited to the study by the author and his co-investigator (Dr Alex Arthur, clinical research fellow) (Figure 42).

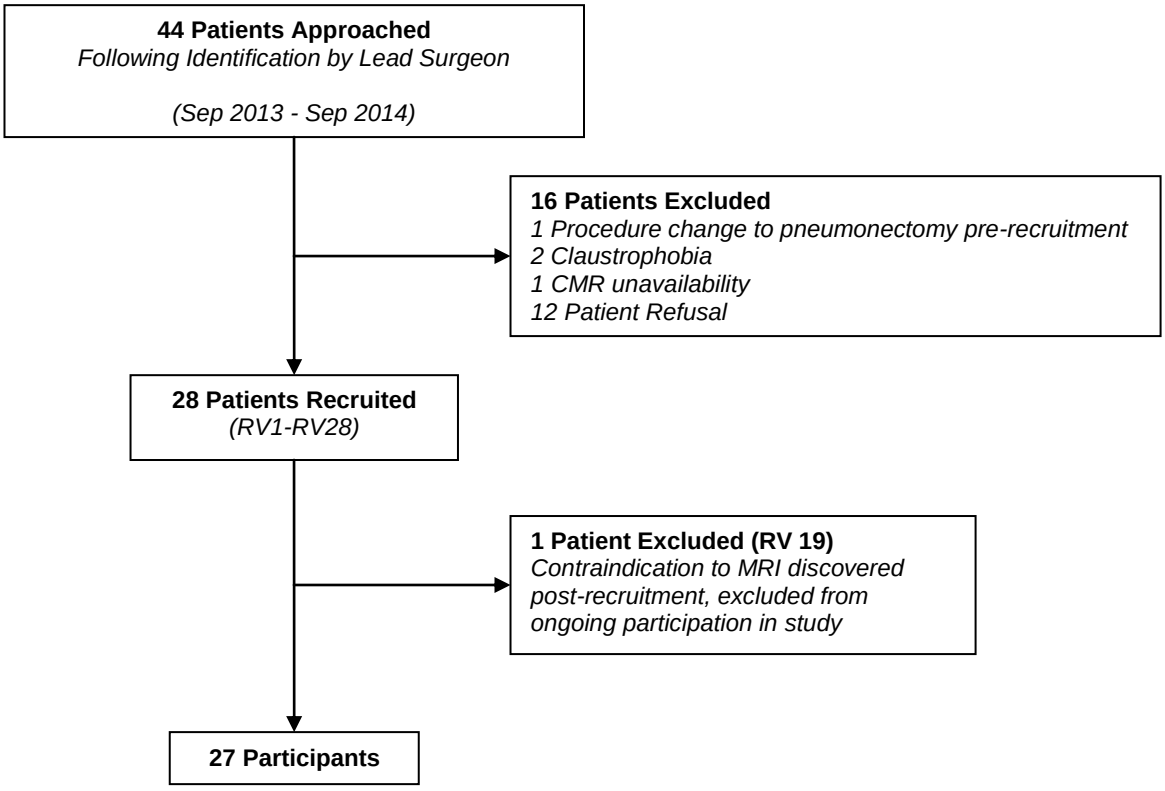


Figure 42. Study Recruitment consort diagram

One patient (RV19) was excluded from further participation in the study due to the unexpected discovery of an embedded piece of ferromagnetic material in their chest wall during pre-op scanning, meaning no usable images of the heart could be obtained. There were no clinical sequelae, but as they were unable to take any part in the main study, this patient was removed from all further analyses. Baseline demographic data on the remaining 27 patents are presented in Table 17, pg 164.

Twenty-six patients underwent lobectomy or bilobectomy (incorporating the right middle lobe); one patient required unplanned intra-operative conversion to pneumonectomy and is included in all analyses. Sensitivity analysis was performed without this patient for the primary outcome and is described in section 5.3.1, pg 180. The majority of participants had a diagnosis of primary lung cancer and operative characteristics are detailed in Table 18, pg 165.

Epidural placement was possible in the majority of patients (24, 85.1%) and this was usually continued until POD 3. No patients required intensive care admission post-operatively and median high dependency unit stay was two days (47.2 hours). Median hospital stay was 8 days. One patient had a prolonged air leak requiring additional intercostal catheter drainage and spent three weeks in hospital. Twenty-five patients attended for 2 month follow-up; one patient was sick at another hospital with a broncho-pleural fistula and the other declined to attend. Only two patients developed post-op arrhythmia; both of whom developed atrial fibrillation (AF), one on POD 1 and the other on POD 7. Both responded to medical management (amiodorone and digoxin respectively). Post-op clinical data is summarised in Table 19, pg 166.

Patient Demographics	*n*	Descriptive Statistics
Age (years)	*27*	67.0 (59.0,74.0)
Female Sex	*27*	17 (62.9%)
Height (cm)	*27*	163.3 (9.0)
Weight (kg)	*27*	69.9 (13.4)
BMI (kgm^{-2})	*27*	26.1 (3.9)
Smoking Status		
Current Smoker		13 (46.4%)
Ex-Smoker		12 (42.9%)
Never Smoked		2 (7.1%)
Pack Years History	*25*	38.2 (21.7)
Pre-operative Pulmonary Function		
SaO2 on Air (%)	*27*	96.4 (1.7)
FEV_1 (L)	*27*	1.9 (1.6, 2.4)
FEV_1/FVC (%)	*27*	64.1 (14.8)
% Predicted FEV_1 (FEV_1%)	*27*	87.5 (25.1)
TLCO (ml/kPa/min)	*27*	5.2 (1.7)
% Predicted TLCO (TLCO%)	*27*	66.6 (15.2)
Co-morbidities		
History of Cancer	*27*	7 (25.9%)
COPD	*27*	6 (22.2%)
Hypertension	*27*	9 (33.3%)
IHD	*27*	6 (22.2%)
Diabetes Mellitus	*27*	0
PVD	*27*	5 (18.5%)
Obesity	*27*	2 (7.4%)
Alcoholism	*27*	0
Thoracoscore (%)	*27*	0.7 (0.5, 0.8)
ASA score	*27*	
1		0
2		2 (7.4%)
3		25 (92.6%)
4		0
5		0

Table 17. Baseline demographic data
Values are number (%), mean (SD) or median (IQR). *n* represents number of patients available for each parameter. BMI = body mass index, SaO_2 = oxygen saturation, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, TLCO = transfer factor for carbon monoxide,

COPD = chronic obstructive pulmonary disease, IHD = ischaemic heart disease, PVD = peripheral vascular disease, ASA = American Society of Anesthesiologists.

Characteristic	*n*	Descriptive Statistics
Resection Type	*27*	
Pneumonectomy		1 (3.7%)
Lobectomy		22 (81.5%)
Bilobectomy		4 (14.8%)
Right Sided Procedure		17 (63%)
Pulmonary Segments Resected		5 (3, 5)
ppoFEV_1 %	*27*	67.66 (20.8)
ppoTLCO%	*27*	51.2 (11.6)
Pathology	*27*	
Primary Lung Cancer		24 (88.9%)
Other Malignant		1 (3.7%)
Benign Disease		2 (7.4%)
Lung Cancer Staging	*24*	
Stage	**TNM Subset**	
1A	T1a N0	5
	T1b N0	4
1B	T2a N0	9
2A	T2b N0	2
2B	T2b N1	1
3A	T2a N2	1
	T3 N2	1
	T4 N0	1
Volatile Anaesthetic Agent	*27*	
Desflurane		1 (3.7%)
Isoflurane		3 (11.1%)
Sevoflurane		23 (85.2%)
Duration		
Duration of surgery (mins)		146 (116, 169)
Duration of OLV (mins)		56 (48, 84)

Table 18. Operative data
Values are number (%), mean (SD) or median (IQR), *n* represents number of patients available for each parameter. ppo = predicted post-op , FEV_1 = forced expiratory volume in 1 second, TLCO = transfer factor for carbon monoxide, OLV = one lung ventilation.

Characteristic	*n*	Descriptive Statistics
Analgesia	*27*	
Epidural		23 (85.1%)
Epidural discontinued operative day		1 (4.3%)
Epidural discontinued POD 2		2 (8.7%)
Epidural discontinued POD 3		18 (78.3%)
Epidural discontinued POD 4		2 (8.7%)
Paravertebral Infusion and PCA (PV & PCA)		4 (14.8%)
PV & PCA discontinued POD 1		1 (25%)
PV & PCA discontinued POD 2		1 (25%)
PV & PCA discontinued POD 3		2 (50%)
Fluid administration (L)		
Intra-op	*27*	0.9 (0.4)
Operative day (to 07:59 POD 1)	*27*	1.7 (1.4, 2.2)
to 07:59 POD 2	*17*	2.3 (2.0, 2.5)
to 07:59 POD 3	*6*	1.9 (1.4, 2.7)
Cumulative fluid administration by morning POD 2	*17*	5.0 (4.3, 5.2)
HDU Fluid Balance (L)		
Operative day (to 07:59 POD 1)	*27*	1.0 (0.6, 1.4)
To 07:59 POD 2	*17*	0.1 (-0.5, 0.7)
To 07:59 POD 3	*6*	-0.6 (-1.2, 0.3)
Cumulative fluid balance morning POD 2	*17*	1.1 (0.4, 1.8)
Vasoconstrictor required during HDU admission	*27*	
Nor-adrenaline		9 (33.3%)
Arrhythmia		
Atrial Fibrillation	*2*	2 (7.4%)
Follow Up		
Number attending for 2 month follow up	*25*	25
Time from operative day to follow up (Days)	*25*	57 (14.0)
Length of stay		
HDU (Hours)	*27*	47.2 (29.2, 53.5)
Hospital (Days)	*27*	8 (7, 11)

Table 19. Post-operative clinical data
Values are number (%), mean (SD) or median (IQR [range]). No patients required Nor-adrenaline at the time of MRI scanning on POD 2. cumulative fluid balance and cumulative fluid administration on the morning of POD 2 is for those patients still in HDU only. POD = post-op day, PCA = Patient controlled analgesia, HDU = high dependency unit.

From 1st January 2013 to 31st December 2014, 1169 patients underwent lung resection at the Golden Jubilee National hospital. This period encompassed the complete study duration. Although the cohort recruited was selected from patients presenting for surgery under a single surgeon, Table 20 illustrates no significant differences in the age, sex, operative side, pulmonary function and Thoracoscore of those participating in the study and those not taking part.

Characteristic	Study Participants n=27	Non Study Participants n=1142	p value
Age	67.0 (59.0,74.0)	67 (59.0, 73.0)	0.956*
Female Sex	17 (62.9%)	622 (54.5%)	0.381†
Right Sided Procedure	17 (62.9%)	688 (60.2%)	0.775†
FEV1	1.9 (1.6, 2.4)	2.0 (1.6, 2.6) *(n=555)*	0.455*
FEV_1%	86.0 (66.5, 104.5)	88.0 (73.8, 102.0) *(n=558)*	0.816*
TLCO%	65.0 (55.0, 75.0)	69.0 (57.0, 83.0) *(n=494)*	0.439*
Thoracoscore	0.7 (0.5, 0.8)	0.9 (0.4, 2.0) *(n=944)*	0.069*

Table 20. Characteristics of study participants and non study participants undergoing lung resection at the Golden Jubilee National Hospital between Jan 2013 and Dec 2014
Values are number (%) and median(IQR). Where the dataset was incomplete,*(n)* represents the number of patients with data available. *Mann-Whitney U-test, † Chi-squared test.

4.7.2 Functional status, quality of life and six-minute walk test distance

Functional status and quality of life was assessed pre-op, at 2-months and 1 year post-op. All patients completed the self-reported questionnaire pre-op. All patients presenting for 2-month follow-up (92.6%) completed the questionnaire and 22 participants (81.5%) returned the postal questionnaire at 1 year. Mean (SD) time to 2-month follow-up was 55.9 (13.1) days.

4.7.2.1 Functional status

Self reported functional status was assessed in three domains. Using the World Health Organisation performance status (WHO-PS), there is a trend towards a *decrease* in the proportion of patients who were WHO-PS zero (fully active) at 2-months (p=0.09, McNemar's test [MT]). There is no change in the proportion who

were WHO-PS zero at 1 year (p=0.180, MT) (Table 21, pg 169 and Figure 43, pg 170). Medical Research Council dyspnoea scale (MRC-DS), showed a trend towards an increase in the proportion of patients who were limited by their breathlessness (MRC-DS ≥3) at 2-months (p=0.063, MT). There was an increase in the proportion who were limited by breathlessness from 7.4% pre-op to 27.3% at 1-year (p=0.031, MT, Table 21 and Figure 44, pg 170). New York Heart Association (NYHA) classification showed no change in the proportion of patients who were NYHA 1 (no symptoms and no limitations) at 2-months or at 1 year (p=0.754 and p=0.625 respectively, both MT) (Table 21 and Figure 45, pg 171).

There was no association between pre-op %predicted FEV_1 (FEV_1%), pre-op %predicted TLCO (TLCO%), pre-op FEV_1/FVC ratio and pre-op WHO-PS, MRC-DS and NYHA score (p>0.161 for all, Spearman's correlation coefficient). There was association between ppoTLCO% and WHO-PS at 2-months (r=-0.441, p=0.027, Spearman's correlation coefficient). There was association between ppoFEV_1% and both, MRC-DS and NYHA class at one year (r=-0.516, p=0.020 and r=-0.556, p=0.009 respectively, both Spearman's correlation coefficient). There was no association between respiratory variables and functional outcome at other time points (p>0.075 for all, Spearman's correlation coefficient).

Six minute walk testing (6MWT) was performed pre-op and at 2-months. Two patients did not have a 6MWT performed pre-operatively; this was as a result of one patient declining and the other because of unavailability of a safe area for testing to take place. There was no change in the median [IQR] distance walked from pre-op (412m [360, 486]) to 2-months (420m [362.5, 473.5], p=0.639, Wilcoxon rank sum test). Although there was no change in median distance walked, there was a decrease in the number of patients who *could* complete the test. Twenty five patients performed testing pre-op. At 2-months, 25 patients attended for follow-up but four declined walking due to shortness of breath. Seven participants had their 6MWT drop by more than 28m (the MICD for 6MWT in COPD, see section 4.2.5.3, pg 135). Four patients had an increase in walking distance by more than the MID accounting for the lack of change in median distance.

There was no association between pre-op FEV_1%, TLCO%, FEV_1/FVC ratio and pre-op 6MWT distance (p>0.506, Pearson's correlation coefficient for both). There

was no association between ppoFEV_1%, ppoTLCO% and 6MWT distance at 2-months (p>0.935, Pearson's correlation coefficient). There was no difference in the ppoFEV_1% and ppoTLCO% between those patients who had a significant reduction in their 6MWT distance (by >28m or were unable to walk) and those who were able to walk the same distance or further (p>0.765, Mann-Whitney U-test).

Functional Status	**Descriptive Statistics**				
	Time Point				
	Pre-op	**2-Months**		**1 Year**	
	n=27	*n=25*		*n=22*	
WHO-PS			p value		p value
0	17 (63.0%)	10 (40.0%)		8 (36.4%)	
1	7 (25.9%)	10 (40.0%)		13 (59.1%)	
2	2 (7.4%)	5 (20.0%)	0.092*	1 (4.5%)	0.180*
3	1 (3.7%)	0		0	
4	0	0		0	
MRC dyspnoea scale					
1	9 (33.3 %)	6 (24.0%)		6 (27.3%)	
2	16 (59.3%)	13 (52.0%)		10 (45.5%)	
3	1 (3.7%)	4 (16.0%)	0.063*	5 (22.7%)	0.031*
4	1 (3.7%)	1 (4.0%)		0	
5	0	1 (4.0%)		1 (4.5%)	
NYHA classification					
I	9 (33.3%)	7 (28.0%)		5 (22.7%)	
II	17 (63.0%)	16 (64.0%)	0.754*	14 (63.6%)	0.625*
III	1 (3.7%)	2 (8.0%)		3 (13.6%)	
IV	0	0		0	

Table 21. Self reported functional Status
Values are number (%). WHO-PS = World Health Organisation performance status. MRC = Medical Research Council. NYHA = New York Heart Association. * = McNemar's Test compared to pre-op. For WHO performance status (PS) comparison is made between proportion PS 0 and proportion PS 1, 2, 3 or 4, For MRC dyspnoea scale (MRC) comparison is made between proportion MRC 1 & 2 and proportion MRC 3, 4 or 5, for NYHA classification (NYHA) comparison is made between proportion NYHA 1 and proportion NYHA 2, 3 or 4. Definitions of each score as per appendix 3.

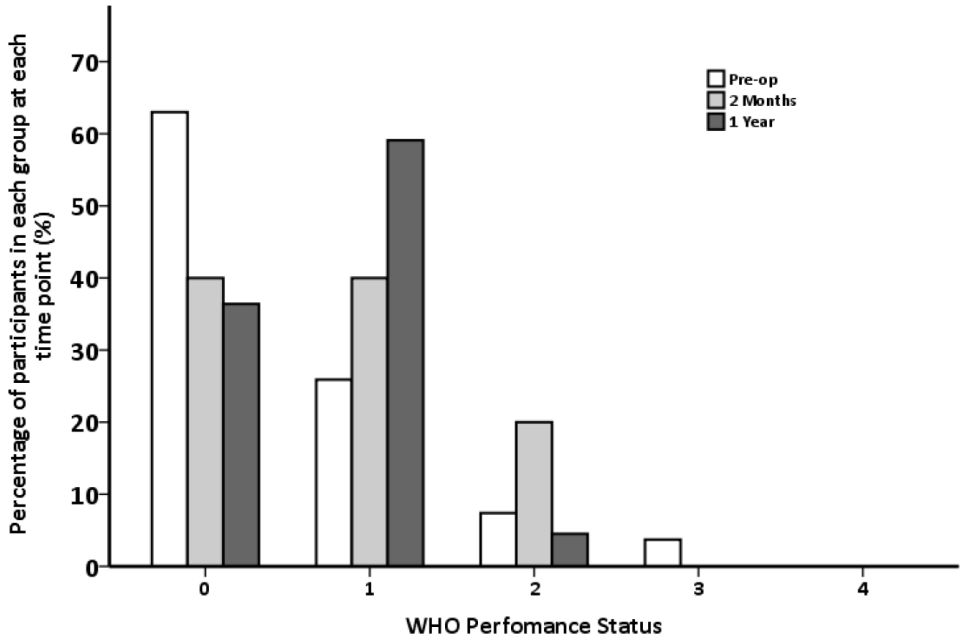


Figure 43. World Health Organisation (WHO) Performance Status
Percentage of participants in each performance status category at each time point. Definitions as per Appendix 3.

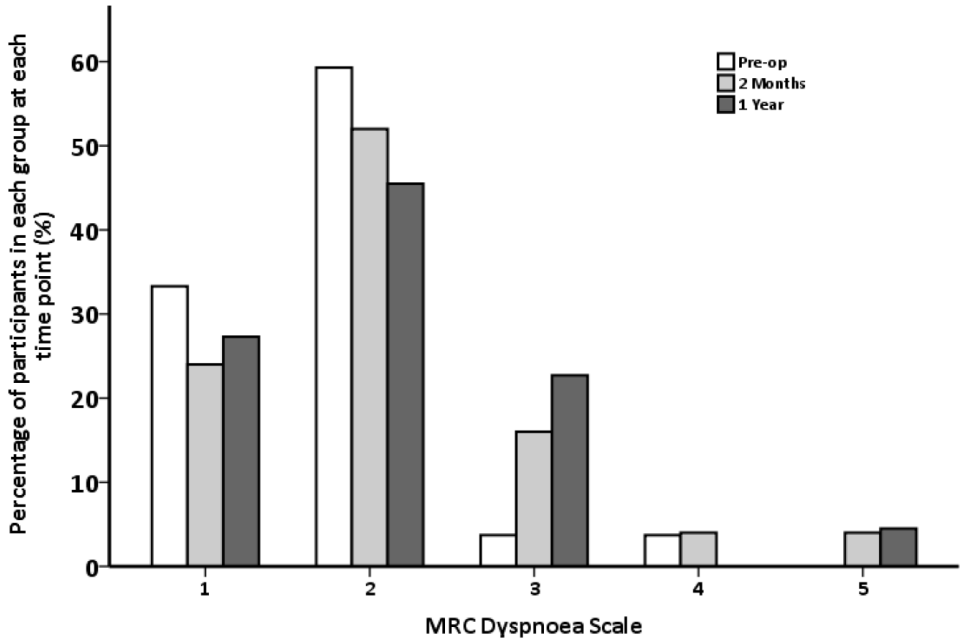


Figure 44. Medical Research Council (MRC) Dyspnoea Scale
Percentage of participants in each group at each time point. Definitions as per Appendix 3.

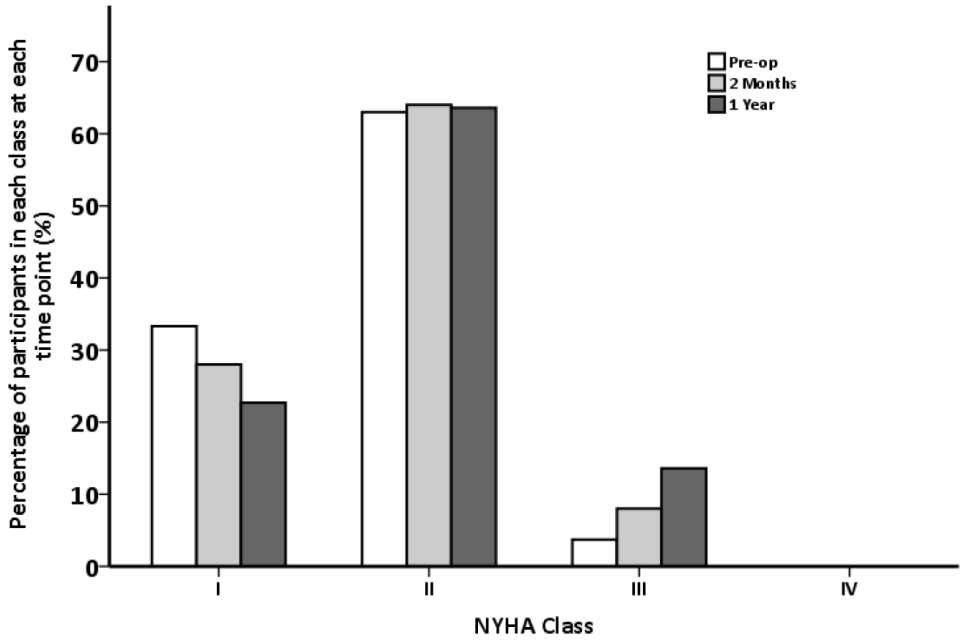


Figure 45. New York Heart Association (NYHA) functional classification
Percentage of study participants reporting any problem in each class at each time point. Definitions as per Appendix 3.

4.7.2.2 Quality of life

Quality of life was assessed using the EuroQOL 5 domain score (EQ5D). This score allows creation of a health utility score from the unique responses in each domain. There were no changes in the health utility score over the period of the study (p=0.228, Friedman's test). When examining the individual domains of the EQ5D score (Table 22, pg 173 and Figure 46, page 172) there is a trend towards an increase in the proportion of patients reporting problems with their mobility (EQ5D>1) at 2-months (p=0.063, MT). There is an increase in the proportion of patients describing problems with their mobility and self-care (EQ5D>1) at one year (p=0.031 and p=0.016 respectively, both MT). There were no changes in the proportions reporting problems (EQ5D>1) in the other domains (usual activities, pain/discomfort and anxiety/depression) at either 2-months or at one year (p>0.125 for all, MT).

The global health score is obtained by asking the patient to grade their 'global' health from 0-100. This changed over the course of the study (p=0.011, one way repeated measures ANOVA) with a significant deterioration at 2-months and one year (p=0.044 and 0.012 respectively, both paired samples t-test).

There was no association between pre-op FEV_1%, pre-op TLCO%, pre-op FEV_1/FVC ratio and pre-op health utility score or pre-op global health score ($p>0.076$ for all, Pearson's correlation coefficient). There was no association between these pre-op pulmonary function results and any of the individual domains of EQ5D pre-operatively ($p>0.095$ for all, Spearman's correlation coefficient).

There was no association between ppoTLCO%, ppoFEV_1% and health utility score or global health score, both at 2-months and one year ($p>0.54$ for all, Pearson's correlation coefficients). There was no association between the predicted post-op pulmonary function results and any of the individual domains of EQ5D at 2-months. There was negative association between ppoFEV_1% and both mobility ($r=-0.531$, $p=0.013$, Spearman's correlation coefficient) and usual activities ($r=-0.434$, $p=0.049$, Spearman's correlation coefficient) at one year. There was no association between ppoFEV_1% and the remaining domains ($p>0.152$ for all, Spearman's correlation coefficient). There was no association between ppoTLCO% and any of the individual domains of EQ5D at one-year. ($p>0.658$ for all, Spearman's correlation coefficient).

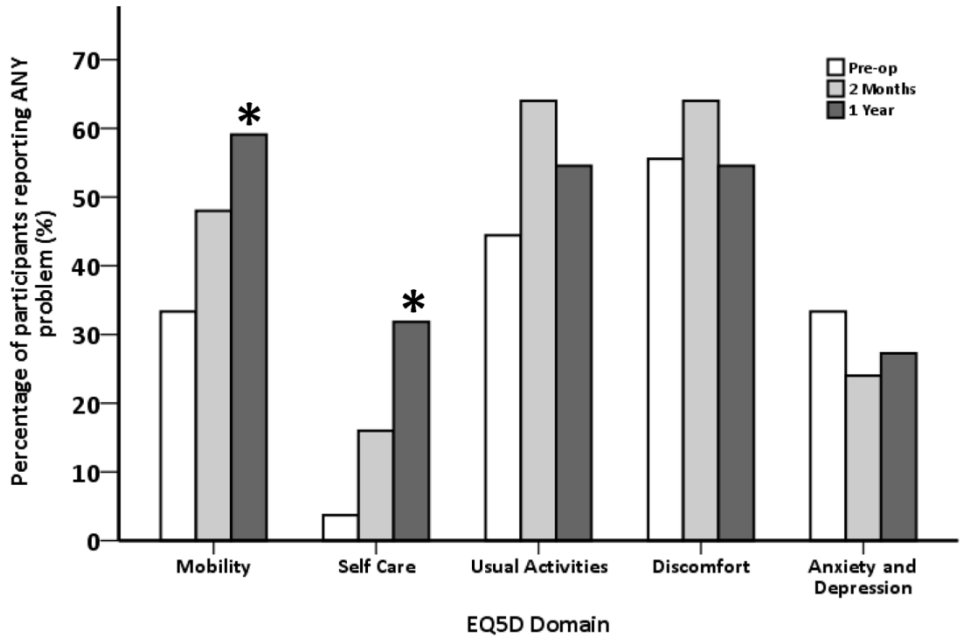


Figure 46. EuroQol 5 domain (EQ5D) responses
Percentage of study participants reporting any problem in each of the five 'EQ5D' domains at each time point. * = significant difference to pre-op (McNemar's test).

EQ5D Quality of Life domain	Descriptive Statistics				
	Time Point				
	Pre-op	2-Months		1 Year	
	n=27	*n=25*		*n=22*	
Mobility			p value*		p value*
1	18 (66.7%)	13 (52.0%)		9 (40.9%)	
2	7 (25.9%)	8 (32.0%)		6 (27.3%)	
3	1 (3.7%)	4 (16.0%)	0.063#	7 (31.8%)	0.031#
4	1 (3.7%)	0		0	
5	0	0		0	
Self-Care					
1	26 (96.3%)	21 (84.0%)		15 (68.2%)	
2	1 (3.7%)	4 (16.0%)		7 (31.8%)	
3	0	0	0.125#	0	0.016#
4	0	0		0	
5	0	0		0	
Usual Activities					
1	15 (55.6%)	9 (36.0%)		10 (45.5%)	
2	10 (37.0%)	9 (36.0%)		5 (22.7%)	
3	2 (7.4%)	6 (24.0%)	0.125#	7 (31.8%)	0.453#
4	0	0		0	
5	0	1 (4.0%)		0	
Pain / Discomfort					
1	12 (44.4%)	9 (36.0%)		10 (45.5%)	
2	10 (37.0%)	12 (48.0%)		8 (36.4%)	
3	2 (7.4%)	4 (16.0%)	0.453#	4 (18.2%)	0.999#
4	3 (11.1%)	0		0	
5	0	0		0	
Anxiety / Depression					
1	18 (66.7%)	19 (76.0%)		16 (72.7%)	
2	7 (25.9%)	5 (20.0%)		3 (13.6%)	
3	2 (7.4%)	1 (4.0%)	0.453#	3 (13.6%)	0.727#
4	0	0		0	
5	0	0		0	
Health Utility Score (0-1)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.072†	0.8 (0.6, 1.0)	0.446†
Global Health Score (0-100)	79.6 (15.1)	77.2 (12.2)	0.044‡	74.3 (17.1)	0.012‡

Table 22. Self reported quality of life
Values are number (%), mean (SD) or median (IQR). EQ5D = EuroQOL 5 Dimension. * = comparison to pre-op. # = McNemar's Test compared to pre-op (all are comparison of proportion quality of life (QOL) score 1 with proportion QOL score 2, 3, 4 or 5). † = Wilcoxon rank sum test compared to pre-op, ‡ = paired t-test compared to pre-op. Definitions of each level as per appendix 3.

4.7.3 Discussion

This study recruited 27 patients to examine the RV response to lung resection. The study protocol as a whole was well tolerated with 25 patients (92.6%) attending for 2-month follow-up and 22 patients (81.5%) returning postal follow-up at one year. The cohort recruited to this study were representative of all patients undergoing surgery at the Golden Jubilee National Hospital during the study period.

A deterioration in functional capacity following lung resection is demonstrated. This was determined subjectively by questionnaire (MRC-DS and EQ-5D) and objectively by use of the 6MWT. An MRC dyspnoea scale of three, four or five corresponds to severe disability as a result of dyspnoea and this study has demonstrated a trend towards an *increase* in the proportion of patients disabled by dyspnoea at 2-months and an increase in the proportion disabled by dyspnoea at one year[258]. Although there was no change in the *median* 6MWT distance at 2-months, the proportion who declined to walk as a result of dyspnoea increased.

The deterioration in functional capacity following lung resection has previously been well described in this population, with work documenting an increase in subjective dyspnoea scores[24, 35]. Deterioration in exercise capacity following surgery has been demonstrated with cardiopulmonary exercise testing[286, 287] and shuttle walk testing[288]. In a mixed pneumonectomy and lobectomy cohort[o], Win et al. demonstrated a deterioration in shuttle walk test distance at 1-month, 3-months and 6-months following lung resection[288]. The deterioration in distance walked was larger in the pneumonectomy group compared to the lobectomy group and there was evidence of some recovery in distance walked at 6-months.

The current investigation demonstrates a decline in quality of life following lung resection. A score of one in an EQ5D domain describes "*no problems"* within that domain, with a score of two corresponding to *"slight problems"* and a score of five corresponding to being *"unable"* to perform that function. This study also demonstrates there is a *decrease* in the proportion of participants who had no problems with mobility or self-care at one year. The scores in individual domains can be used to calculate a summary score which is based on population

[o] 110 consecutive patients prospectively recruited, 73 lobectomy and 37 pneumonectomy.

responses to the same questions. This shows that despite the deterioration in mobility and self-care, there is no change in the summary health-utility score.

There is a small but significant change in global health score by POD 2 and a larger change by one year. This score is determined from a visual analogue scale with the respondent recording their self-rated health on a vertical scale with the endpoints labelled *"best imaginable health state"* and *"worst imaginable health state* (see appendix 4)*."* The change by one year (79.6 to 74.3) is smaller than the minimally important clinical difference in this measure of seven[289]. This deterioration although *statistically* significant, is therefore of the magnitude that would not be considered *clinically* relevant[290]. This decline in health related quality of life has been documented before, with previous work showing a deterioration in physical functioning, mental health, social functioning and pain[22, 23, 35, 39, 291-293]. Many studies suggest ongoing problems *years* following lung resection[22, 24, 291].

As described in section 1.1.4, pg 23, the inconsistent association between pulmonary function and post-op morbidity (functional capacity and quality of life) has been previously described. This study demonstrates negative association between ppoTLCO% and WHO-PS at 2-months. Additionally there is negative association between ppoFEV_1% and both, MRC-DS and NYHA class at one year. There is no association between pulmonary function and both, 6MWT distance and quality of life.

The lack of consistent association between pulmonary function and both, functional capacity and quality of life suggests that other factors, such as cardiovascular function, may influence these changes following lung resection.

4.7.3.1 Strengths and weaknesses

The study protocol was well tolerated with only one patient who was able to return at 2-months, declining follow-up. Return of postal follow-up questionnaires at one year was above 80%.

The multiple comparisons (21 for comparison of pulmonary function and functional status outcomes, 49 for comparison of pulmonary function and quality of life outcomes) and small sample size mean the findings described are at high risk of type I error.

4.8 Conclusion

This chapter provides generic results for the studies within this thesis examining the RV response to lung resection. The study protocol was well tolerated with only one patient declining follow-up at 2-months. Twenty-eight patients were recruited to the study but as a result of a contraindication to CMR imaging (implanted ferromagnetic material), one patient was excluded from ongoing trial participation. One patient required intra-operative conversion to pneumonectomy and is included in all results.

The findings regarding declining functional status are confirmatory of previous work in this patient group. In this cohort there is a suggestion of deterioration in functional status, with an increase in the proportion with disabling dyspnoea and a reduction in the number of participants able to complete the 6MWT. There was deterioration in the mobility and self-care domains of quality of life scoring at one year.

Chapter 5 Cardiovascular Magnetic Resonance Results

5.1 Introduction

This chapter describes the results of the cardiovascular magnetic resonance (CMR) imaging component of this study. Firstly, reproducibility of CMR assessment of RV function is reported. Changes in RV and LV function over time, along with changes in ventricular volumes are described next. The association of pre-op and intra-op variables with RV function will then be assessed. Finally, on an exploratory basis, comparison of RV function with post-op outcomes is made.

CMR imaging was well tolerated with all patients completing the scan protocol pre-operatively; twenty-two (81.5%) on post-op day (POD) 2 and 24 (88.9%) at 2-months. Due to an administration error, one participant did not have short axis images obtained pre-operatively so it was not possible to calculate ventricular volumes meaning 26 patients are included in the analysis at this time point. Of the five patients unable to complete the protocol on POD 2; three declined, one was unwell with persistent air-leak requiring additional inter-costal catheter drainage and CMR transfer was deemed unsafe. A final patient had an epidural catheter in-situ that was CMR incompatible resulting in imaging being contraindicated[294]. Of the three patients unable to complete the protocol at 2-months, one declined, one was within six weeks of cataract surgery (a contraindication to CMR imaging) and the third was unwell in another hospital with broncho-pleural fistula and was unable to attend for imaging. This gave 72 scans for dual reported analysis.

5.2 Assessment of reproducibility

5.2.1 Inter and intra-observer variation of ventricular volume measurements

The measured parameters of RV end diastolic volume (RVEDV) and end systolic volume (RVESV) showed good inter-observer variation with intraclass correlation coefficients (ICC) for agreement of 0.86 and 0.84 respectively (Figure 47 and Table 23, pg 178). There was also good intra-observer variation for RV volumes with ICCs > 0.92 (Table 24, pg 179). Left ventricular volumes showed better inter-

observer and intra-observer variation than RV volumes, with ICCs >0.87 and >0.97 respectively.

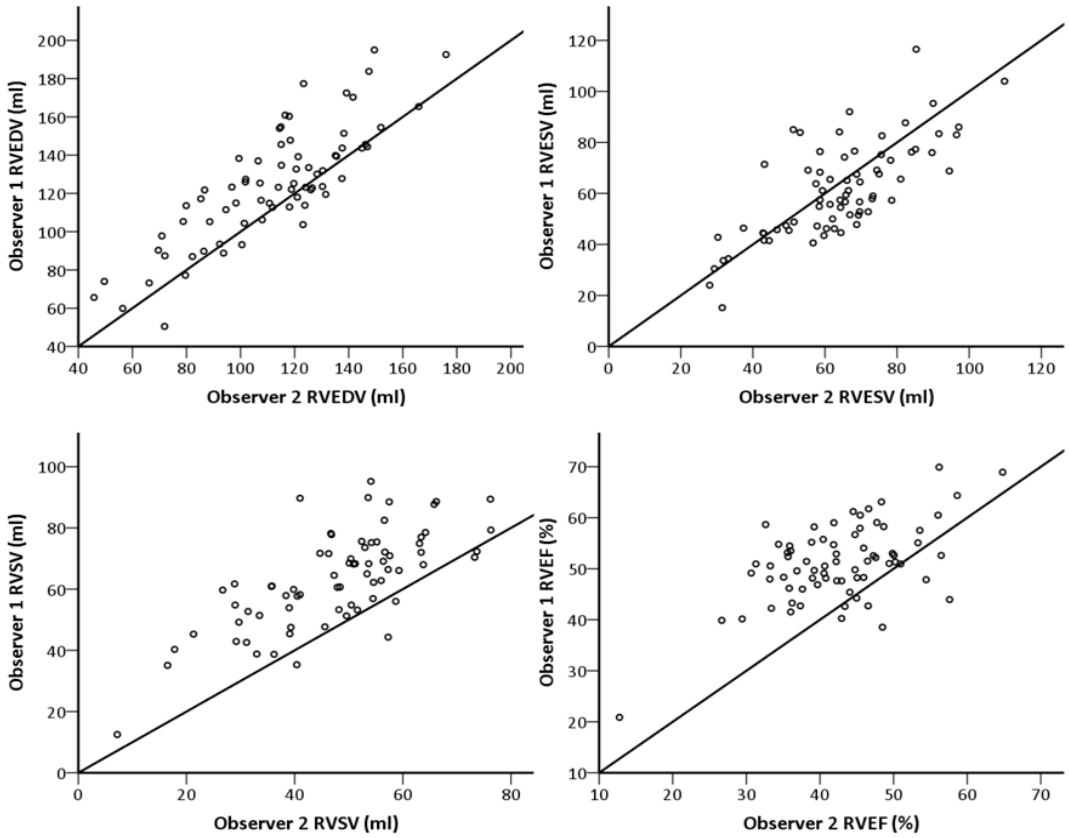


Figure 47. Association between observer1 and observer 2 for RV variables
Solid line is the line of identity. Reproducibility statistics as per Table 23, pg 178. RV = right ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction.

Inter-observer variation (n = 72)			
		CV (%)	**ICC Agreement (95% CI)**
RV	**EDV (ml)**	9.97	0.86 (0.56, 0.94) p<0.001
	ESV (ml)	12.23	0.84 (0.75, 0.90) p<0.001
	SV (ml)	21.75	0.64 (-0.20, 0.86) p<0.001
	EF (%)	15.10	0.53 (-0.15, 0.79) p<0.001
LV	**EDV (ml)**	5.9	0.95 (0.91, 0.97) p<0.001
	ESV (ml)	14.3	0.87 (0.74, 0.93) p<0.001
	SV (ml)	12.5	0.82 (0.36, 0.93) p<0.001
	EF (%)	9.6	0.71 (0.29, 0.86) p<0.001

Table 23. Inter-observer variability for ventricular volumes and ejection fraction
Coefficient of variation (CV) calculated as per Equation 8, pg 138, intraclass correlation coefficient (ICC) calculated as mixed effect, absolute agreement. LV = left ventricle, RV = right ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction.

Intra-observer variation (n = 10)			
		CV (%)	ICC Agreement (95% CI)
RV	EDV (ml)	5.0	0.92 (0.67, 0.98) p=0.001
	ESV (ml)	6.6	0.94 (0.77, 0.99) p<0.001
	SV (ml)	11.4	0.89 (0.59, 0.97) p=0.001
	EF (%)	8.8	0.85 (0.44, 0.96) p=0.003
LV	EDV (ml)	2.7	0.99 (0.94, 1.00) p<0.001
	ESV (ml)	5.4	0.97 (0.89, 0.99) p<0.001
	SV (ml)	5.4	0.96 (0.68, 0.99) p<0.001
	EF (%)	3.6	0.93 (0.68, 0.98) p<0.001

Table 24. Intra-observer variability for ventricular volumes and ejection fraction
Coefficient of variation (CV) calculated as per Equation 8, pg 138, intraclass Correlation coefficient (ICC) calculated as mixed effect, absolute agreement. LV = left ventricle, RV = right ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction.

5.2.2 Impact of surgery on reproducibility

The influence of surgery on reproducibility was assessed using CV at each time point. CV for assessment of the RV appears to deteriorate from pre-op to both post-op time points (Table 25).

Inter-observer coefficient of variation (%)				
		Pre-op	POD 2	2-Months
		n=26	n=22	n=24
RV	EDV (ml)	9.1	8.3	12.4
	ESV (ml)	12.2	14.9	9.8
	SV (ml)	18.2	21.8	25.6
	EF (%)	12.9	16.8	15.9
LV	EDV (ml)	5.2	6.1	6.5
	ESV (ml)	14.6	15.8	12.5
	SV (ml)	11.4	14.5	11.7
	EF (%)	9.9	11.6	7.3

Table 25. Coefficient of variation over time
POD = post-op day, CV = coefficient of variation, LV = left Ventricle, RV = right Ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction.

The influence of side of resection on reproducibility was also assessed (Table 26). Post-operatively, when assessing RV function there appears to be an increase in CV for those having right sided surgery compared to those having left sided surgery.

Inter-observer coefficient of variation (%)							
		Pre-op		POD 2		2-Months	
		Left	Right	Left	Right	Left	Right
		n=10	n=16	n=9	n=13	n=8	n=16
RV	EDV (ml)	10.5	8.2	7.3	9.0	8.8	14.3
	ESV (ml)	9.1	14.2	12.3	16.7	11.2	9.1
	SV (ml)	20.4	16.8	15.8	25.9	17.3	29.7
	EF (%)	13.2	12.8	11.5	20.5	13.8	16.9
LV	EDV (ml)	5.2	5.2	6.8	5.6	4.2	7.6
	ESV (ml)	13.2	15.4	17.6	14.5	10.0	13.8
	SV (ml)	9.4	12.6	14.7	14.4	10.0	12.6
	EF (%)	8.6	10.7	12.6	11.0	7.1	7.4

Table 26. Coefficient of variation by side of surgery over time
CV = Coefficient of variation, LV = left ventricle, RV = right ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction.

5.3 Changes in cardiac function

Heart rate (HR) and cardiac output (CO) increased from a baseline level on POD 2 before returning to pre-op levels at 2-months (Table 27, pg 182).

5.3.1 Right ventricular function over time

One-way repeated measures analysis of variance (ANOVA) determined there was a significant difference in RVEF over the duration of the study (p=0.003). Data were normally distributed pre-op and at POD 2. There was one outlier at the 2-month time point, this result was identified as the lowest RVEF by both observers (Figure 47, pg 178) and was included for analysis[P]. Sensitivity analysis showed

[P] RV 13 is identified on a number of occasions through this study as an outlier. Despite minimal changes in cardiac function by POD2, this patient presented at 2-month follow-up with severe biventricular dysfunction, with RVEF of 16.9% and LVEF of 24.0%. The participant was

there was no difference in the final result when performing the test without the outlier (p=0.003). Paired samples t-tests revealed that RVEF decreased significantly from 50.45% (6.92) pre-op, to 45.61% (4.45) on POD 2 (p<0.0005) and remained decreased at 44.89% (7.74) by 2-months (p=0.002, Figure 48 and Table 27, pg 182).

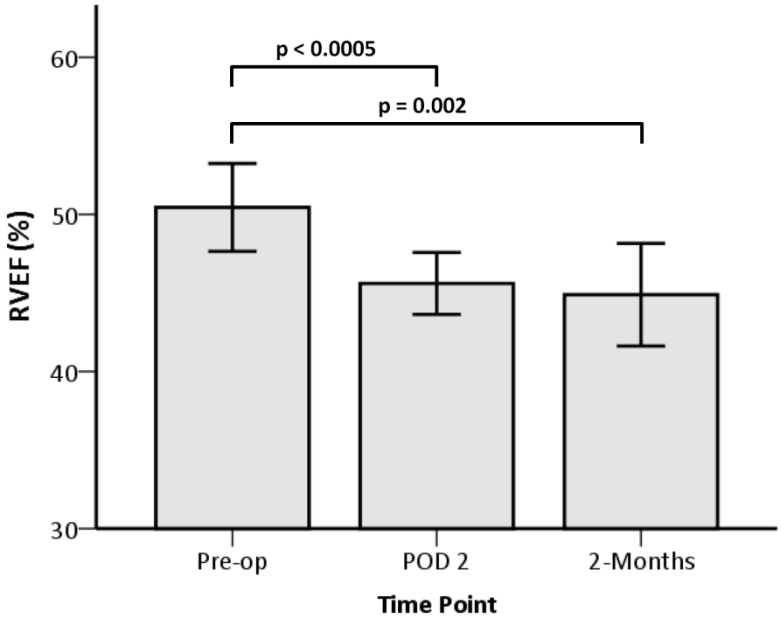


Figure 48. Right ventricular ejection fraction (RVEF) over time
Bar (error bars) represent mean (95% CI). one-way repeated measures ANOVA, p=0.003. Pairwise comparisons with paired samples t-test. RVEF = right ventricular ejection fraction, POD = post-op day.

The mean reduction in RVEF from pre-op to POD 2 was 4.84%. As can be seen from Figure 49 (pg 182) there appears to be a consistent drop in RVEF across the majority of participants. The upper quartile (those patients with the largest deterioration) had a median (IQR) change in RVEF in excess of 10% over this time.

reviewed by cardiology and had been felt to have had a myocardial infarction in the follow-up period. They were followed up as an out-patient and by their general practitioner.

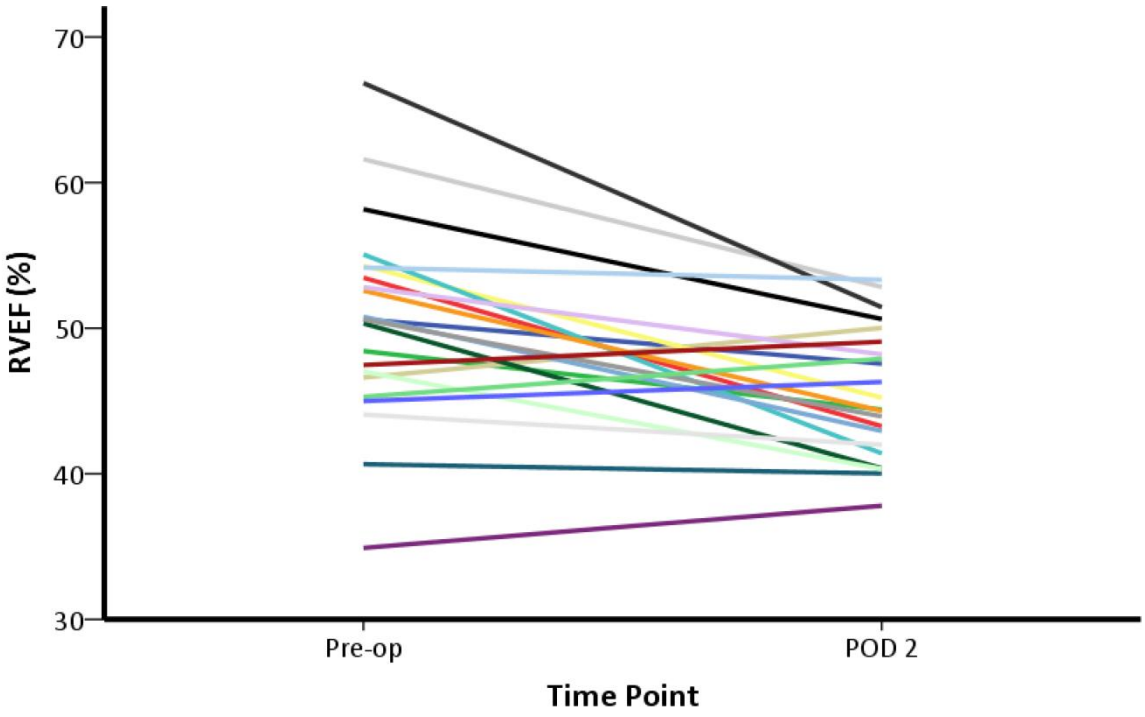


Figure 49. Change in right ventricular ejection fraction (RVEF) from pre-op to POD 2
Each coloured line represents an individual patient. n = 27. RVEF = right ventricular ejection fraction, POD = post-op day.

	Pre-op	POD 2	2 Months	p-value
	n=26	n=22	n=24	
HR (bpm)	64.4 (13.0)	77.0 (11.0) #	69.4 (10.3) ¥	0.002*
CO	6.6 (1.7)	8.0 (1.6) #	6.5 (1.7) ¥	0.004*
RVEF (%)	50.45 (6.92)	45.61 (4.45)#	44.89 (7.74)#	0.003*
RVEDV (ml)	119.13 (25.35)	125.93 (22.47)	109.40 (31.59)# ¥	0.019*
RVESV (ml)	59.80 (17.14)	68.60 (14.48)#	59.83 (17.63)¥	0.040*
RVSV (ml)	59.32 (12.01)	57.33 (10.70)	49.57 (16.47)#	0.002*

Table 27. Right ventricular ejection fraction and volumes over time
Values are mean (SD). * = one-way repeated measures ANOVA. # = significant difference from pre-op. ¥ = significant difference from POD 2. HR = Heart rate, CO = cardiac output, RVEF = right ventricular ejection fraction, RVEDV = right ventricular end diastolic volume, RVESV = right ventricular end systolic volume, RVSV = right ventricular stroke volume, POD = post-op day.

Changes in RV volume measurements over time are shown in Table 27 above and Figure 50, below. RVEDV was lower at 2-months compared to other time points ($p<0.017$, paired t-test). RVESV was higher at POD 2 compared to other time points ($p<0.004$, paired t-test) and the RVSV was lowest at 2 months compared to pre-op ($p=0.0005$, paired t-test).

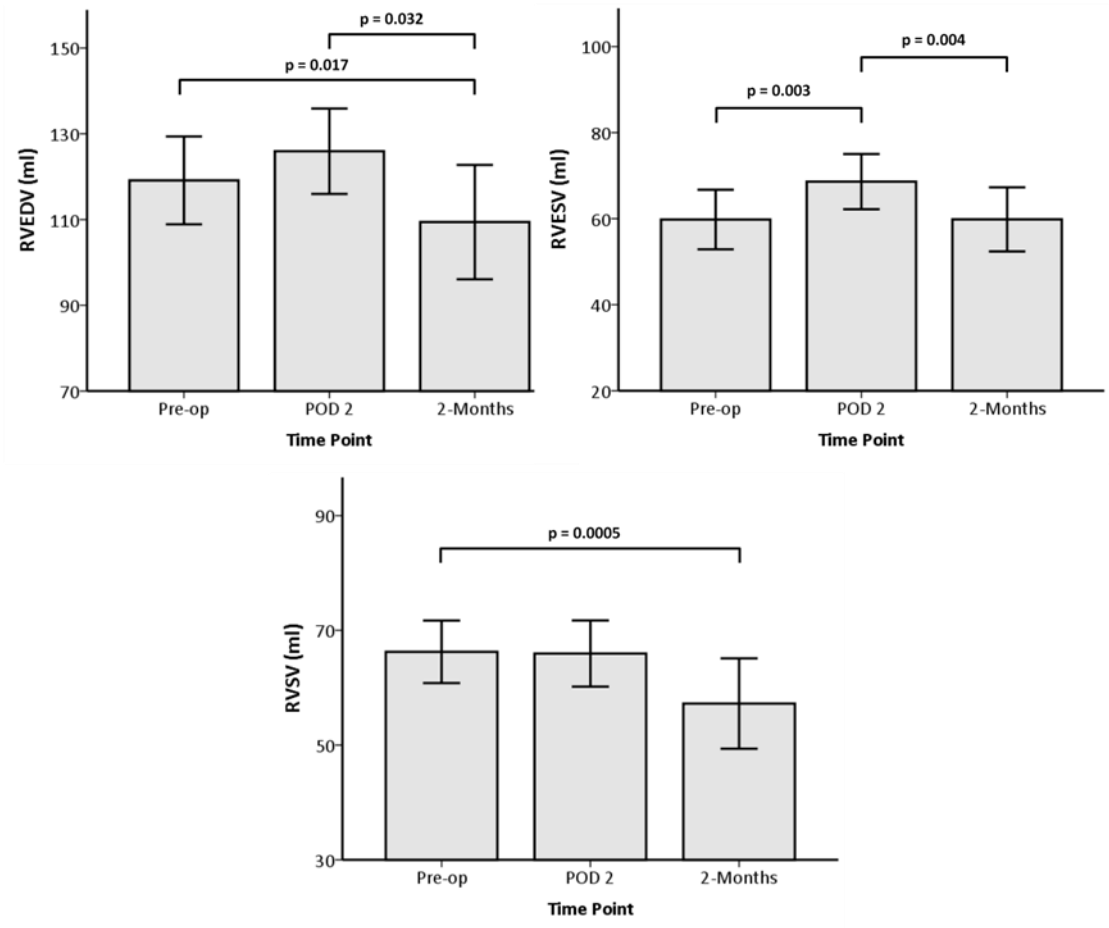


Figure 50. Right ventricular volumes over time
Bar (error bars) represent mean (95% CI). One-way repeated measures ANOVA (results as per Table 27). Pairwise comparisons with paired samples t-test. RVEDV = right ventricular end diastolic volume, RVESV = right ventricular end systolic volume, RVSV = right ventricular stroke volume, POD = post-op day.

5.3.2 Left ventricular function over time

There was no difference in LVEF over the study period (repeated measures ANOVA, $p=0.621$, Figure 51 and Table 28, pg 184). The data were normally distributed pre-op and at POD 2. There was one outlier at the 2-month time point (participant described on pg 180), this result was identified as the lowest LVEF by both observers (figure not shown) and was retained in all analyses. As the

assumption of sphericity was violated a Greenhouse & Geisser adjustment was made and a corrected p-value reported.

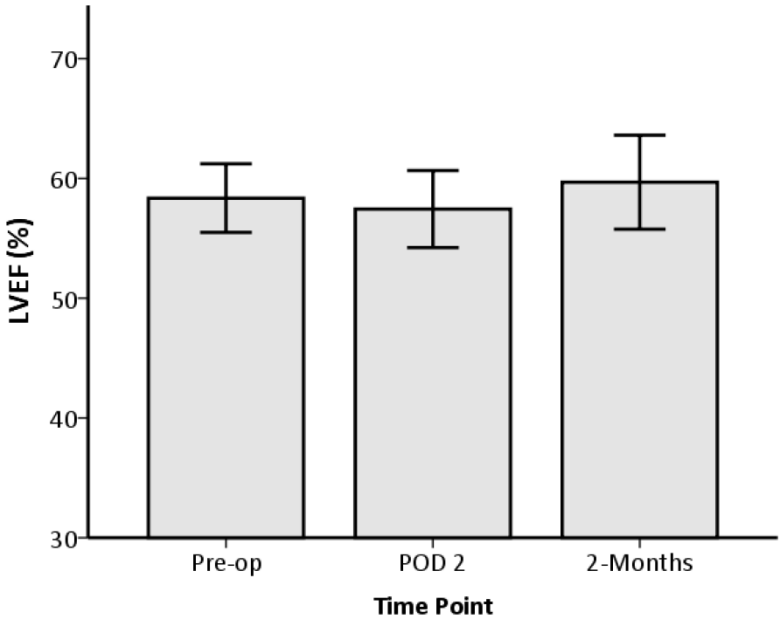


Figure 51. Left ventricular ejection fraction (LVEF) over time
Bar (error bars) represent mean (95% CI). One-way repeated measures ANOVA with Greenhouse & Geisser adjustment p = 0.621. LVEF = left ventricular ejection fraction, POD = post-op day.

Changes in LV volume measurements over time are shown in Table 28 and Figure 52 (pg 185). LVEDV, LVESV and LVSV were all lower at 2-months compared to pre-op (p<0.017, paired t-test). LVEDV and LVESV were also lower at 2-months compared to POD 2 (p<0.033, paired t-test).

	Pre-op	POD 2	2 Months	p value
	n=26	n=22	n=24	
LVEF (%)	58.35 (7.09)	57.44 (7.26)	59.68 (9.30)	0.621*
LVEDV (ml)	109.18 (19.49)	106.31 (19.18)	93.62 (28.21)#¥	0.001*
LVESV (ml)	45.96 (13.17)	46.00 (14.17)	37.72 (13.06)#¥	0.019*
LVSV (ml)	63.22 (11.73)	60.32 (9.01)	55.90 (17.97)#	0.004*

Table 28.Left ventricular ejection fraction and volumes over time
Values are mean (SD). * = one-way repeated measures ANOVA. # = significant difference from pre-op. ¥ = significant difference from POD 2. LVEF = left ventricular ejection fraction, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, LVSV = left ventricular stroke volume, POD = post-op day.

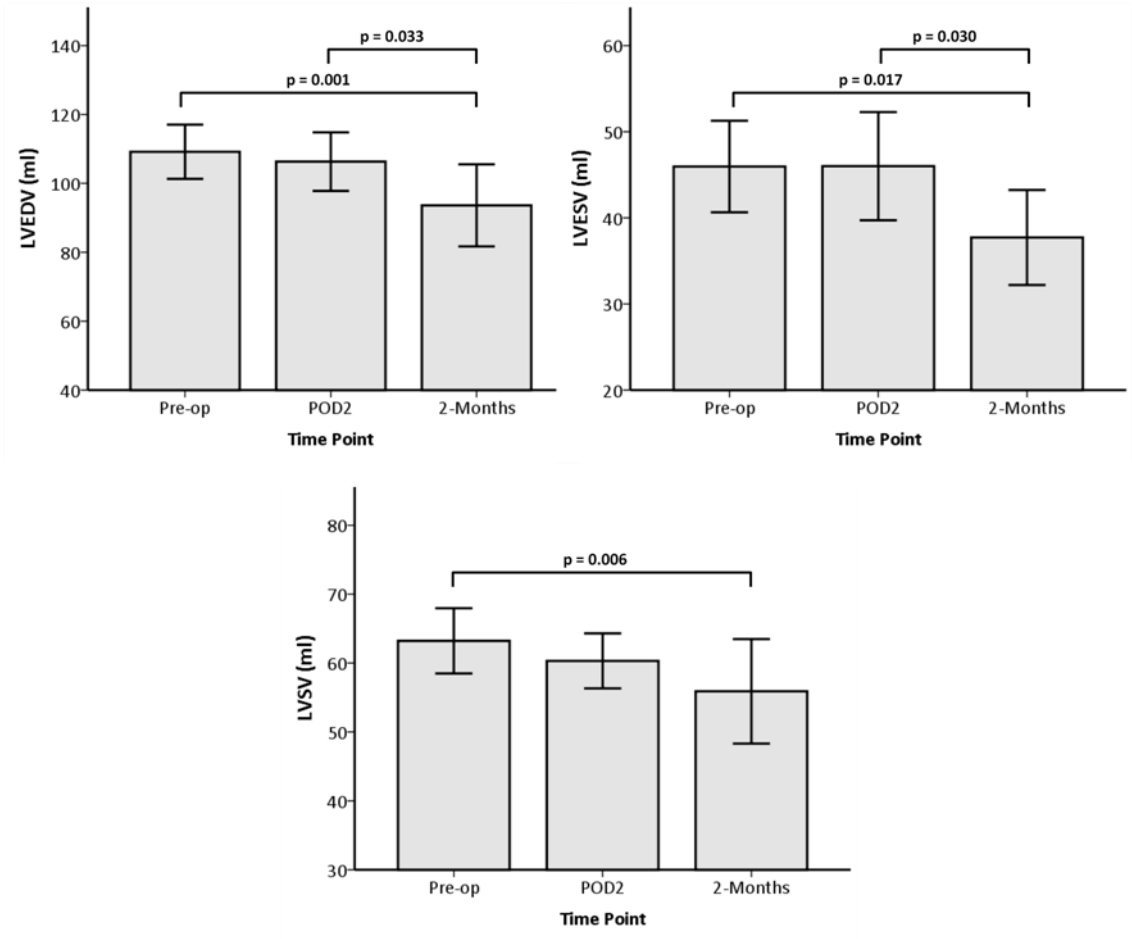


Figure 52. Left ventricular volumes over time
Bar (error bars) represent mean (95% CI). One-way repeated measures ANOVA (results as per Table 28). Pairwise comparisons with paired samples t-test. LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, LVSV = left ventricular stroke volume, POD = post-op day.

5.4 Changes in RV function compared to pre-op and intra-op variables

5.4.1 *Relative* change in right ventricular ejection fraction

Examining changes in RVEF (ΔRVEF), relative to baseline allows interpretation in the context of *pre-op* RVEF. For example, an absolute change in RVEF of 5% by POD 2 may be less significant if $RVEF_{preop}$ was 70% (relative change of 7.1%) compared to $RVEF_{preop}$ of 35%, where this would represent a 14.3% *relative* change. Unless otherwise stated when describing ΔRVEF they are relative to pre-op.

5.4.2 Relationship of pre-op right ventricular function and changes in right ventricular ejection fraction

There is strong negative association between $RVEF_{preop}$ and $\Delta RVEF_{POD2\text{-}preop}$ (r=-0.712, p<0.0005, Figure 53). This shows that those patients with better pre-op RV function, were more likely to have a larger drop in RVEF by POD 2.

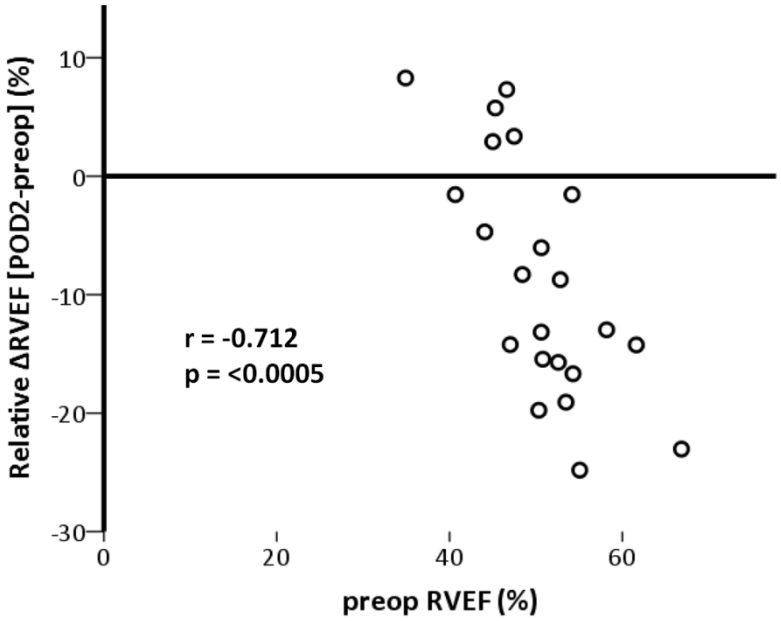


Figure 53. Relationship of $RVEF_{preop}$ and relative $\Delta RVEF_{pod2\text{-}preop}$.
Pearson's correlation coefficient.

When making a similar analysis of $RVEF_{preop}$ and $\Delta RVEF_{2months\text{-}preop}$, there is no association (Figure 54, pg 187), however on visual inspection of the scatter plot there appears to be linear association with a significant outlier (bottom of the plot, indicated by arrow). This patient has been previously described as an outlier at 2-months (footnote P, pg 180). Sensitivity analysis with this patient excluded, showed a strong negative association between the two variables (r=-0.691, p<0.0005, Pearson's correlation coefficient).

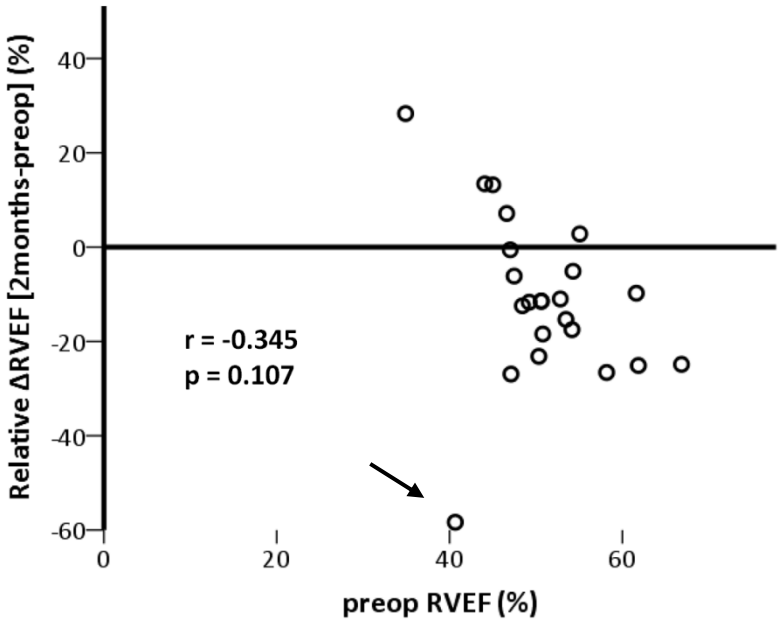


Figure 54. Relationship of $RVEF_{preop}$ and relative $\Delta RVEF_{preop\text{-}2months}$.
Pearson's correlation coefficient. Black arrow indicates outlier described in section 5.4.2.

5.4.3 Right ventricular function and baseline demographics

Association was sought between patient demographics and the measures of RV function at each time point. The comparisons are all displayed in Table 29, pg 188 and there was no association between RVEF and age, pre-op SaO_2, pre-op respiratory function and Thoracoscore ($p>0.057$ for all). In addition, other than TLCO%, there were no associations between *changes* in RVEF ($\Delta RVEF_{POD2\text{-}preop}$ and $\Delta RVEF_{2months\text{-}preop}$) and any of the pre-op demographics (Table 29, pg 188, all $p> 0.190$).

		RVEF			Relative ΔRVEF	
		pre-op	**POD 2**	**2-Months**	**POD2-preop**	**2months-preop**
Age	r	-0.161	-0.036	-0.113	0.271	-0.014
	p	0.432	0.872	0.599	0.223	0.949
Pre-op SaO_2	r	0.345	0.313	0.324	-0.290	-0.024
	p	0.085	0.156	0.122	0.190	0.915
FEV_1%	r	-0.202	-0.219	0.030	0.023	0.186
	p	0.332	0.339	0.893	0.920	0.408
TLCO%	r	-0.379	0.024	-0.006	**0.517**	0.260
	p	0.057	0.915	0.980	**0.014**	0.232
Log_{10} Thoracoscore	r	-0.251	-0.186	-0.214	0.072	-0.053
	p	0.215	0.406	0.316	0.749	0.809

Table 29. Association between pre-op demographics and RV function
Associations are all Pearson's correlation coefficient. RVEF = Right ventricular ejection fraction, POD = post-op day, SaO_2 = oxygen saturation, FEV_1% = percent predicted forced expiratory volume in 1 second, TLCO% = percent predicted transfer factor for carbon monoxide. Significant associations are highlighted in **bold**.

As is evident from Table 29 the association of $RVEF_{pre\text{-}op}$ and TLCO% approached significance (r=0.517, p=0.057). Visual inspection of the data (Figure 55, pg 189) showed that there was an outlier in the data in the upper left corner of the scatter plot skewing the correlation statistic, this patient had no valid reason for exclusion. This apparent negative relationship does not fit with previous hypotheses regarding lung function and RV function. If *this* relationship were true, better RV function would be associated with poorer lung function. Sensitivity analysis with this patient excluded showed no association between TLCO% and $RVEF_{pre\text{-}op}$ (r=-0.196, p=0.348).

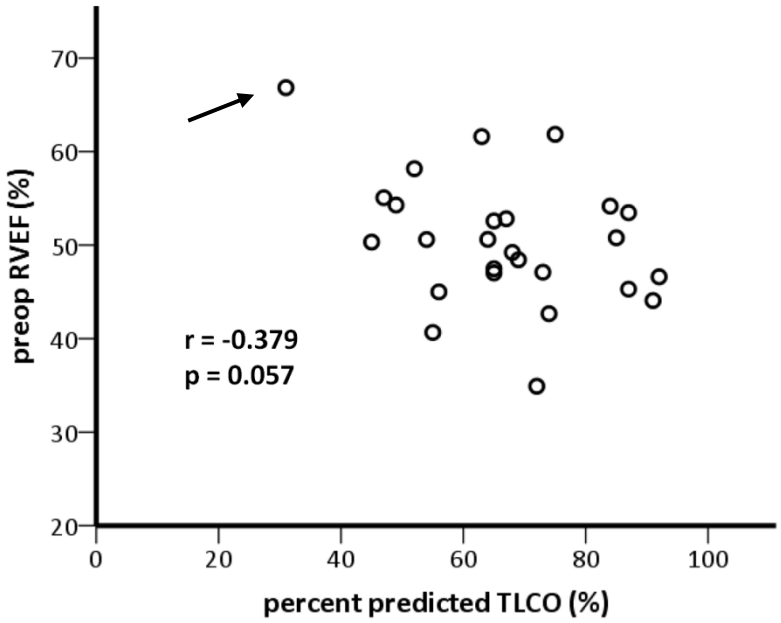


Figure 55. Relationship of $RVEF_{preop}$ and TLCO%
Pearson's correlation coefficient. RVEF = right ventricular ejection fraction, TLCO = transfer factor for carbon monoxide. Black arrow indicates outlier described in section P, pg 180.

There was strong positive association between $\Delta RVEF_{POD2\text{-}preop}$ and pre-op TLCO% (Figure 56). This suggests that poorer pre-op lung function is associated with a larger change in RVEF by POD 2.

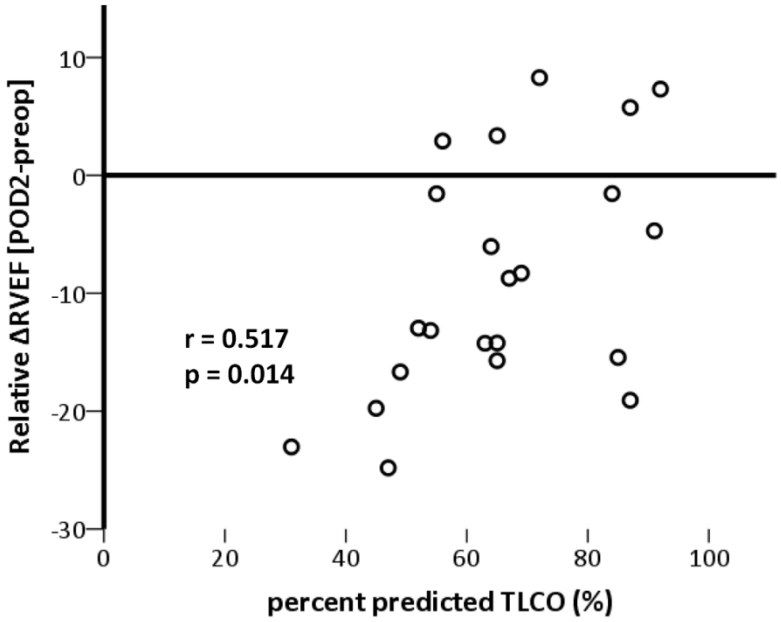


Figure 56. Relationship of $\Delta RVEF_{preop\text{-}POD2}$ and pre-op TLCO%
Pearson's correlation coefficient. RVEF = right ventricular ejection fraction, POD = post-op day, TLCO = transfer factor for carbon monoxide.

5.4.4 Right ventricular function and operative data

To explore the impact of surgical and anaesthetic factors on post-op RV function, association was sought between each of the variables described in Table 30 and *post-op* RV function. The significance for association of these operative factors are displayed in Table 30 with other factors further explored below. There were no associations between RVEF (or ΔRVEF) at any time point and; number of pulmonary segments resected, pathology type and volatile anaesthetic group (Table 30, all p>0.234). There was no association between RVEF (or ΔRVEF) at any time point and; duration of surgery (p>0.153) or duration of one lung ventilation (p>0.121, results not shown).

		RVEF		Relative ΔRVEF	
		POD 2	2-Months	POD2-preop	2months-preop
Pulmonary segments resected	r	0.023	-0.093	-0.177	-0.328
	p	0.919	0.665	0.431	0.137
Pathology type	p	0.363	0.636	0.895	0.381
Volatile anaesthetic Group	p	0.234	0.509	0.864	0.639

Table 30. Significance for association of operative variables and RV function
Number of pulmonary segments was analysed using Spearman's correlation coefficient. Pathology type and volatile anaesthetic group were all analysed using the Kruskal-Wallis Test. Variables are as defined in Table 18 (Operative data in generic methods section, chapter 4). RVEF = right ventricular ejection fraction, POD = post-op day.

5.4.5 Right ventricular function and predicted post-operative pulmonary function

There is a strong positive association between ppoTLCO% and $\Delta RVEF_{POD2\text{-}preop}$ (r=0.682, p<0.0005, Pearson's correlation coefficient, Figure 57, pg 191). There was no association between ppoTLCO% and RVEF, or $\Delta RVEF_{2months\text{-}preop}$ at other time points (p > 0.121 for all). There were no associations between RVEF (or ΔRVEF) and ppoFEV_1% (p > 0.164 for all).

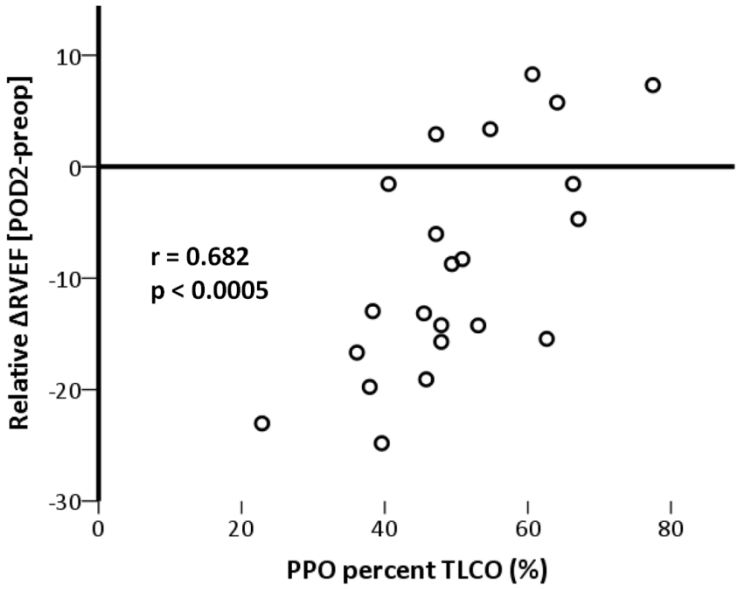


Figure 57. Relationship of relative $\Delta RVEF_{preop\text{-}POD2}$ and ppoTLCO%.
Pearson's correlation coefficient. RVEF = right ventricular ejection fraction, POD = post-op day, PPO = predicted post-op , TLCO = transfer factor for carbon monoxide.

5.4.6 Right ventricular function and analgesia

The study protocol included epidural placement in all patients. As this was not feasible in four patients, a sensitivity analysis of the impact of analgesic technique on post-op RV function was performed. There was no relationship between the use of epidural or paravertebral analgesia for either absolute RVEF post-operatively or ΔRVEF ($p > 0.273$ for all, Figure 58).

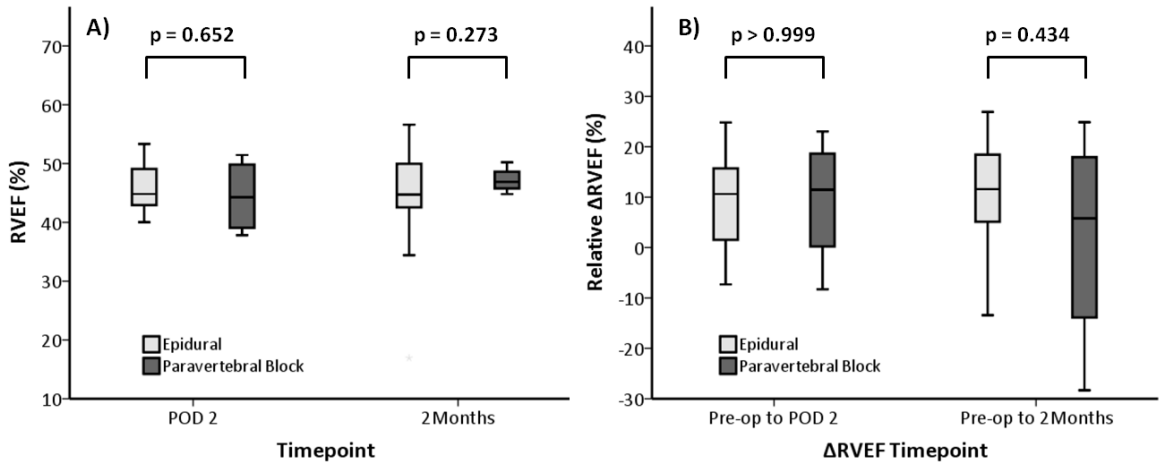


Figure 58. A) RVEF and B) Relative ΔRVEF for each primary analgesic technique
All Mann-Whitney U-Test. Light grey = epidural group (n=23), Dark Grey = paravertebral group (n=4). RVEF = right ventricular ejection fraction, POD = post-op day.

The above analysis includes all patients in each primary analgesic group, this does not take account of whether the method was functional or not.

5.4.7 Right ventricular function, intra-op fluid administration and post-operative fluid balance

Mean intra-op fluid administration was 933.3 ml (402.9) but as fluid tended to be administered in 500ml aliquots, 26 of the values of fluid administration were multiples of 500. This did not allow fluid administration to be treated as a continuous variable. Intra-op fluid administration was therefore categorised in ranges of ≤500ml (n=9), 501-1000ml (n=13) and >1000ml (n=5).

$RVEF_{pre\text{-}op}$ did not influence the amount of intra-op fluid given (p=0.971, Kruskal Wallis test, Figure 59A). There was no difference in RVEF or ΔRVEF across the fluid administration ranges at all post-op time points (p>0.538 for all, Kruskal Wallis test, Figure 59A & B).

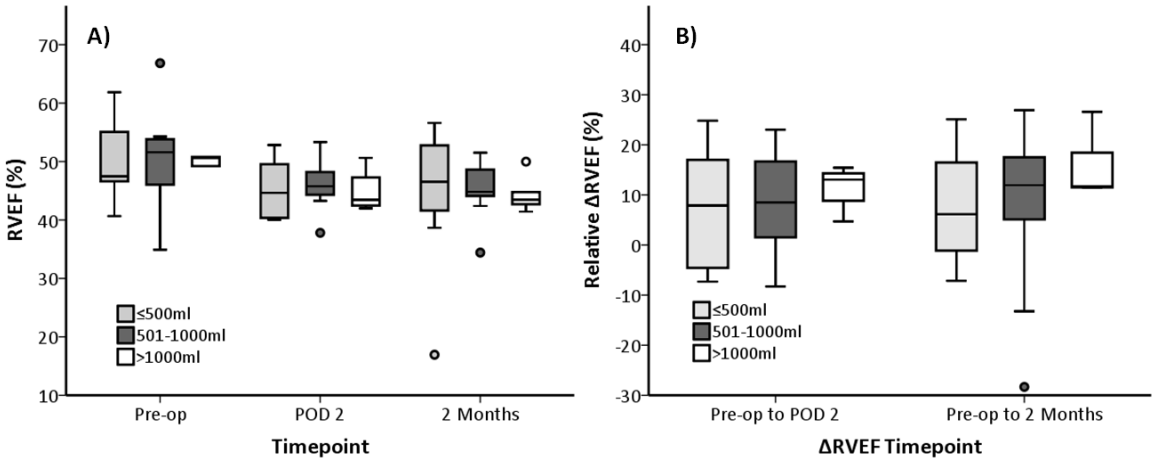


Figure 59. A) RVEF and B) Relative ΔRVEF for each fluid administration group
A) No difference in RVEF across groups of fluid administration at each time point, all Kruskal Wallis Test; Pre-op (p=0.971), POD 2 (p=0.728), 2-Months (p=0.538). B) No difference in ΔRVEF across groups at each time point, all Kruskal Wallis; Pre-op to POD 2 (p=0.934) and Pre-op to 2 Months (p=0.718). *Light grey = ≤500ml, Dark Grey = 501-1000ml, White = >1000ml.*

There was no association between RVEDV measurements (absolute and ΔRVEDV) at *any* time point with intra-op fluid administration or HDU fluid balance (p>0.059 for all, not shown). There was no association between RVEF (or ΔRVEF) with both; cumulative fluid administration and fluid balance on the morning of POD 2, (p>0.534 for all, not shown).

5.5 Right ventricular function and post-operative outcomes

5.5.1 Right ventricular function and post-operative cardiovascular outcomes

Only two patients developed post-op atrial fibrillation, one on post-op day one and the other on post-op day seven. No other arrhythmias developed post-operatively. Detailed statistical analysis would be meaningless but pre-operatively and on POD 2, these two patients were not outliers for RVEF or $\Delta RVEF_{POD2\text{-}preop}$.

Nine participants required a vasoconstrictor during the post-op period. In this group the only vasoconstrictor used was nor-adrenaline (NA)[Q]. NA was discontinued in all patients by the morning of POD 2 (i.e. no patients were on a vasoconstrictor during POD 2 CMR imaging). There was no difference in the $RVEF_{pre\text{-}op}$ of those patients who would go on to require NA post-operatively (Figure 60A). Post-operatively there was no difference in the RVEF and ΔRVEF in those patients requiring NA and those not requiring a vasoconstrictor (Figure 60A & B).

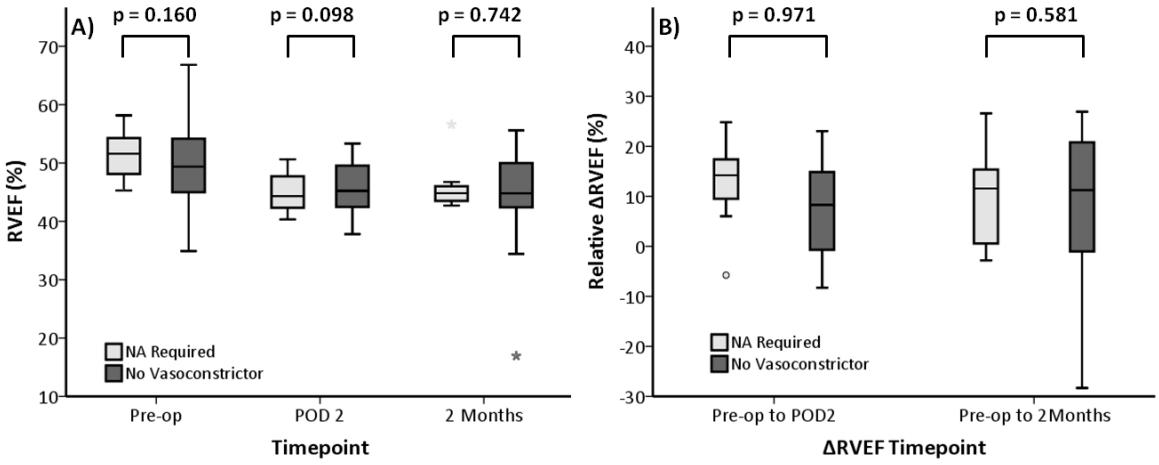


Figure 60. A) RVEF and B) Relative ΔRVEF for each vasoconstrictor group
All Mann-Whitney U-Test. Light grey = nor-adrenaline group, Dark Grey = No vasoconstrictor.

[Q] In our institution, the use of nor-adrenaline for epidural induced hypotension is standard practice.

5.5.2 Right ventricular function and duration of high dependency unit and hospital stay

The association of $RVEF_{pre\text{-}op}$ and length of High Dependency Unit (HDU) stay approached significance (r=-0.372, p=0.061, Spearman's correlation coefficient) and there was strong association between $RVEF_{POD2}$ and HDU length of stay (Figure 61, p=0.001).

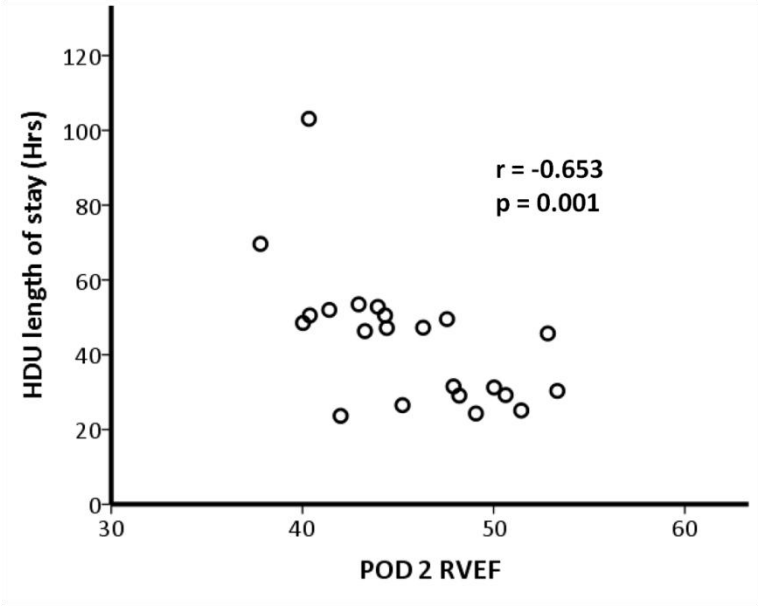


Figure 61. RVEF against length of HDU stay
Spearman's correlation coefficient. HDU = high dependency unit, RVEF = right ventricular ejection fraction.

There was no association between $\Delta RVEF_{POD2\text{-}preop}$ and duration of HDU stay (p=0.505, Spearman's correlation coefficient). There was no association of $RVEF_{pre\text{-}op}$, $RVEF_{POD2}$ and $\Delta RVEF_{POD2\text{-}preop}$ with length of hospital stay (p>0.361).

5.5.3 Right ventricular function and six minute walk test performance

As described in section 4.7.2.1, pg 167 there was no deterioration in median 6 minute walk test (6MWT) distance from pre-op to 2-months. At 2-months there were 4 patients who were unable to walk and seven who had a 6MWT distance which had dropped by more than the minimal important distance of 28m. There was no association between RVEF and relative ΔRVEF at any time point with pre-op 6MWT or 2-month 6MWT (p>0.087, Pearson's correlation coefficient).

When examining those participants with an unchanged (or increased) 6MWT and those with a deterioration in 6MWT (by more than 28m or unable to walk), there was a difference in RVEF at 2-months (Figure 62 A, p=0.041). This shows a higher RVEF in those participants with a deterioration in 6MWT. This is the opposite to what might be expected with poorer RV function being associated with decreased exercise capacity. At other time points there was no difference in RVEF or relative ΔRVEF between the two groups.

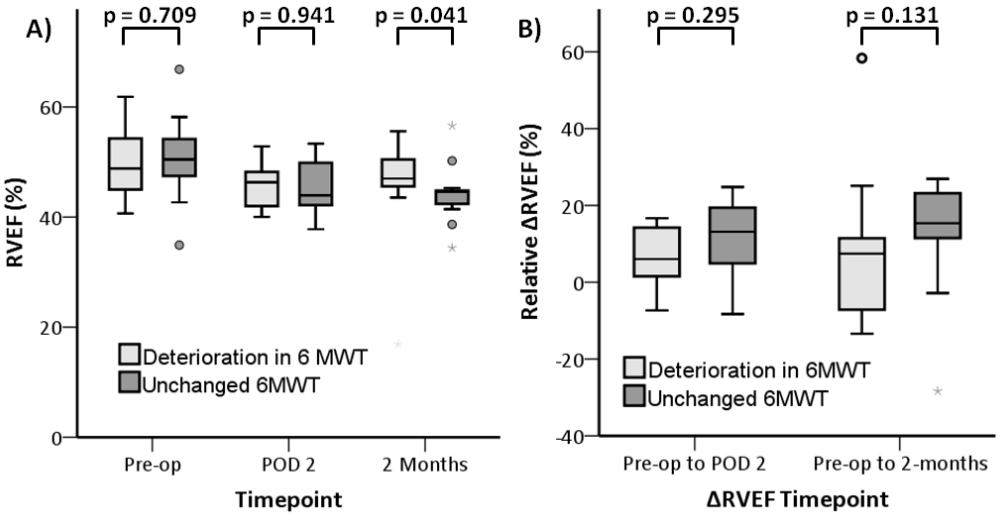


Figure 62. A) RVEF and B) Relative ΔRVEF for each 6MWT group
All Mann-Whitney U-Test. p-values as illustrated. Light grey: Deterioration in 6MWT of >28m or unable to walk. Dark Grey: Unchanged 6mWT or deterioration of ≤ 28m. *6MWT: 6 Minute Walk Test*. Unchanged 6MWT n=14, Deteriorated 6MWT n=11.

5.6 Right ventricular function, functional outcomes and quality of life

Tables displaying all associations examining functional outcomes and quality of life are provided in Appendix 4.

5.6.1 Association between pre-op right ventricular function, pre-op functional status and pre-op quality of life

There was no association between $RVEF_{preop}$ and pre-op functional status measures, global health score or any measure of the EQ5D scoring system.

5.6.2 Association between post-operative right ventricular function, post-operative functional outcomes and post-operative quality of life

There was no association between $RVEF_{POD2}$, $RVEF_{2months}$, relative $\Delta RVEF_{pod2\text{-}preop}$, relative $\Delta RVEF_{2months\text{-}preop}$ and any of the measures of functional status or any component of EQ5D at 2-months.

There was no association between $RVEF_{POD2}$, $RVEF_{2months}$, relative $\Delta RVEF_{POD2\text{-}preop}$ and global health score at 2-months ($p>0.093$ for all). There was association between relative $\Delta RVEF_{2months\text{-}preop}$ and global health score at 2-months ($r=0.438$, $p=0.037$, Spearman's correlation coefficient) however, visual inspection of the scatter plot (not shown) revealed a significant effect from an outlier (participant discussed, footnote P pg 180). Sensitivity analysis with this patient excluded meant that significant association was lost ($r=0.264$, $p=0.234$, Spearman's correlation coefficient).

There was no association between $RVEF_{POD2}$, $RVEF_{2months}$, relative $\Delta RVEF_{POD2\text{-}preop}$, relative $\Delta RVEF_{2months\text{-}preop}$ and; functional status measures, global health score or any component of EQ5D at one year.

5.7 Discussion

The main finding of this investigation (the first using CMR to sequentially describe changes in RV function following lung resection) is that RV function deteriorates by POD 2 (primary outcome) and remains depressed at 2-months. This is evidenced by a median *relative* decrease in RVEF of 10.9% from baseline on POD 2, with four patients experiencing a *relative* decrease of RVEF in excess of 20.0%. The observed changes in RV function occur despite preservation of LV function, suggesting changes following lung resection primarily affect the right ventricular-pulmonary vascular unit.

CMR was feasible and well tolerated post-operatively with more than 80% of patients completing the examination protocol. RVEF assessment was reproducible with coefficients of variation (CV) between 12.9% and 16.8% over the duration of the study. As this was the first study to describe CMR for assessment of ventricular function in a lung resection cohort, CVs in this population have not previously been described. Work in normal subjects and those with cardiac pathology have shown CVs for RVEF between 8.0 and 10.7%[115]. Pre-op values in the current study were similar to this with a CV of 12.9%, which deteriorated to 16.8% by POD 2 suggesting surgery has an impact on CMR reproducibility. Post-hoc analyses suggest surgical side is also important to observed variability. Pre-op CV's were similar for those having left or right sided resections (12.8% and 13.2% respectively) but post-operatively those patients with right sided resections had larger CVs (20.5% on POD 2) than those having left sided surgery (11.5%). There is no apparent difference at 2-months. Surgery and side did not appear to impact on the reproducibility for left ventricular CMR measurements.

Although the heart sits within the left thoracic cavity and it may be expected that surgery on this side would impact on reproducibility, the opposite is true. Previous studies using CMR to examine cardiac position following lung resection has shown lateral shift of the RV[209]. In the post-op period this would bring the heart, particularly the anteriorly located RV free wall, closer to the surgical site. The present of post-op haemothorax and/or pneumothorax, with inter costal drains, may play a role in the ability to accurately contour the RV at this stage. Future studies using CMR in this population for mechanistic research, may wish to prioritise patients undergoing left sided resections.

In the setting of acutely increased afterload, the RV responds by attempting to increase systolic function in an attempt to maintain RV-PA coupling (homeometric auto-regulation as described in section 1.2.3.9, pg 39). This is followed by heterometric autoregulation (section 1.2.3.9, pg 39) with dilatation to preserve cardiac output[55, 159, 160]. By POD 2 following lung resection, RVEDV and RVESV have increased (by 6.8ml and 8.6ml respectively) from pre-op levels. Although the increases are small absolute volumes, this may demonstrate evidence of heterometric autoregulation in the acute phase following lung resection.

At 2-months following surgery biventricular volumes are lower than compared to pre-op values, with RVEDV, LVEDV and LVESV all reduced. Due to the proportion of changes this resulted in ongoing decreased RVEF and unchanged LVEF.

With half of the participants having a relative decrease in RVEF over 10% and four participants having a decrease in excess of 20%, it could be reasonably hypothesised that a reduction of this magnitude would result in clinical sequelae. Unfortunately this investigation, with its sample size, does not allow *robust* assessment of the clinical implications of post-op RV dysfunction and any results would be under-powered and hypothesis generating only. However, the impact of pre-op factors, surgical variables and anaesthetic technique on post-op RV function were examined on an *exploratory* basis, along with the impact of RV function on post-op outcomes. The majority of pre-op variables demonstrated no association with post-op RV function. Age, sex, smoking status, pre-op SaO_2, pre-op FEV_1 and Thoracoscore showed no association. There was association between $RVEF_{preop}$ and $\Delta RVEF_{POD2\text{-}preop}$, with better pre-op RV function present in those who would have a bigger drop in RVEF post-operatively (Figure 53, pg 186). This could be considered figuratively as a *'bigger you are, the harder you fall'* association. A similar association has previously been demonstrated by Lewis et al.[44] in a pneumonectomy cohort. At the time of PA clamping (Figure 63, pg 199); those patients with normal RVEF (≥45%) generally showed a significant decline in RVEF (p=0.0006), whereas most with subnormal levels (RVEF <45%) showed no change[44].

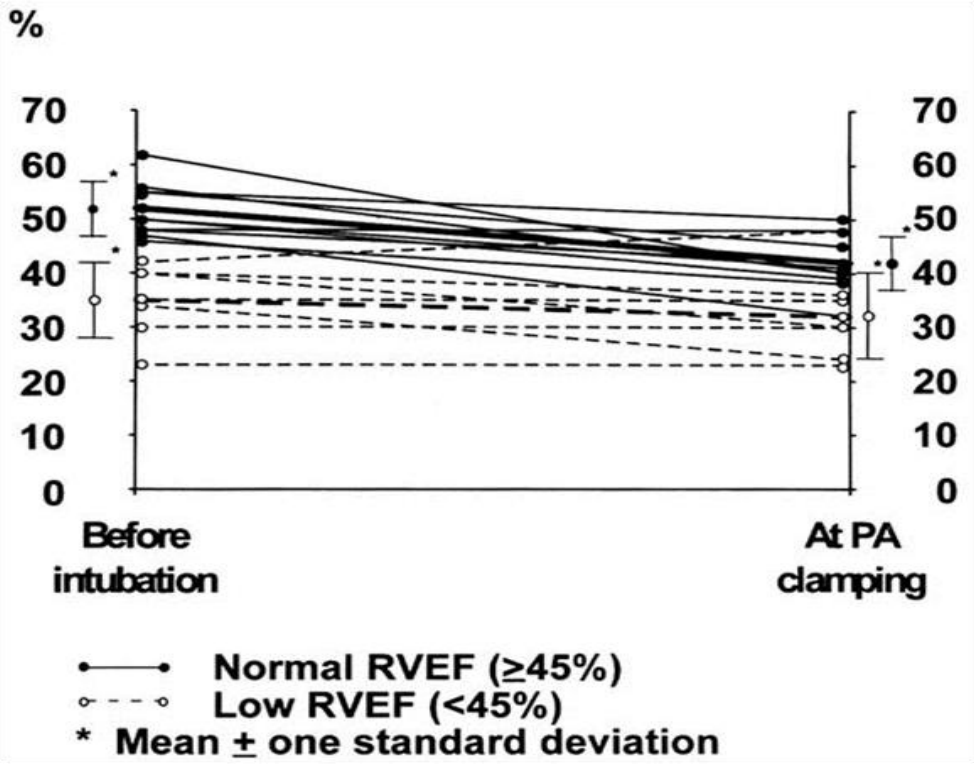


Figure 63. Change in RVEF at time of PA clamping.
From Lewis et al.[44]. RVEF on Y-axis. RVEF = right ventricular ejection fraction. PA = pulmonary artery.

Another comparable clinical example is from the study by Matyal et al. which examined RV myocardial performance index (RV-MPI) at the time of OLV in a cohort undergoing lung resection[43]. This demonstrated that patients with *better* baseline RV function (as measured by MPI) were more likely to develop SVT than those with poorer RV function. They hypothesised;

> "*this resulted from these subjects having a degree of compensated cardiac dysfunction as a result of a chronically elevated pulmonary vascular resistance or afterload, which allows them to better tolerate acute changes in ventricular afterload or volume.*"
>
> Matyal et al.[43]. (2010)

The pattern of change in the current study could support this concept of pre-conditioning. It could be hypothesised those patients with poorer RV function pre-op, have previously been exposed to increases in afterload resulting from their underlying pathology, meaning they are better equipped to cope when they undergo surgery.

This study demonstrated moderate positive association between pre-op lung function (as signified by TLCO%, Figure 56, pg 189) and deterioration in RV function by POD 2. This demonstrates poorer *pre-op* lung function was associated with a larger decrease in RVEF by POD 2. In severe COPD an association between poor pulmonary function and RV-PA haemodynamics has previously been demonstrated, with higher PA pressures present in those with a lower TLCO%[295]. It could be hypothesised that the larger drop in RVEF in those with poorer lung function results from these patients being vulnerable to changes in pulmonary haemodynamics. There is also a strong positive association between *predicted* post-op lung function (ppoTLCO%) and change in RVEF by POD 2 (Figure 57, pg 191). This suggests those patients with poorer pulmonary function *post-operatively*, have a larger drop in RVEF by POD 2. This should be interpreted with caution as post-op lung function (ppoTLCO%) and pre-op lung function (TLCO%) are significantly associated ($r=0.895$, $p<0.0005$, Pearson's correlation coefficient, not shown).

This study has demonstrated that patients with better pre-op RV function and those with poorer pre-op respiratory function, are likely to have a larger deterioration in RV function following lung resection. Although not possible to demonstrate with the current investigation, this may be demonstrating two independent mechanisms. A group at higher risk of deterioration in RV function, would therefore be those presenting with *good* pre-op RV function and *poor* pulmonary function. In contrast, those with poor pre-op RV function and good pulmonary function may be protected when undergoing lung resection.

Previous work has suggested the extent of lung resection (mainly lobectomy v pneumonectomy[45, 199, 201, 202, 206]) may impact on the degree of post-op RV dysfunction. This investigation included only lobectomy patients (with one intra-op conversion to pneumonectomy) and the median (IQR) number of resected segments was only 5 (3, 5) meaning any association between size of resection and post-op RV function would be hard to demonstrate. The one pneumonectomy patient was not an outlier for any RV function variable, at any time point and was retained in all analyses. There was no association between post-op RV function and both; resection side and pathology type.

The impact of anaesthetic factors on post-op RV function was explored. Thoracic epidural has been shown to negatively affect RV contractility (with preserved coupling) at times of increased afterload[85, 296]. Although small numbers in the paravertebral group (n=4), there was no difference in post-op RV function depending on analgesic technique. The importance of fluid balance in patients following lung resection is well established, with excess fluid administration associated with lung injury post-operatively[297]. Given the potential interplay of RV function and acute lung injury (especially the more severe form, ARDS), the impact of fluid volume administration on post-op RV function was assessed. In this investigation the volume of fluid administered and fluid balance in the peri-operative period had no influence on post-op RV function and volume (RVEF and RVEDV). Our institution practices a fluid restrictive approach in patients following lung resection. The low volume of fluid administered, along with low variability means any impact on post-op RV function would be difficult to demonstrate.

Previous work has suggested association between peri-operative changes in RV function and both; development of complications[43, 45, 176] and poor long-term functional status[44, 201]. This study demonstrates a strong association between $RVEF_{POD2}$ and post-op HDU stay. The reasons for remaining in critical care are multi-factorial and this investigating may be highlighting that post-op RV function is one of the factors important in this patient group. There were no other significant associations between RV function and post-op outcomes. This study was unable to find any association between RV function and; 6MWT results, functional status and quality of life.

This thesis consistently refers to the post-operative changes in RV function as 'dysfunction.' However, the author acknowledges that the changes may be demonstrating an adaptive change in cardiovascular mechanics, with the right ventricle compensating for changes occurring following lung resection.

5.7.1 Strengths and limitations

The first use of CMR (a non-invasive reference method for assessment of RV function) in this patient cohort, with dual analysis of RV parameters by blinded clinicians, is a significant strength of this study.

This investigation made no assessment of the loading conditions experienced by the RV so further work is required to examine the mechanisms of RV dysfunction following lung resection. Mechanisms of post-op RV dysfunction are explored in chapter 9.

Although association was sought on an exploratory basis, this size of this study did not allow robust clinical correlation and future work should assess the clinical implications of RV dysfunction. Additionally, this study made no assessment of RV function during exercise; previous work in this patient group has consistently demonstrated marked changes in pulmonary haemodynamics and RV function on exercise (Table 5, pg 82)[172, 174]. Although the deterioration in RVEF observed in this cohort is modest, the author suggests the changes observed at rest would be exacerbated during exercise, potentially limiting functional capacity.

CMR is a reference method for assessing RV volumes but its widespread use in this group is limited, firstly by availability and secondly by suitability in the immediate post-op patient. Although withdrawals were well within the number allowed by the studies power analysis, a group of participants were unable to undergo CMR assessment post-operatively. The requirement for transfer, also meant assessment was performed at discrete time points with no continuous monitoring possible. A validated bedside alternative, potentially utilising trans-thoracic echocardiography, biomarkers or a combination would have utility in this population. The use of echocardiography and biomarkers to assess RV function following lung resection is explored in chapters 6, 7 and 8.

5.8 Conclusion

This is the first study showing that RV function is impaired not just in the immediate post-op period following lung resection, but remains depressed months later, long in to the recovery period. Although this study was unable to demonstrate association with clinical outcomes, in other settings RV dysfunction is associated with poor prognosis and reduced exercise capacity. The author hypothesises that the changes in RVEF are likely to have clinical sequelae and may provide a target for clinical interventions allowing amelioration of post-op cardiorespiratory morbidity.

The challenges of CMR imaging in this population mean the validation of alternative methods of assessing RV function would have utility.

Chapter 6 Conventional Echocardiographic Parameters of Right Ventricular Systolic Function

This chapter describes conventional echocardiographic parameters of RV systolic function; Fractional area change (FAC), Tricuspid annular plane systolic excursion (TAPSE) and S' Wave velocity at the tricuspid annulus (S'Wave). It will first describe the availability and reproducibility of each imaging modality, it will then describe changes in each parameter over time. The final step will be comparison with cardiovascular magnetic resonance (CMR) determined RV ejection fraction ($RVEF_{CMR}$) as a reference method of assessing RV function.

Trans thoracic echocardiography (TTE) was well tolerated with all 27 patients (100%) completing the scan protocol pre-operatively, 26 (96.3%) on post-op day (POD) 2 and 24 (88.9%) at 2-months. The one patient not scanned on POD 2 declined echo imaging. Of the patients not imaged at 2-months, two declined and one was unwell at another hospital. This gave a total of 77 scans available for analysis.

6.1 Imaging availability and reproducibility

6.1.1 Imaging availability

All echocardiographic parameters were dual reported by the author and echocardiography technicians (ET's) from blinded images. Ten of the anonymised and randomised scans were dual by the author for assessment of intra-observer variability. There was disparity in imaging availability[R] for FAC between the author and the ET's, particularly on POD 2 where the author obtained results on 12 patients (46.2%) in contrast to the ET's who managed imaging on 25 patients (96.2%). For the other variables (TAPSE and S'Wave) imaging was available in the majority of patients (>88.5%) at each time point with no disparity between the author and ET's (Table 31, pg 205).

[R] Availability in this context refers to the ability to obtain a result from the echocardiographic image provided. Availability will have been affected by the quality of the image and by the interpretation by the observer.

	Pre-op		POD 2		2-Months	
	(n=27)		(n=26)		(n=24)	
	ET	Author	ET	Author	ET	Author
FAC	26 (96.3%)	18 (66.7%)	25 (96.2%)	12 (46.2%)	23 (95.8%)	20 (83.3%)
TAPSE	27 (100%)	26 (96.3%)	23 (88.5%)	23 (88.5%)	24 (100%)	23 (95.8%)
S' Wave	27 (100%)	27 (100%)	23 (88.5%)	23 (88.5%)	24 (100%)	24 (100%)

Table 31. Availability of echocardiographic imaging at each time point
POD = post-op day, ET = echocardiography technician, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

The impact of operative side on imaging availability was explored. Table 32 demonstrates it was not possible to determine FAC, for as many patients undergoing left sided resections (compared to right sided) pre-operatively and on POD 2, with this pattern reversed at 2-months. When determining TAPSE on POD 2 there is less paired imaging available for those undergoing left sided resections. For the other time points and other modalities, there was no impact of side of resection on availability of imaging.

	Pre-op		POD 2		2-Months	
Resection side	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
	(n=10)	**(n=17)**	**(n=9)**	**(n=17)**	**(n=8)**	**(n=16)**
FAC	5 (50.0%)	12 (70.6%)	3 (33.3%)	8 (47.1%)	7 (87.5%)	12 (75.0%)
TAPSE	9 (90.0%)	17 (100%)	7 (77.8%)	16 (94.1%)	8 (100%)	15 (93.8%)
S' Wave	10 (100%)	17 (100%)	8 (88.9%)	15 (88.2%)	8 (100%)	16 (100%)

Table 32. Paired image availability (by author *and* echotechs) for echocardiographic parameters by side of resection at each time point
POD = post-op day, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

6.1.2 Imaging reproducibility

A summary of the inter-observer and intra-observer variability of each of the echocardiographic parameters is provided in Table 33 (pg 206). There was poor reproducibility for FAC, signified by a coefficient of variation (CV) of 15.8% and a

non-significant intraclass correlation coefficient. TAPSE and S'Wave demonstrated excellent inter, and moderate intra-observer variability.

Inter-Observer Variability			
	Paired Measures	**CV (%)**	**ICC Agreement (95% CI)**
FAC (%)	n=47	15.8%	0.12 (-0.16, 0.38) p=0.207
TAPSE (mm)	n=72	2.6%	0.94 (0.90, 0.97) p<0.0005
S' Wave (cm/s)	n=74	5.5%	0.91 (0.86, 0.94) p<0.0005

Intra-Observer Variability			
	Paired Measures	**CV (%)**	**ICC Agreement (95% CI)**
FAC (%)	n=10	12.6%	0.20 (-0.21, 0.65) p=0.192
TAPSE (mm)	n=10	3.9%	0.71 (0.23, 0.92) p=0.006
S' Wave (cm/s)	n=10	9.0%	0.77 (0.15, 0.94) p<0.0005

Table 33. Inter and intra-observer variability for echocardiographic measures of systolic function
Coefficient of Variation (CV) calculated as per Equation 8, pg 24, intraclass Correlation coefficient (ICC) calculated as mixed effect, absolute agreement. FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

The impact of surgery on imaging reproducibility was assessed by examining the CV's at each time point (Table 34). There is an apparent improvement in CV for FAC by POD 2, however this must be taken in the context that paired imaging (by both author *and* ET) was only available for 11 patients (42.3%) at this time point. Surgery did not appear to impact on CV's for the other variables.

Inter-Observer Variation			
	Pre-op	**POD 2**	**2-Months**
	CV (%)	**CV (%)**	**CV (%)**
FAC	18.3	9.5	17.2
TAPSE	2.5	2.4	2.9
S'Wave	5.5	5.9	5.1

Table 34. Coefficient of variation for echocardiographic variables over time
POD = post-op day, CV = coefficient of variation, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

The impact of side of surgery on reproducibility was also assessed (Table 35). There was a suggestion of better reproducibility for FAC with those undergoing left sided resections in contrast to those undergoing right sided resections. However, as described above, it was not possible to determine FAC for as many patients undergoing left sided procedures as for those undergoing right and this may impact on these figures. There was no obvious impact of side on the reproducibility of TAPSE and S'Wave values.

Inter-Observer Variation		
	CV (%)	
Resection side	**Left**	**Right**
FAC	12.4	15.9
TAPSE	2.9	2.5
S'Wave	5.1	5.6

Table 35 Coefficient of variation for echocardiographic variables by side of resection
CV = coefficient of variation, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

6.1.3 Bland Altman Analysis

Bland Altman (BA) analysis between the two observers (the author and ET's) for FAC, despite minimal bias (-2.9%), showed unacceptable limits of agreement (-27.1, 21.4%, Figure 64, pg 208). BA analysis for TAPSE showed minimal bias (-0.5mm) and acceptable limits of agreement (-2.9, 1.9mm) with no evidence of systematic variability (Figure 65, pg 208). BA analysis for S'Wave showed minimal bias (-0.1cm/s) and acceptable limits of agreement (-2.1, 1.8cm/s) with no evidence of systematic variability (Figure 66, pg 209).

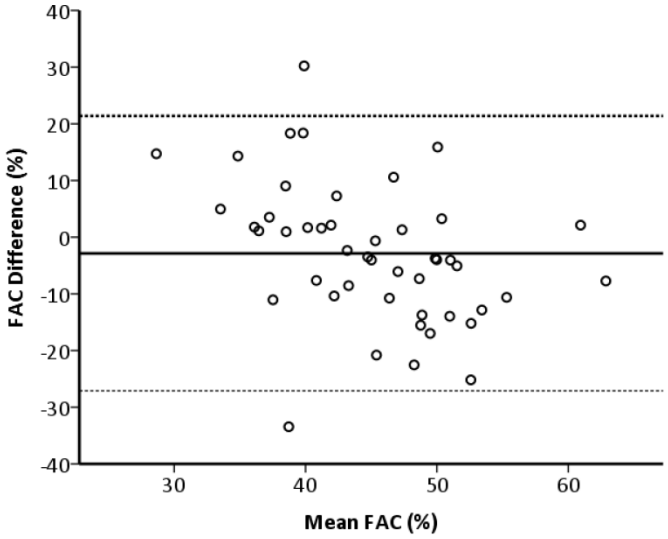


Figure 64. Bland Altman analysis of fractional area change (FAC) measurements (n = 47)
Solid line represents mean bias (-2.9%) and dashed lines represent 95% limits of agreement (-27.1, 21.4%).

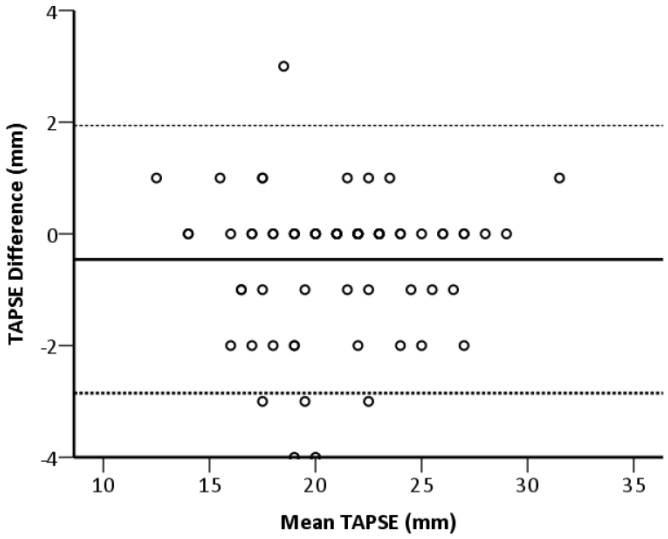


Figure 65. Bland Altman analysis of tricuspid annular plane systolic excursion (TAPSE) measurements (n = 72)
Solid line represents mean bias (-0.5mm) and dashed lines represent 95% limits of agreement (-2.9, 1.9mm).

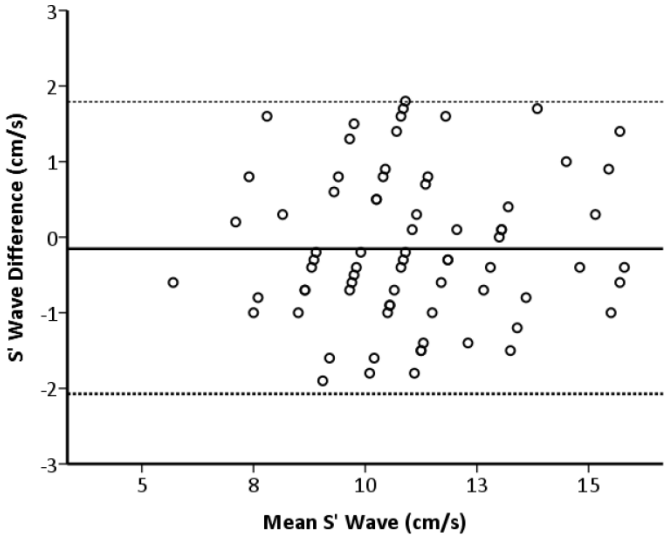


Figure 66. Bland Altman analysis of S' Wave velocity at the tricuspid annulus (S' Wave) measurements (n = 74)
Solid line represents mean bias (-0.1cm/s) and dashed lines represent 95% limits of agreement (-2.1, 1.8cm/s).

6.2 Changes over time

One-way repeated measures analysis of variance (ANOVA) determined there was no significant difference in FAC over the duration of the study (p=0.089, Figure 67, pg 210 and Table 36, pg 211). Changes in TAPSE over time approached significance (p=0.057, Figure 68, pg 210 and Table 36, pg 211) and there was a change in S'wave over time with an increase from 10.4cm/s pre-op to 12.1cm/s on POD 2 (p=0.009) before returning to baseline levels (Figure 69, pg 211 and Table 36, pg 211) .

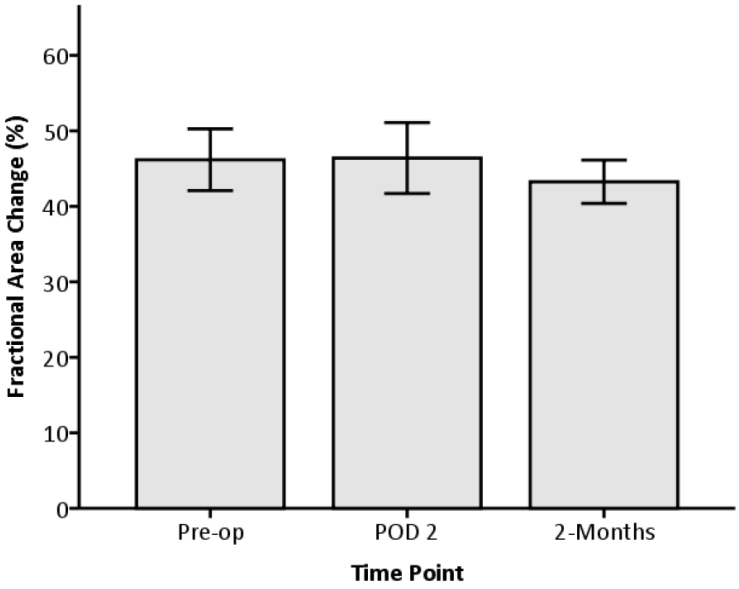


Figure 67. Fractional area change (FAC) over time
Bar (error bars) represent mean (95% CI). One-way repeated measures ANOVA p=0.089. POD = post-op day.

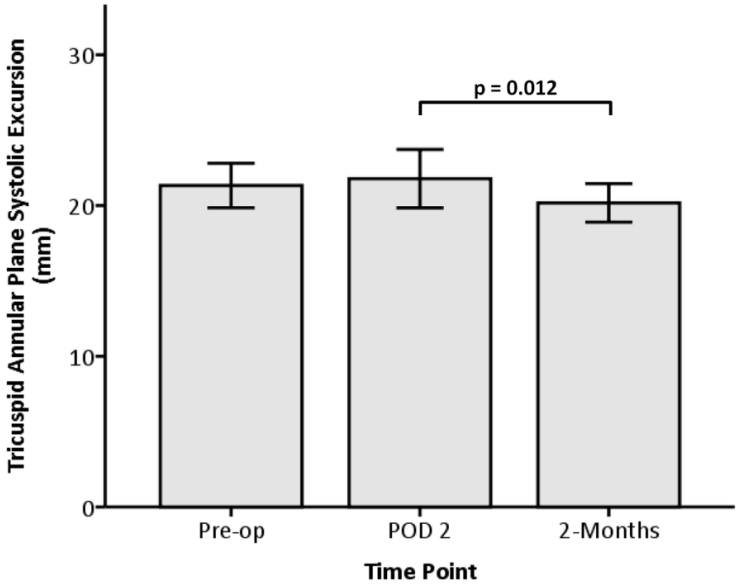


Figure 68. Tricuspid annular plane systolic excursion (TAPSE) over time
Bar (error bars) represent mean (95% CI). One-way repeated measures ANOVA p=0.057. Pairwise comparisons with paired samples t-test. POD = post-op day.

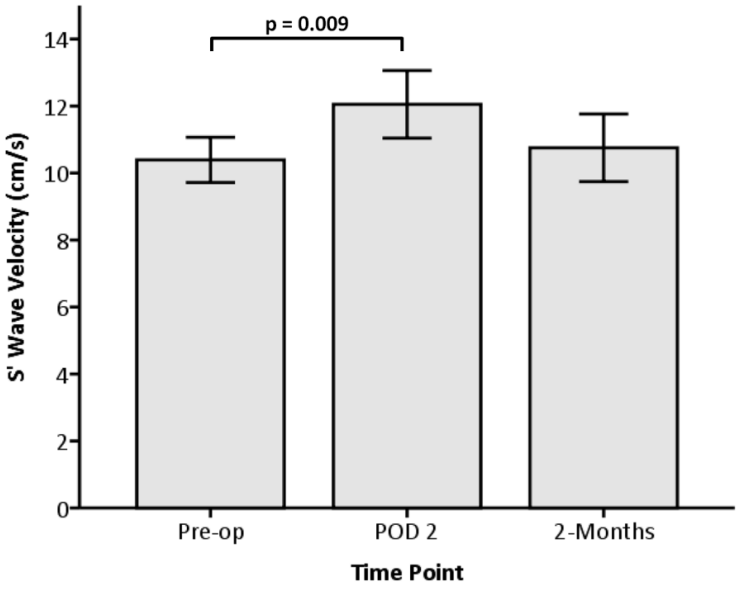


Figure 69. S' Wave velocity at the tricuspid annulus (S'Wave) over time
Bar (error bars) represent mean (95% CI). One-way repeated measures ANOVA p=0.014. Pairwise comparisons with paired samples t-test. S'Wave = S' Wave velocity at the tricuspid annulus, POD = post-op day.

	Pre-op	POD 2	2-Months	p-value
FAC (%)	n=17	n=11	n=19	0.089*
	46.2 (8.0)	46.4 (7.0)	43.3 (6.0)	
TAPSE (mm)	n=26	n=23	n=23	0.057*
	21.3 (3.7)	21.8 (4.5)	20.2 (3.0)†	
S' Wave (cm/s)	n=27	n=23	n=24	0.014*
	10.4 (1.7)	12.1 (2.3)#	10.8 (2.4)	

Table 36. Echocardiographic parameters of RV function over time
Values are mean (SD). * = one-way repeated measures ANOVA. # = significant difference from pre-op. † = Significant difference from POD 2. FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus, POD = post-op day.

6.3 Comparison of echo parameters of systolic function with cardiovascular magnetic resonance determined measures of right ventricular function

6.3.1 Pooled analysis

Pooled analysis of all paired measures across all time points was performed and revealed no association between $RVEF_{CMR}$ and FAC (Pearson's correlation coefficient, p=0.374, Figure 70). There was weak positive association between both TAPSE (r=0.337, p=0.006, Figure 71), S'Wave (r=0.290, p=0.017, Figure 72, pg 213) and $RVEF_{CMR}$. All displayed in Table 37, pg 213.

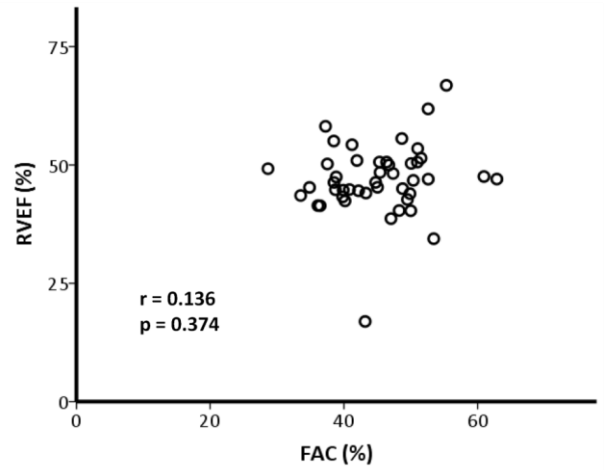


Figure 70. Relationship between FAC and CMR determined RV ejection fraction ($RVEF_{CMR}$)
RVEF = right ventricular ejection fraction, FAC = fractional area change. Pearson's correlation coefficient (pooled analysis).

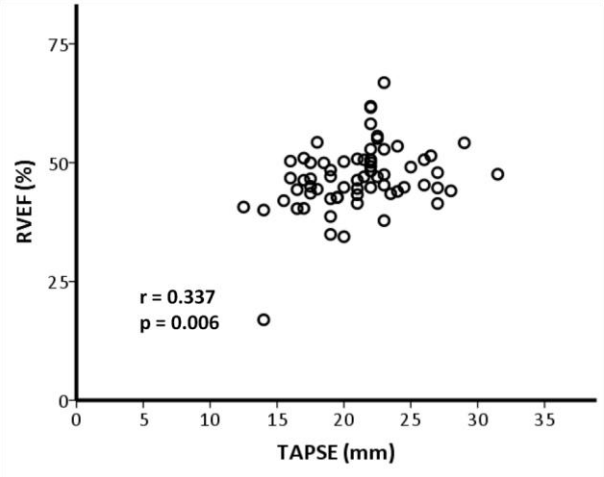


Figure 71. Relationship between TAPSE and CMR determined RV ejection fraction ($RVEF_{CMR}$)
RVEF = right ventricular ejection fraction, TAPSE = tricuspid annular plane systolic excursion. Pearson's correlation coefficient (pooled analysis).

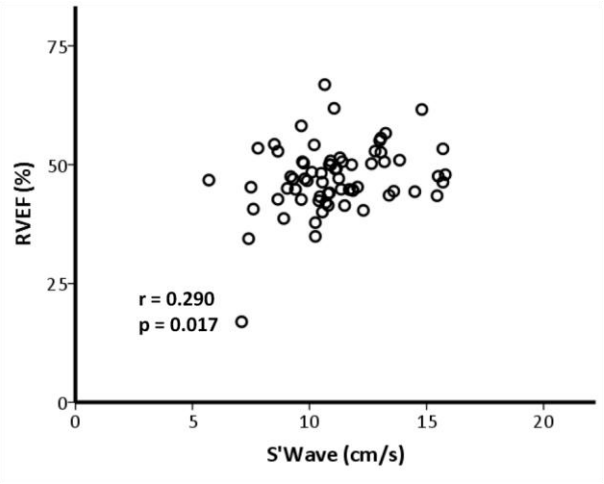


Figure 72. Relationship between S'Wave and CMR determined RV ejection fraction ($RVEF_{CMR}$)
RVEF = right ventricular ejection fraction, S'Wave = S' Wave velocity at the tricuspid annulus. Pearson's correlation coefficient (pooled analysis).

There was weak pooled association between TAPSE, S'Wave and RVEF. Following within-subject (ANCOVA) analysis, there was no evidence of association between any of the echocardiographic variables and $RVEF_{CMR}$ (Table 37).

Pooled analysis (Pearson's)				
		FAC	**TAPSE**	**S' Wave**
$RVEF_{CMR}$	r	0.136	**0.337**	**0.290**
	p	0.374	**0.006**	**0.017**

Within-subject analysis (ANCOVA)				
		FAC	**TAPSE**	**S' Wave**
$RVEF_{CMR}$	r	0.271	0.051	0.120
	p	0.292	0.777	0.493

Table 37. Association between echocardiographic measures of systolic function and $RVEF_{CMR}$
RVEF = right ventricular ejection fraction, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus. ANCOVA = analysis of covariance. Significant results are highlighted in **bold.**

The ability of the three pooled echocardiographic methods to detect poor RV function, defined by $RVEF_{CMR}$ of ≤45%, was assessed using area under the receiver operating characteristic curve analysis (Figure 73 and Table 38, pg 214). TAPSE was the only variable to show predictive power (AUROCC 0.65, p=0.039);

a value of 21.25mm had 65.8% sensitivity and 71.4% specificity for detecting an $RVEF_{CMR}$ of ≤45%.

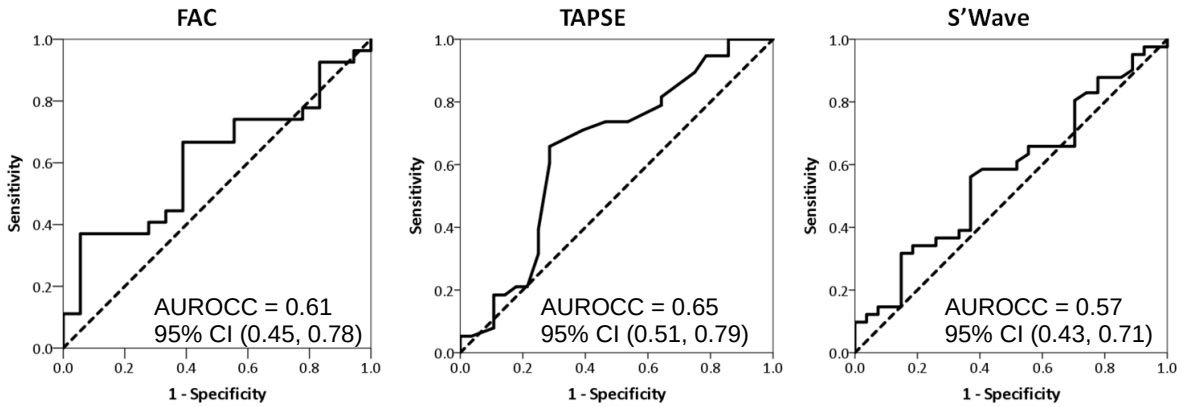


Figure 73. Receiver operating characteristic curves to identify $RVEF_{CMR}$ ≤45% using echocardiographic parameters
FAC = Fractional area change, TAPSE = Tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus, AUROCC = Area under the receiver operating characteristic curve.

	FAC	TAPSE	S'Wave
		$RVEF_{CMR}$ ≤45%	
AUROCC (95%CI)	0.61(0.45, 0.78)	0.65 (0.51, 0.79)	0.57 (0.43, 0.71)
p	0.211	0.039	0.325
Cut-off value[S]	-	21.25mm	-
Sensitivity	-	65.8%	-
Specificity	-	71.4%	-
PPV	-	75.7%	-
NPV	-	60.6%	-

Table 38. Predictive performance of echo parameters to detect $RVEF_{CMR}$ ≤45%
AUROCC = Area under the receiver operating characteristic curve, PPV = Positive predictive value, NPV = negative predictive value, RVEF = Right ventricular ejection fraction, FAC = Fractional area change, TAPSE = Tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

[S] Defined by Youden's index (Maximum combination of sensitivity and specificity).

6.3.2 Trend analysis

Trend analysis was performed to assess the ability of each of the echocardiographic techniques to detect *changes* in $RVEF_{CMR}$. Change in each of the echo parameters (ΔFAC, ΔTAPSE and ΔS' Wave) was plotted against change in $RVEF_{CMR}$ ($\Delta RVEF_{CMR}$). The associations are demonstrated in Figure 74, Figure 75, and Figure 76, pg 216.

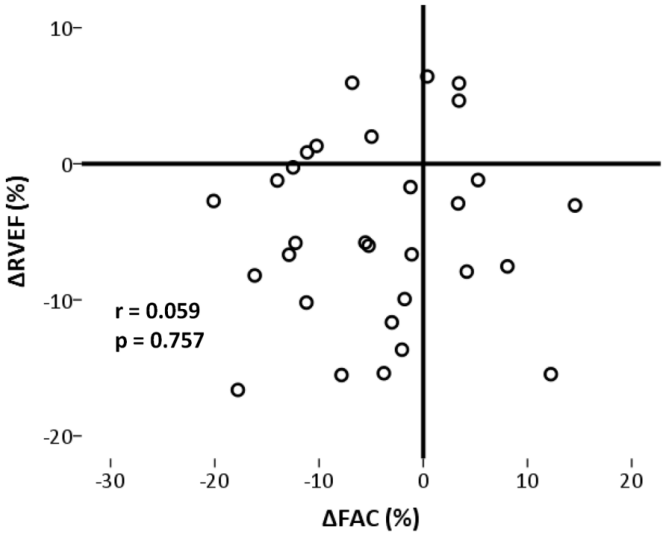


Figure 74. Changes in FAC against corresponding changes in $RVEF_{CMR}$
n = 30, Pearson's correlation coefficient. RVEF = right ventricular ejection fraction, FAC = fractional area change.

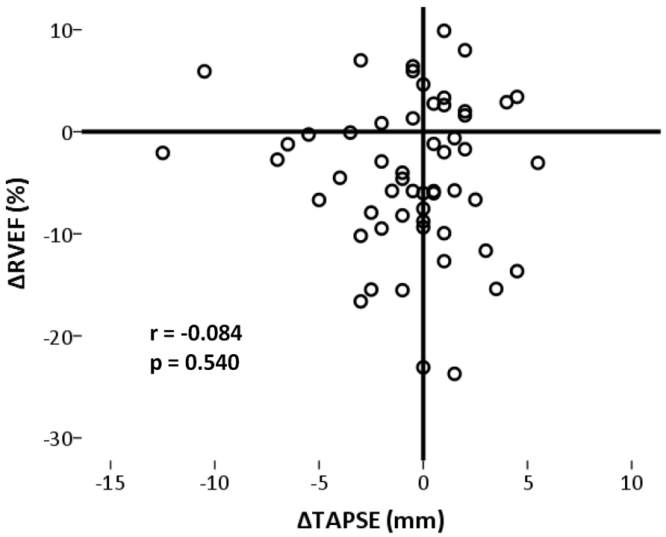


Figure 75. Changes in TAPSE against corresponding changes in $RVEF_{CMR}$
n = 55, Pearson's correlation coefficient. RVEF = right ventricular ejection fraction, TAPSE = tricuspid annular plane systolic excursion.

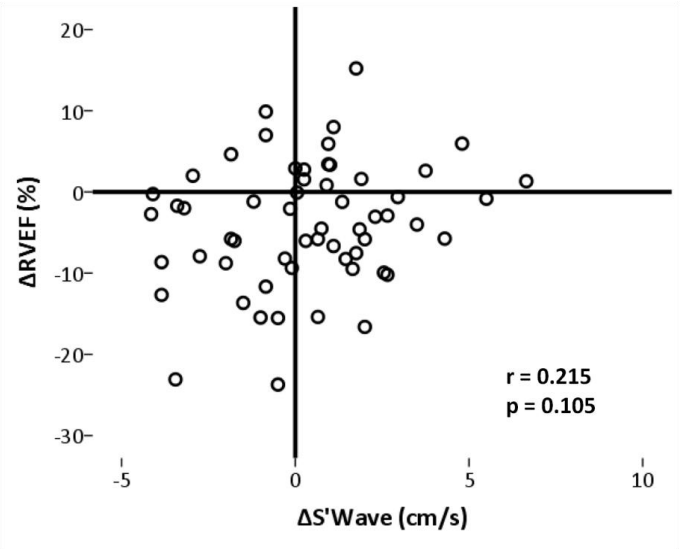


Figure 76. Changes in S'Wave against corresponding changes in $RVEF_{CMR}$
n = 58, Pearson's correlation coefficient. RVEF = right ventricular ejection fraction, S'Wave = S'Wave velocity at the tricuspid annulus.

None of the echocardiographic parameters showed any association between a change in their measurement and a change in $RVEF_{CMR}$. The predictive ability of each of the echo techniques to detect a *change* in $RVEF_{CMR}$ was further assessed. The standard deviation of $\Delta RVEF_{CMR}$, 7.55%, was used as the minimal change that would be useful to determine from echocardiography and AUROCC analysis was performed. None of the echocardiographic parameters were able to detect a change in $RVEF_{CMR}$ of >7.55% (p>0.069, Figure 77 and Table 39, pg 217).

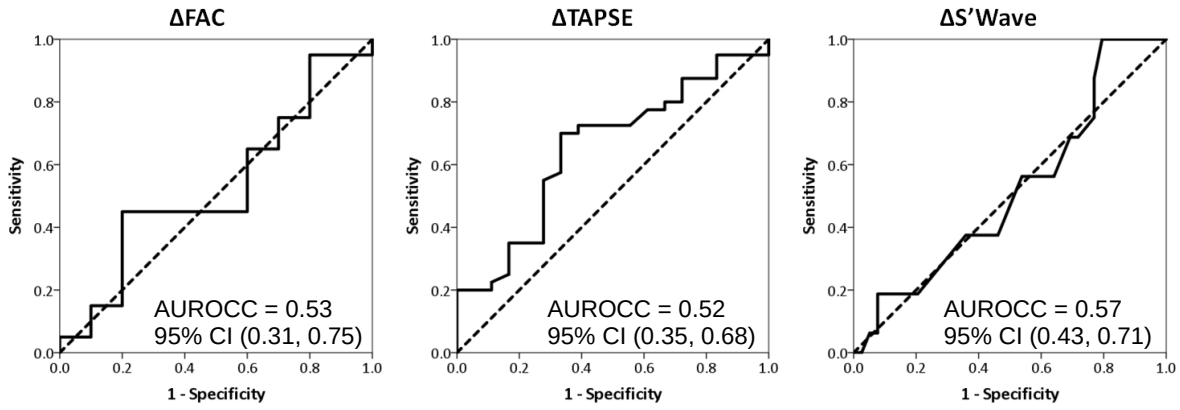


Figure 77. Receiver operating characteristic curves to identify $\Delta RVEF_{CMR}$ ≥7.55% using Δechocardiographic parameters
FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

	ΔFAC	ΔTAPSE	ΔS'Wave
		ΔRVEF >7.55%	
AUROCC (95%CI)	0.53 (0.31, 0.75)	0.52 (0.35, 0.68)	0.57 (0.43, 0.71)
p	0.792	0.838	0.069

Table 39. Receiver operating characteristic analysis to detect ΔRVEF >7.55%
AUROCC = area under the receiver operating characteristic curve, RVEF = right ventricular ejection fraction, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus.

6.4 Discussion

This aim of this investigation was to validate conventional measures of RV systolic function (FAC, TAPSE and S'Wave) against an established reference method for assessment of RV function ($RVEF_{CMR}$) in a lung resection cohort. Its main finding is that none of these established parameters have utility in this population.

The TTE imaging protocol was well tolerated and acceptable to patients, with all participants completing the protocol pre-operatively and the majority completing it in the post-op period. Despite the vast majority of patients being able to undergo imaging, not all echo parameters were available in all patients. Prior to this investigation, the author hypothesised that TTE would be more difficult in those patients undergoing left sided resections than those having right sided surgery, with a significant impact on image availability, quality and reproducibility. This is because the majority of TTE imaging is performed through the left side of the thorax (through rib spaces). The presence of drains, pneumothorax and additional fluid following left sided surgery may impact on the ability to obtain usable images with the impact diminishing by 2-months, when drains were removed and patients were well in to the recovery period.

There was some evidence that side of resection was important on imaging *availability* in the immediate post-op period. On POD 2 dual reported TAPSE was available in 77.8% of those who had left sided resections in contrast to 94.1% of those who had right sided resections. In those with available imaging, side did not impact on *reproducibility* with CV's similar for both left and right sided surgeries. There was no such trend when determining S'Wave as this was equally *available* in left and right sided resections at all time points with no difference in *reproducibility*.

On POD 2 paired FAC results were available in 33.3% of patients undergoing left sided resections and 46.2% of those undergoing right sided resections. This was in contrast to the reproducibility figures where CV were much better on POD 2 in contrast to other time periods (9.5% vs 18.3 and 17.2%). These figures do not tell the whole story; in patients undergoing FAC assessment the echocardiography technicians (ET's) obtained a result in 74/77 (96.1%) of patients and the author obtained a result in 50/77 (64.9%) of images. This was worse on POD 2 when the

ET's obtained a result on 96.2% of images and the author obtained results on 46.2% of images. In previous work by Kjaergaard et al.[132]. (in a non-thoracic surgery cohort) images were of sufficient quality to determine a FAC result in 82% of patients. This is still substantially better than the 64.9% availability by the author in this cohort. The hypothesised deterioration in imaging following thoracic surgery may account for poor quality images but would not account for why one observer was able to obtain values and the other was not.

On reviewing the images that the author was unable to obtain a FAC result for, it would appear a much more punitive approach was utilised, in that if the apex of the RV free wall was not available a value would not be calculated. This is in contrast to the ET's who calculated values for the RV that was visible. This will have falsely improved the CV on POD 2 when only those images with the clearest endocardial border having been selected by the author. Sensitivity analysis incorporating only those values obtained by the ET's showed no improvement in the performance of FAC when compared with $RVEF_{CMR}$, with a Pearson's correlation coefficient of 0.117 (p=0.345) and ANCOVA of 0.06 (p=0.712). Fractional area change showed poor inter- and intra-observer variability (CV's of 15.8% and 12.6% respectively) with intraclass correlation coefficients (ICC's) that failed to achieve statistical significance. In addition, on Bland Altman (BA) analysis there was no evidence of agreement between two observers. All of these characteristics indicate that FAC is not a reproducible and would be unsuitable as a measurement technique in this population.

RV area estimation can be challenging in cases of sub-optimal image quality and the above inconsistency highlights how there is still *subjectivity* with regards to RV assessment. Recognising this subjectivity, guidelines from the American Society of Echocardiography recommend the integration of *quantitative* and *qualitative* assessment of RV parameters[128, 298].

In contrast to FAC, TAPSE and S'wave were available in the majority of patients and showed good inter- and intra-observer variability (CV's of ≤9.0% for all). BA analysis of these variables showed good agreement with minimal bias. This suggests that TAPSE and S'Wave are reproducible and *may* be useful as measurement techniques in this population.

There were minimal changes in all the echocardiographic parameters over the duration of the study and none mirrored the changes in $RVEF_{CMR}$ described in Chapter 5. FAC showed no change over time. TAPSE decreased from 21.8mm on POD 2 to 20.2mm at 2-months. Although this was a statistically significant change (p=0.012), it was a small absolute change (of 1.6mm) and was still at a considerable level above the lower reference value for *normal* TAPSE (16mm)[128]. S'Wave increased on POD 2 from 10.4cm/s to 12.1cm/s. This suggests *improved* RV systolic function on POD 2 following lung resection, returning to baseline by 2-months. This is in contrast to the results obtained by $RVEF_{CMR}$ which shows that RV function deteriorates by POD 2 and remains depressed at 2-months. Again, all of the values were above the lower reference value for normal systolic function by S'Wave (10cm/s)[128].

Using $RVEF_{CMR}$ as a reference method this investigation attempted to validate the use of these echocardiographic parameters in this population. The first step was pooled analysis of the echo variables which showed weak association between TAPSE, S'Wave and $RVEF_{CMR}$. When taking account of the within-subjects correlation from the repeated measures nature of the data, there was no evidence of a relationship between $RVEF_{CMR}$ and any of the echocardiographic variables.

Analysis so far suggests that FAC, TAPSE and S'Wave are not suitable as a *continuous* measure of RV function. To assess the ability of each of the parameters to predict poor RV function (signified by $RVEF_{CMR} \leq 45\%$, a previously described cut-off for poor RV function)[121, 299] area under the receiver operating characteristic curve (AUROCC) analysis was performed. This demonstrated that FAC and S'Wave had no predictive ability for 'poor RV function'. TAPSE showed some discriminatory ability with AUROCC of 0.65 (95% CI 0.51, 0.79). Johnson has suggested that when it comes to prediction, an AUROCC of *"0.75 is good and greater than 0.8 is exciting,"* the AUROCC for TAPSE falls considerably lower than this[242]. Additionally, the 95%CI for this AUROCC are close to 0.5 and the ability of TAPSE to determine $RVEF_{CMR} \leq 45\%$ is not adequate for clinical or research use.

As well as the ability of the parameters to determine *absolute* values of $RVEF_{CMR}$, their ability to detect *changes* of $RVEF_{CMR}$ was assessed. This analysis showed that there was no association between a change in $RVEF_{CMR}$ and any change in the echocardiographic parameters. The ability of the parameters to detect a

change of $RVEF_{CMR}$ of ≥7.55% was assessed using AUROCC analysis. The standard deviation of $\Delta RVEF_{CMR}$ (7.55%) was used as this represented a c*linical* change in RVEF would be desirable to detect in this population. None of the parameters showed any ability to determine a change in RVEF ≥7.55%.

In summary, despite excellent reproducibility for TAPSE and S'Wave, they have no relationship to $RVEF_{CMR}$ and are unable to provide information on absolute values of $RVEF_{CMR}$ or changes in $RVEF_{CMR}$ in this population. FAC showed no reproducibility and no ability to predict values of $RVEF_{CMR}$. This finding is in contrast to previous work in *other populations* which has shown that these parameters have good association with $RVEF_{CMR}$[121, 122, 131, 132, 300] (Table 40, pg 222).

As can be seen in Table 40, in other studies FAC has correlation coefficients ranging from non-significant to 0.84, and good ability to predict poor RV function with an AUROCC of up to 0.89. In this investigation there was no association and no predictive ability. Although unlikely based on the available information (poor reproducibility and no linear association for $RVEF_{CMR}$ and $\Delta RVEF_{CMR}$), a complete set of FAC measurements may be able to provide some information on RV function in patients undergoing lung resection. It is unlikely to achieve the levels described in previous studies.

The studies in Table 40 show correlation coefficients for TAPSE ranging from non-significant to 0.48. It has also shown AUROCC of 0.66 to 0.85. The data in the current study has shown pooled association between $RVEF_{CMR}$ and TAPSE of 0.38 which is lost when taking account of within subjects correlation. An AUROCC of 0.65 was obtained, which is similar to the level of 0.66 described by Focardi et al.[121]. In their article they describe surprise at this lower level of agreement between TAPSE and $RVEF_{CMR}$, with the discordance attributed to TAPSE being a "*qualitative"* assessment in contrast to $RVEF_{CMR}$ which is a more "*accurate quantitative"* method. In the two studies in Table 40 examining S'wave, there is evidence of moderate association with correlation coefficients of 0.48-0.52. S'wave also has good discriminative capability with AUROCC of 0.80 for $RVEF_{CMR}$≤30%. Again, S'Wave showed no association in this cohort and no predictive ability.

The reason why these echo parameters may be predictive in other populations, but not in the current lung resection cohort is discussed next.

Study	Population	Parameter	Association	Prediction
			Correlation coefficient	AUROCC
Schenk et al.[301] (2000)	n = 32 *patients presenting for lung transplantation*	FAC	0.84	-
Kjaergaard et al.[132] (2006)	n = 34 *17 prior STEMI* *7 prior PE* *10 normal*	FAC	0.34 (ns)	-
		TAPSE	0.48	-
Anavekar et al.[300] (2007)	n = 36 *mixed*	FAC	0.80	-
Pavlicek et al.[122] (2011)	n = 223 (mixed) *38 normal* *36 IHD* *51 CM* *12 VHD* *30 TOF* *19Transposition* *29 other CHD* 8 PH	FAC	0.47	RVEF≤50% = 0.73 RVEF≤30% = 0.88
		TAPSE	0.34	RVEF≤50% = 0.72 RVEF≤30% = 0.79
		S'Wave	0.48	RVEF≤50% = 0.78 RVEF≤30% = 0.80
Focardi et al.[121] (2015)	n = 63 (mixed) *21 ?myocarditis* *8 IDC* *10 HCM* *10 ARVD* *5 Infiltrative CM* *9 other*	FAC	0.77	RVEF≤45% = 0.78
		TAPSE	0.45	RVEF≤45% = 0.66
		S'Wave	0.52	-
Hamilton Craig et al.[131] (2016)	n = 92 *- 46 normal* *- 46 others* *(CHD, ARVD, Ebsteins anomaly, PH, septal defects)*	FAC	-	RVEF≤45% = 0.89
		TAPSE	-	RVEF≤45% = 0.85

Table 40. Summary of literature comparing $RVEF_{CMR}$ with FAC, TAPSE and S'Wave
Correlation coefficients are all Pearson's, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, ns = non significant, S'Wave = S' Wave velocity at the tricuspid annulus, AUROCC = area under the receiver operating characteristic curve, STEMI = ST elevation myocardial infarction, PE = pulmonary embolus, IHD = ischaemic heart disease, VHD = valvular heart disease, TOF = tetralogy of fallot, CHD = congenital heart disease, IDC = idiopathic dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ARVD = arrhythmogenic right ventricular dysplasia, CM = cardiomyopathy, Transposition = transposition of the great arteries.

A number of reasons may account for why these variables have shown good association in other populations but not in this cohort. First, may be as a result of the inherent differences of the patients themselves; as can be seen in Table 40 (pg 222), the majority of studies had heterogeneous examples of cardiovascular disease with likely dysfunction. Of the entire cohort in the current investigation, 22.2% had IHD and none had active cardiac failure. The mechanism of RV dysfunction may be important; with elevated afterload popularly hypothesised in the lung resection cohort but multiple other mechanisms present in the previous studies. The echocardiographic parameters may be predictive in one population but not in another.

The *range* of $RVEF_{CMR}$ values in the current cohort is also important. In the study by Pavlicek et al. 27 patients (12.1%) had evidence of $RVEF_{CMR}$ ≤30%, this is contrast to one patient (1.5%) in the current investigation. This can be seen in Figure 78 where mean (95%CI) values of $RVEF_{CMR}$ and TAPSE from the current study have been superimposed on results by Pavlicek et al.[122]. The current study has a tighter range of $RVEF_{CMR}$ and TAPSE in comparison to this previous work with the *majority* of values falling outside the range of the current study.

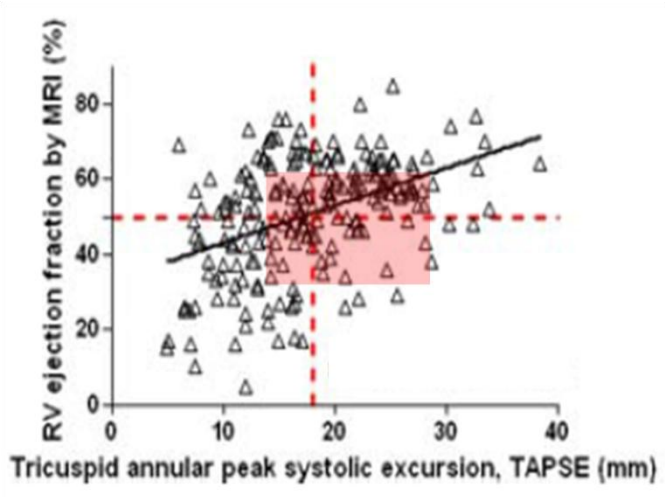


Figure 78. TAPSE and $RVEF_{CMR}$ from Pavlicek et al.[122] with addition of data from current investigation
Red box represents the mean (95% CI) of $RVEF_{CMR}$ and TAPSE from the current investigation. RVEF = 47.1% (33.5, 60.8), TAPSE = 21.10mm (13.75, 28.45).

As described in section 2.3.2, (pg 85), extremes of data can contribute to improved correlation statistics. Studies comparing echocardiographic measures of RV

function may have good correlation coefficients as a result of normal controls and study participants with severe RV dysfunction.

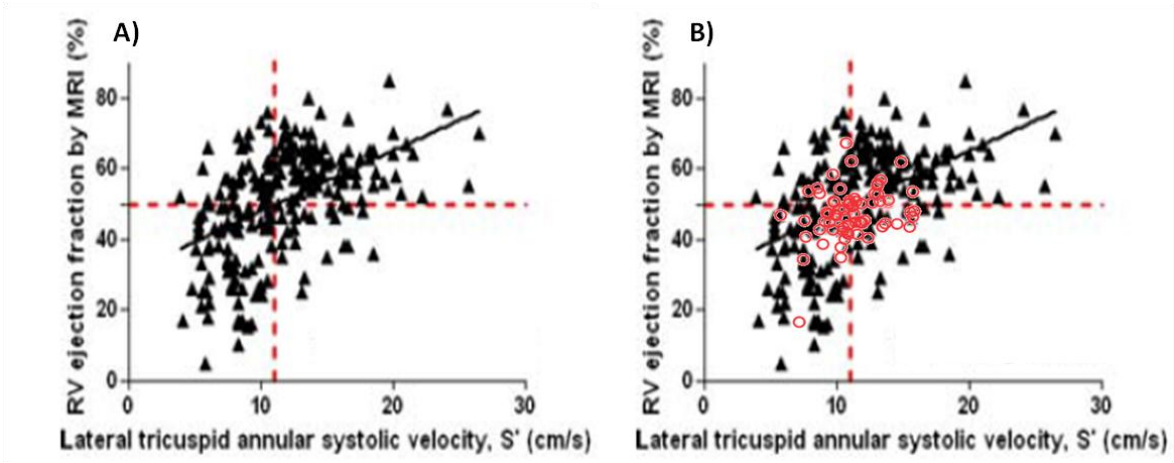


Figure 79. S'Wave velocity and $RVEF_{CMR}$ from Pavlicek et al.[122] with addition of data from current investigation
A) Original figure from Pavlicek et al. showing association of S'Wave and $RVEF_{CMR}$ B) Amended image with addition of S'Wave and CMR data from current investigation.

As can be seen from Figure 79B, the distribution of S'Wave results from the current investigation falls entirely within the distribution of results from the study by Pavlicek et al. (n=223). The impact of normal controls (top right of Figure 79B with $RVEF_{CMR}$ >50%) and those with severe RV dysfunction (bottom left of Figure 79B with $RVEF_{CMR}$ ≤30%) would improve the association and provide better predictive power.

The purpose of this discussion is not to suggest that more patients are required to show association but to account for *why* the variables were not reliable in this population. It appears that the population undergoing lung resection has a lower $RVEF_{CMR}$ than the *normal* population and that when RV dysfunction develops in the post-op period that it is not as severe as those with primary cardiac pathology. This *tighter range* means that association with other parameters is harder to demonstrate. The cohort in this investigation is representative of a *typical* group of patients undergoing lung resection (See Table 20, pg 167) and if the parameters are not able to provide reliable information on RV function then they are not appropriate for use in this population.

In validation studies, the adequacy of the reference method must also be considered[122]. $RVEF_{CMR}$ was used in this investigation as it is established as a

reference method for validation of RV echocardiographic parameters. Despite its widespread use it is not a measure of RV contractility and is highly load dependent. In this setting where the most commonly hypothesised mechanism for RV dysfunction following lung resection is elevated afterload, this is important. Without information on loading conditions, there is a confounder that is not accounted for in this investigation and means that we cannot determine if these echocardiographic parameters can provide *load independent* information on contractility.

6.4.1 Strengths and limitations

A strength of this investigation is that it attempts to validate parameters in a *real world* representative population. This means they are being assessed in the population where they will be used and not extrapolated from other clinical situations. The robust assessment of RV parameters, with dual analysis of anonymised images, assessment of within patient correlation and assessment of trends over time mean we can be confident that these results are valid.

Lack of agreement between the author and echocardiography technicians for determination of FAC is a weakness of this study. With paired analyses only available for 2/3 of the patients, the results for this parameter are not as robust as for TAPSE and S'Wave. Sensitivity analysis using only the values by ET's suggested there was no significant difference to the results displayed.

The deterioration of imaging availability on POD 2 is important as more than 10% of patients (even for S'Wave, the most available of the current imaging parameters) will not have echocardiographic assessment possible in the immediate post-op period. A reliable imaging parameter at this time would have utility in this population.

6.5 Conclusion

The conventional echo parameters FAC, TAPSE and S'Wave are not valid for the assessment of RV function following lung resection. Further work should look at alternative, novel, echocardiographic methods for assessment of RV function and may incorporate the use of biomarkers to improve the identification of patients with poor RV function in the post-op period following lung resection.

Chapter 7 Speckle Tracked Strain Assessment of RV Function

This chapter describes the use of speckle tracked strain (strain) for assessment of RV function. It will first describe imaging availability and reproducibility, it will then describe changes in strain over time and will finally make comparison with $RVEF_{CMR}$ as a reference method for assessment of RV function.

As described in chapter 6, Trans Thoracic Echocardiography (TTE) was well tolerated, with 27 patients (100%) undergoing pre-op echo imaging, twenty-six (96.3%) on POD 2 and twenty-four at 2-months. Following first analysis, there were 17 scans with discrepancy in results between the author and Dr Piotr Sonecki (Consultant cardiologist with an interest in cardiac imaging). These scans were selected for dual analysis with Dr Sonecki; five yielded no further results, six had free wall strain when it wasn't previously available and six had free wall *and* global strain when it wasn't previously available. Global and free-wall strain results were available on 27 patients (100%) pre-operatively, 22 patients (84.6%) on POD 2 and 24 (100%) at 2-months. Of those with imaging unavailable in the immediate post-op period, three (75%) had left sided resections and one (25%) had a right sided resection.

7.1 Intra and inter-observer variability

Strain imaging showed good reproducibility with intraclass correlation coefficients above 0.91 for both inter and intra-observer variability (Figure 80, Figure 81 [pg 227] and Table 41 [pg 228]).

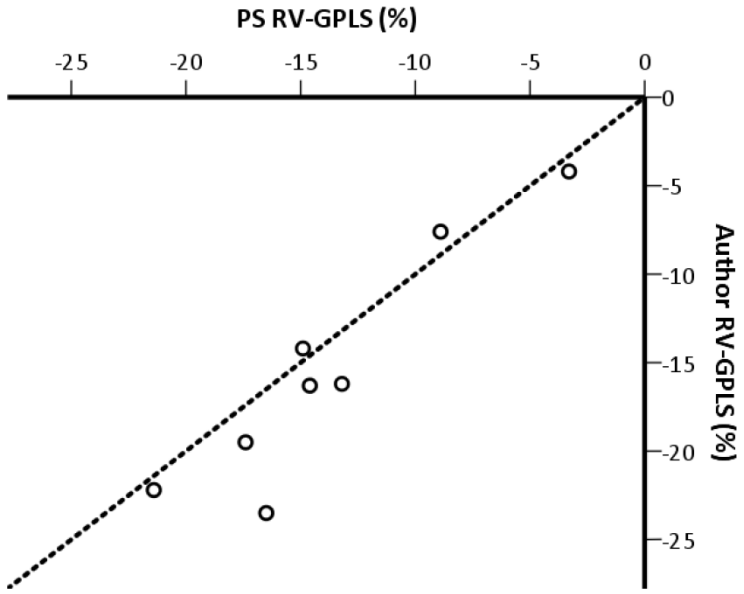


Figure 80. Inter-observer variability of RV strain measurements
n=8. Dashed line is line of identity. RV-GPLS = RV global peak longitudinal strain, PS = Piotr Sonecki (imaging cardiologist).

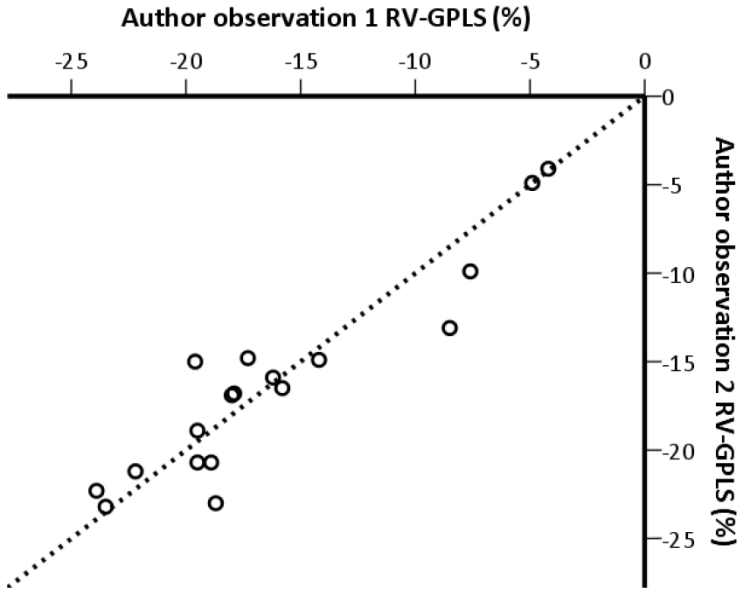


Figure 81. Intra-observer variability of RV strain measurements
n=19. Dashed line is line of identity. RV-GPLS = RV global peak longitudinal strain.

Inter-observer variation			
		ICC Agreement (95% CI)	
RV-GPLS	*(n=8)*	0.913 (0.631, 0.982)	p<0.0005

Intra-observer variation			
		ICC Agreement (95% CI)	
RV-GPLS	*(n=19)*	0.930 (0.823, 0.973)	p<0.0005

Table 41. Inter and intra-observer variation for RV-GPLS measurements
ICC = intraclass correlation coefficient, RV-GPLS = RV global peak longitudinal strain. Intraclass correlation coefficient calculated as mixed effect, absolute agreement with single measures.

7.2 Changes in right ventricular strain over time

As can be seen in Figure 82, Figure 83 and Table 42 (pg 229), there were no changes in either RV-global or RV-free wall peak longitudinal strain (RV-GPLS or RV-FWPLS) over the duration of the study (p>0.229, Friedman's test)[T].

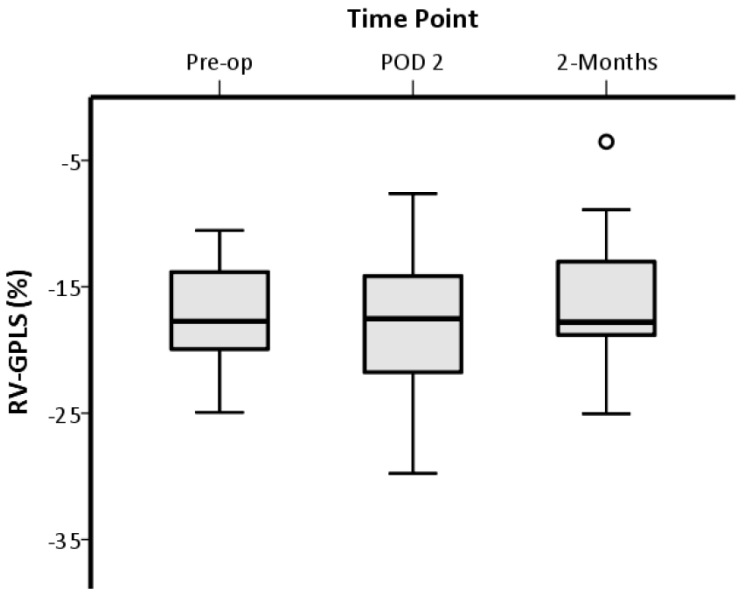


Figure 82. Changes in RV-GPLS over time
Box plots represent median, IQR and range. RV-GPLS = RV free wall peak longitudinal strain, POD = post-op day.

[T] Longitudinal strain represents myocardial shortening and *more negative* values represent better function and values closer to zero represent poorer function.

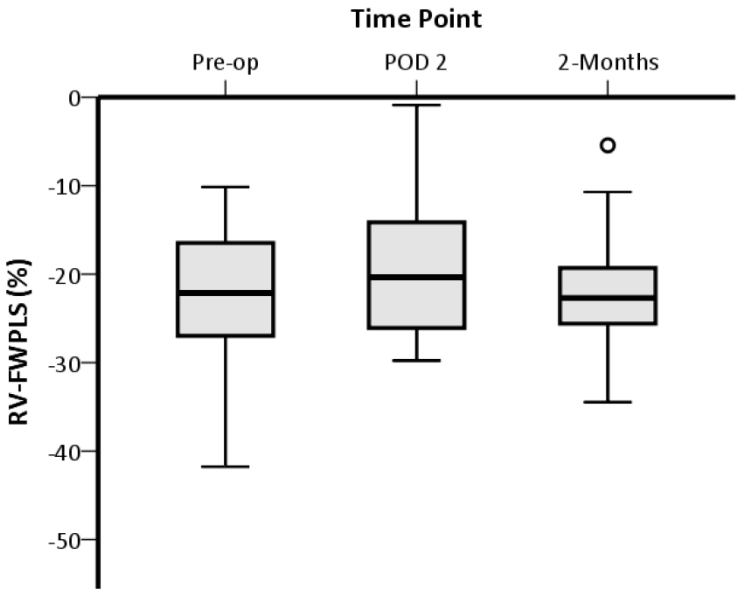


Figure 83. Changes in RV-FWPLS over time
Box plots represent median, IQR and range. RV-FWPLS = RV free wall peak longitudinal strain, POD = post-op day.

	Pre-op	POD 2	2 Months	p-value
	n=27	*n=22*	*n=24*	
RV-GPLS	-17.7 (-20.1, -13.6)	-17.5 (-21.8, -14.1)	-17.8 (-18.8, -12.2)	0.387*
RV-FWPLS	-22.1 (-27.2, -16.0)	-20.4 (-26.5, -13.3)	-22.7 (-26.1, -18.6)	0.229*

Table 42. RV-GPLS and RV-FWPLS values over time
Values are median (IQR). * = Friedman's test. POD = post-op day, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain.

7.3 Association of strain and cardiovascular magnetic resonance determined right ventricular function

Pooled analysis revealed moderate association between RV-GPLS, RV-FWPLS and $RVEF_{CMR}$ (Figure 84, Figure 85 [pg 230] and Table 43 [pg 231]). To allow adjustment for within-subject correlation, analysis of covariance (ANCOVA) was performed allowing within-subject variability to be partitioned out. Following within-subject analysis there was no association between RV-GPLS and $RVEF_{CMR}$, and a trend towards association between RV-FWPLS and $RVEF_{CMR}$ (p=0.054, Table 43).

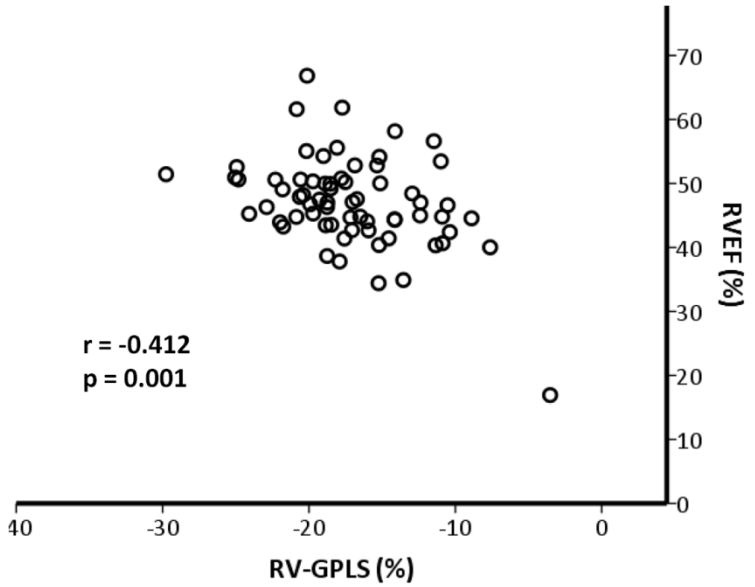


Figure 84. Relationship of RV-GPLS and RV ejection fraction (RVEF)
RVEF = right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain. Pearson's correlation coefficient (pooled analysis).

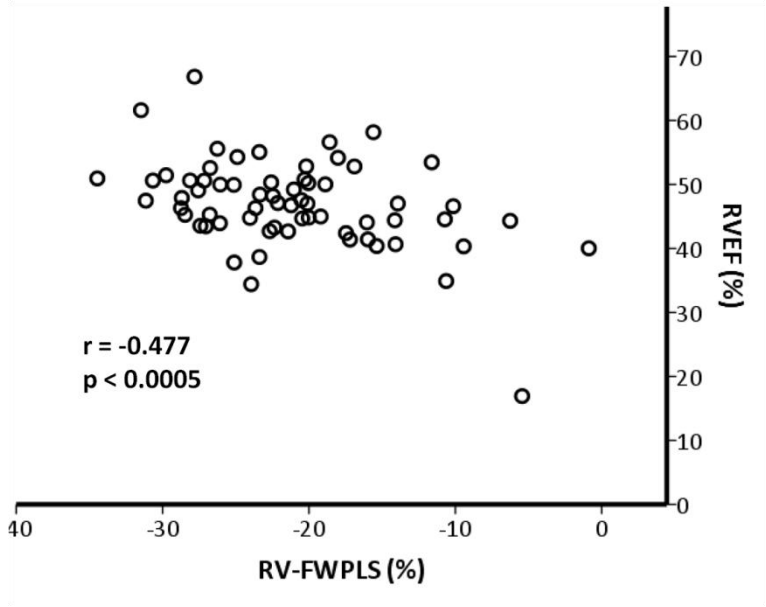


Figure 85. Relationship of RV-FWPLS and RV ejection fraction (RVEF)
RVEF = right ventricular ejection fraction, RV-FWPLS = RV free wall peak longitudinal strain. Pearson's correlation coefficient (pooled analysis).

Pooled analysis (Pearson's)			
		RV-GPLS	**RV-FWPLS**
$RVEF_{CMR}$	r	**-0.412**	**-0.477**
	p	**0.001**	**<0.0005**

Within-subject analysis (ANCOVA)			
		RV-GPLS	**RV-FWPLS**
$RVEF_{CMR}$	r	0.120	0.306
	p	0.454	0.054

Table 43. Association of RV-GPLS and RV-FWPLS with $RVEF_{CMR}$
RVEF = right ventricular ejection fraction, ANCOVA = analysis of covariance, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain. Significant associations are highlighted in **bold.**

The ability of the pooled values of RV-GPLS and RV-FWPLS to detect poor RV function, signified by $RVEF_{CMR}$ of ≤45%, was assessed using area under the receiver operating characteristic curve analysis (Figure 86). Both RV-GPLS and RV-FWPLS achieved significance (Table 44, pg 232).

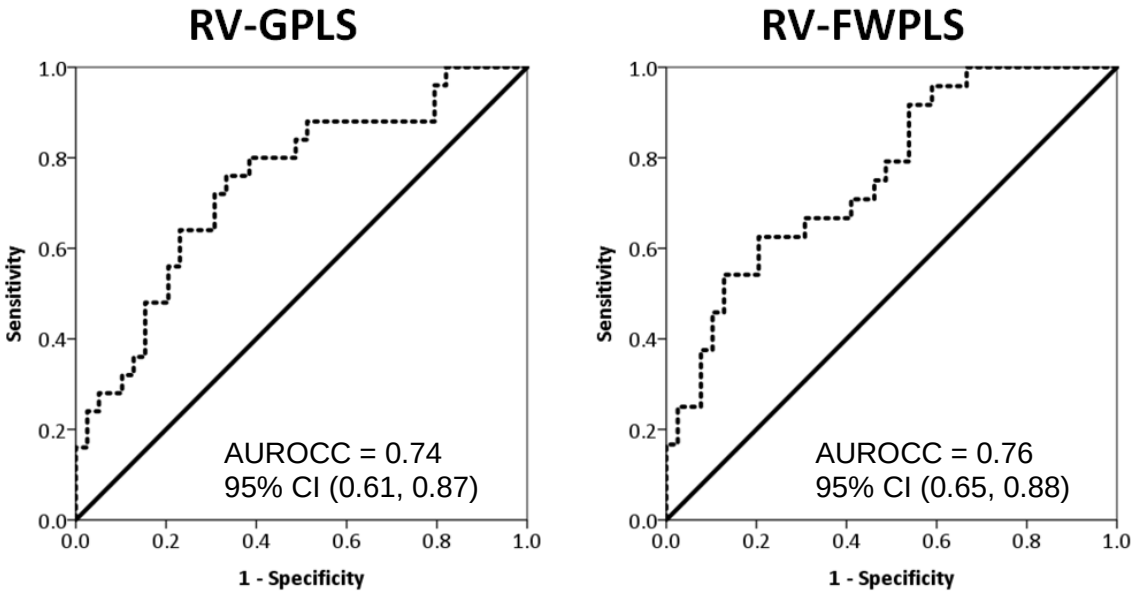


Figure 86. Receiver operating characteristic curves to identify $RVEF_{CMR}$ ≤45% using RV-GPLS and RV-FWPLS
AUROCC = Area under the receiver operator characteristic curve, RVEF = Right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain.

	RV-GPLS	RV-FWPLS
AUROCC (95%CI)	0.74 (0.61, 0.87)	0.76 (0.65, 0.88)
p	0.001	<0.0005
Cut-off value[U]	-17.7%	-20.0%
Sensitivity	76.0%	62.5%
Specificity	66.7&	79.5%
PPV	59.4%	65.2%
NPV	81.3%	77.5%

Table 44. Predictive performance of RV-GPLS and RV-FWPLS to detect $RVEF_{CMR}$ ≤45%
AUROCC = area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value, RVEF = right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain.

To assess the ability of RV-GPLS and RV-FWPLS to perform at each peri-operative stage, analysis was performed at each individual time point (Figure 87 and Figure 88 [pg 233]).

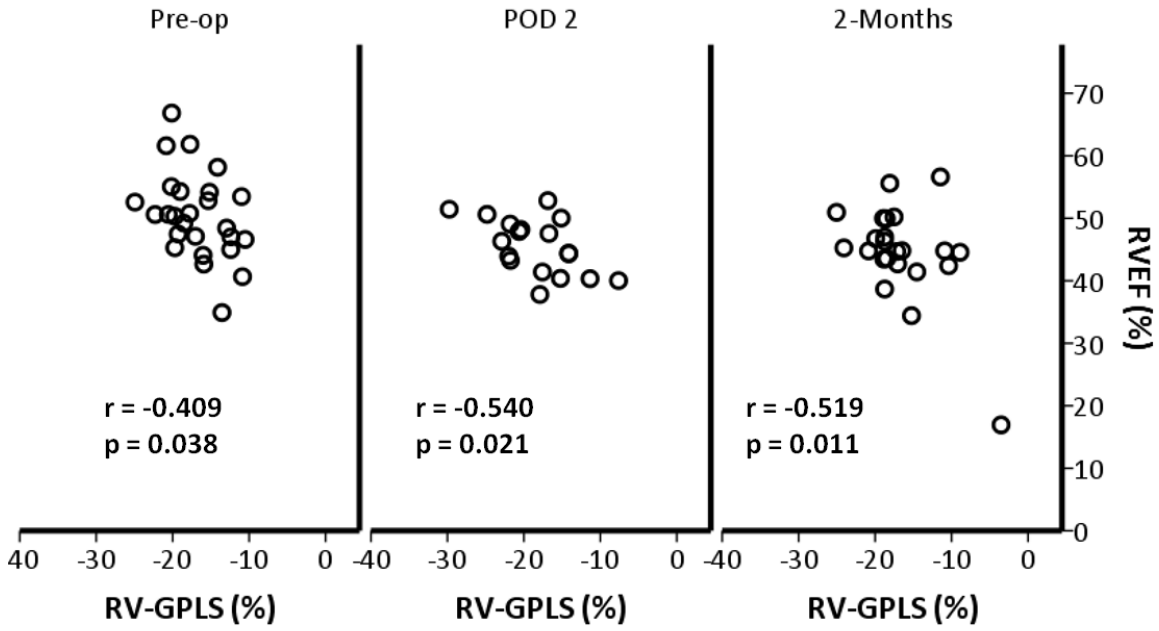


Figure 87. Relationship of RV-GPLS and RV ejection fraction (RVEF) at each time point
RVEF = Right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain, POD = post-op day. Pearson's correlation coefficient (pooled analysis).

[U] Defined by Youden's index (Maximum combination of sensitivity and specificity).

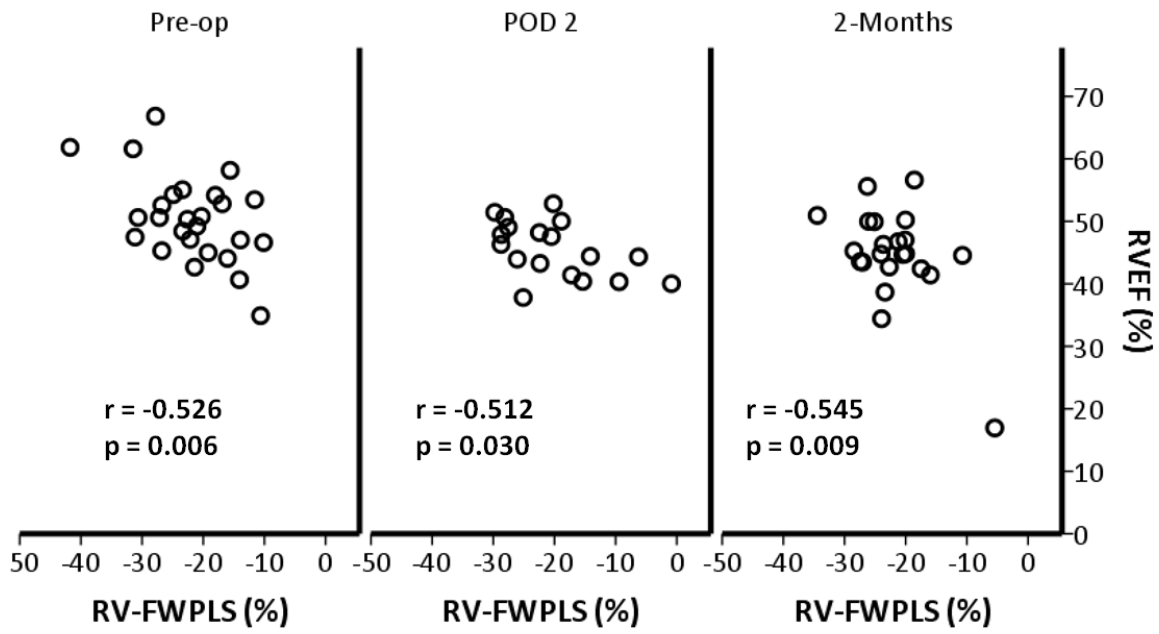


Figure 88. Relationship of RV-FWPLS and RV ejection fraction (RVEF) at each time point
RVEF = right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain, POD = post-op day. Pearson's correlation coefficient (pooled analysis).

This analysis demonstrated moderate association of both RV-GPLS and RV-FWPLS with $RVEF_{CMR}$ at each time point. The ability of the two strain parameters to predict RV dysfunction (signified as RVEF<45%) at each time point was assessed. RV-GPLS showed good predictive ability at each time point (AUROCC 0.78-0.79, Table 45, pg 234). RV-FWPLS showed similar predictive ability pre-op (AUROCC 0.79), no discriminative ability at 2-months (AUROCC 0.68, p=0.147) and excellent predictive ability on POD 2 (AUROCC 0.86, Table 45 [pg 234] and Figure 89 [pg 235]).

		Pre-op	POD 2	2 Months
RV-GPLS	AUROCC (95%CI)	0.79 (0.62, 0.96)	0.78 (0.56, 0.99)	0.79 (0.60, 0.98)
	p	0.047	0.047	0.018
	Cut-off value[V]	-16.5%	-14.6%	-17.3
	Sensitivity	100%	44.4%	67%
	Specificity	67%	100%	90%
	PPV	42%	100%	89%
	NPV	100%	64.3%	69%

		Pre-op	POD 2	2 Months
RV-FWPLS	AUROCC (95%CI)	0.79 (0.62, 0.96)	0.86 (0.69, 1.00)	0.683
	p	0.047	0.009	p = 0.147
	Cut-off value[W]	-21.8%	-18.0%	
	Sensitivity	100%	67%	-
	Specificity	62%	100%	-
	PPV	39%	100%	-
	NPV	100%	75%	-

Table 45. Predictive performance of RV-GPLS and RV-FWPLS to detect $RVEF_{CMR}$ ≤45% at each peri-operative time point
AUROCC = area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value, RVEF = right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain, POD = post-op day.

[V] Defined by Youden's index (Maximum combination of sensitivity and specificity).

[W] Defined by Youden's index (Maximum combination of sensitivity and specificity).

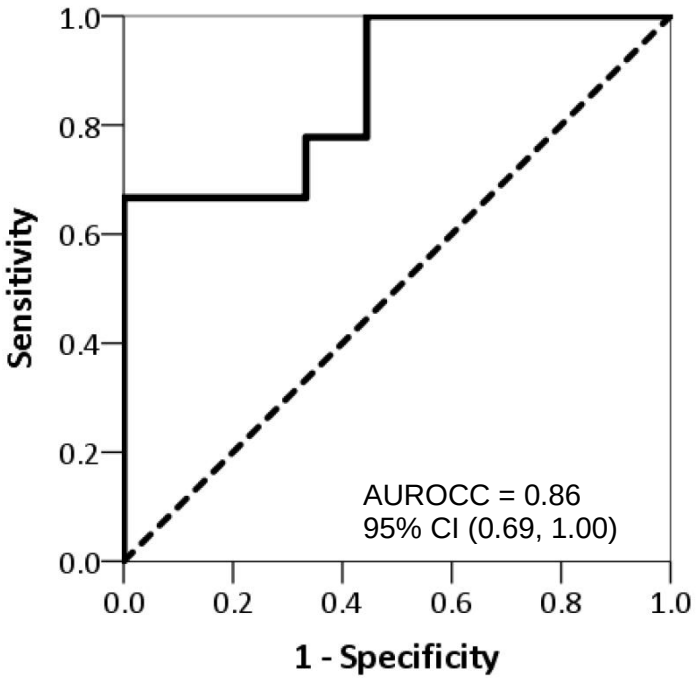


Figure 89. Receiver operating characteristic curve to identify RVEF ≤45% using RV-FWPLS on POD 2
AUROCC = area under the receiver operator characteristic curve, RVEF = right ventricular ejection fraction, RV-FWPLS = RV free wall peak longitudinal strain.

7.4 Trend analysis

Trend analysis was performed to assess the ability of RV-GPLS and RV-FWPLS to detect changes in $RVEF_{CMR}$ between time points. *Change* in the strain parameters (ΔRV-GPLS and ΔRV-FWPLS) was compared with *change* in $RVEF_{CMR}$ (ΔRVEF, Figure 90).

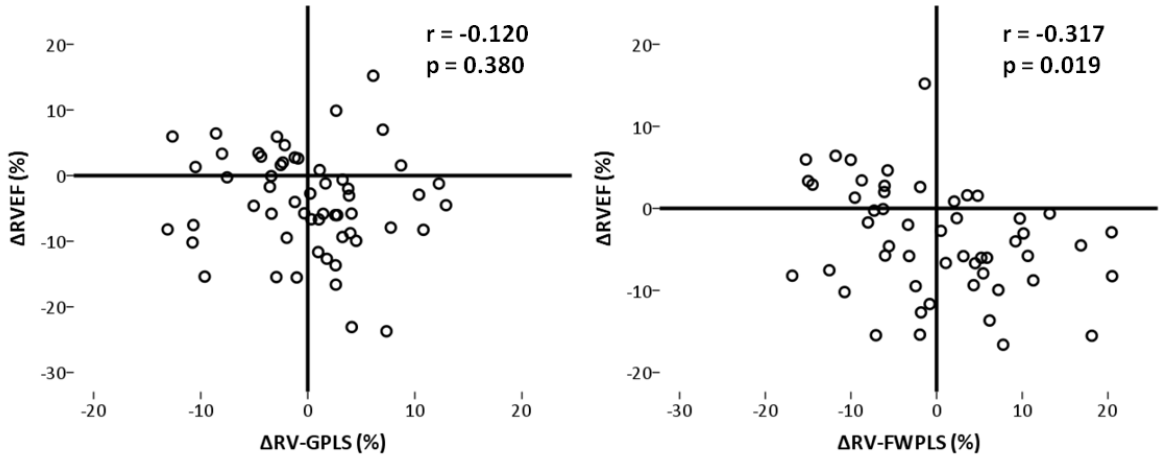


Figure 90. ΔRV-GPLS (n=56) and ΔFWPLS (n=54) against $\Delta RVEF_{CMR}$
Pearson's correlation coefficient as illustrated. ΔRVEF = change in right ventricular ejection fraction, ΔRV-GPLS = change in RV global peak longitudinal strain, ΔRV-FWPLS = change in RV free wall peak longitudinal strain.

There was no association between ΔRV-GPLS and $\Delta RVEF_{CMR}$ (Figure 90). ΔRV-FWPLS showed moderate association with $\Delta RVEF_{CMR}$. The predictive ability of both strain parameters to detect a *change* in $RVEF_{CMR}$ was further assessed. The standard deviation of $\Delta RVEF_{CMR}$, 7.55%, was used as the minimal change that would be useful to determine from strain and AUROCC analysis was performed. Neither parameter showed predictive power for ΔRVEF >7.55% (Table 46).

	ΔRV-GPLS	**ΔRV-FWPLS**
AUROCC (95%CI)	0.62 (0.45, 0.78)	0.58 (0.41, 0.75)
p	0.171	0.331

Table 46. Receiver operating characteristic analysis to detect ΔRVEF >7.55%
AUROCC = Area under the receiver operating characteristic curve, RVEF = Right ventricular ejection fraction, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain.

7.5 Discussion

This investigation describes changes in longitudinal RV strain following lung resection. It also describes validation against a reference method for assessment of RV function. It's main finding is that speckle tracked strain, particularly RV-FWPLS, *may* have utility to determine RV function in this population.

Strain results were available in 100% of patients pre-operatively and at 2-months. As demonstrated in 0, surgery appeared to have an impact on imaging availability with strain results only available in 84.6% of participants on POD 2. Three quarters of unavailable scans were on those patients having left sided resections suggesting this group had difficulties with imaging availability. Where initial results were provided by both authors, strain values were reproducible with good intra class correlation coefficients.

The study has been unable to demonstrate any change in strain over the duration of the study. The lack of change observed is in contrast to a 2016 study by Wang et al. which measured longitudinal RV strain *one week* following lung resection in a mixed pneumonectomy and lobectomy cohort (n=30). They demonstrated RV-GPLS and RV-FWPLS (corrected for heart rate) deteriorated following lung resection, with the magnitude of change larger in the group undergoing pneumonectomy (Figure 91). This study used the same software as utilised in the current investigation and they report no problems with image analysis in the post-op period. Inter and intra-observer variability was similar with ICC's of 0.84 and 0.87.

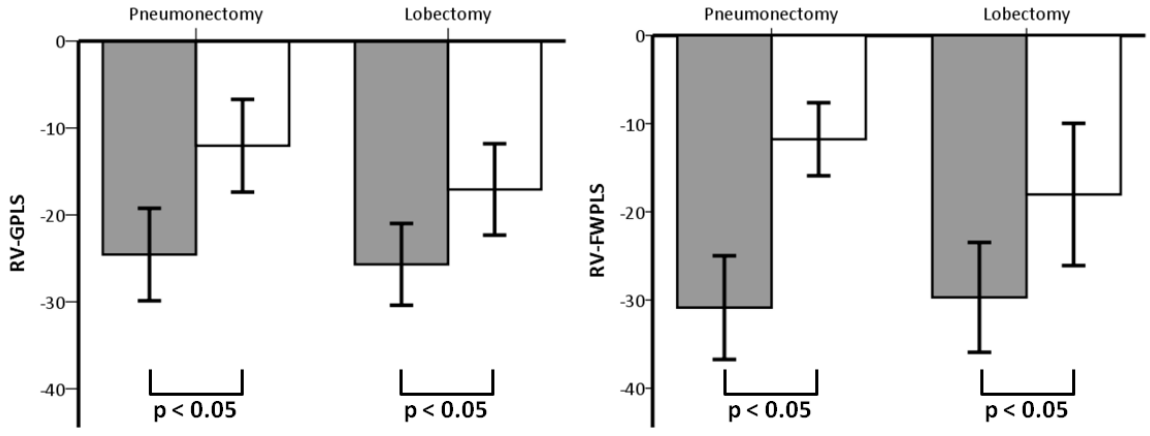


Figure 91. RV-GPLS and RV-FWPLS following lung resection redrawn from Wang et al.[206]
Significant differences within groups as illustrated. RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain, Grey = pre-op, White = one week post-op.

A number of reasons may account for the difference in results between the current investigation and this previous study by Wang et al. The timing of assessment may be important as the current investigation examined patients on POD 2 and it is uncertain whether RV function continues to deteriorate following this time-point. The study population may also impact the results, the population recruited by Wang was younger than the cohort in the current study (57.0±11.4 years vs 65.2±10.8 years) and their protocol excluded patients with hypertension, diabetes and coronary artery disease. In contrast, 33.3% of participants in the current investigation had hypertension and 22.2% had coronary artery disease. The patients being younger and with fewer comorbidities may account for better baseline RV function (RV-FWPLS of -29.7±6.2% in Wang et al. vs RV-FWPLS of -22.2±7.5% in current study). The larger drop in RV function observed by Wang et al. may support the hypothesis described in section 5.7, pg 197 that better RV function pre-operatively, results in a larger drop in RV function following lung resection. This is potentially as a result of prior exposure to elevated RV afterload allowing better tolerance of acute changes at the time of surgery.

As strain parameters have been reported to be influenced by heart rate[302], with higher heart rate resulting in lower strain (poorer function), Wang et al. *"used heart rate as a covariate"* when analysing changes following surgery. The methods within the paper did not describe how this was performed and no response was received when the authors were contacted about their methods (personal communication x 3, February 2017).

The impact of heart rate on strain results in this cohort was assessed on an exploratory basis. There was no association between the strain parameters (RV-GPLS or RV-FWPLS) and heart rate on pooled analysis ($p>0.115$). Two multiple linear regression models incorporating the strain parameters, heart rate and the patient (to account for within patient association) were created. The models for RV-GPLS ($p=0.094$ $r2=0.72$) and RV-FWPLS ($p=0.51$, $r2=0.089$) were both non-significant, with heart rate not making a significant contribution ($p>0.102$ for both) to either. In other studies examining speckle tracked RV strain, no attempt has been made to correct for heart rate[121, 167, 303-305] therefore, no correction has been made in this investigation.

RV strain has been shown to have clinical utility for assessment of RV function, with predictive value in pulmonary hypertension[303, 304], heart failure[306] and acute myocardial infarction[307]. As longitudinal shortening is the major contributor to overall RV performance, longitudinal strain has been suggested as a surrogate for *global* RV function. Unlike other echo parameters, such as TAPSE and S'Wave (section 4.4.2.2.2, pg 151 and section 4.4.2.2.3, pg 152), which measure displacement or velocity of only the basal segment, STE allows analysis of the entire RV free wall and interventricular septum. The RV can additionally be divided in to six segments (three each for the free wall and septum, see Figure 40, pg 158), allowing true *regional* assessment of RV function. Unlike echocardiographic volumetric assessment, there are no geometric assumptions.

Strain measurements are independent of global cardiac movement which can impact Tricuspid Annular Plane Systolic Excursion (TAPSE) and S'Wave velocity at the tricuspid annulus (S'Wave) analysis. As well as the impact of global cardiac translation, TAPSE and S'Wave are also *angle dependent* measures of RV function[308]. Speckle tracked strain is angle *independent*, meaning there is not a reliance on obtaining a low angle of incidence ($<20^{o}$) as is required for tissue Doppler measurements.

Strain assessment of the RV has previously been suggested as a *load independent* measure of RV contractility and this was the rationale for including it in this study[151, 309]. However, when examined robustly this appears to be incorrect, with Missant et al.[310] demonstrating in a sheep model (n=6) that maximal *strain rate* was associated with the slope of the preload recruitable stroke work relationship (a load independent measure of RV contractility). They also demonstrated however, that as afterload increased (from banding of the PA), strain rate was reduced while contractility was unchanged. This suggested that during inotropy, strain rate tracked changes in contractility, but not when afterload was altered suggesting strain rate is not load independent.

A review article examining RV strain by La Gerche et al. provides worked examples of how deformation parameters (such as strain) cannot be load independent and explains that reduced RV deformation is not synonymous with myocardial dysfunction when afterload changes. In disease states with increased *afterload* they described three situations that may occur[149]:

1. *Normal deformation* (strain) as a result of normal afterload *or* increased afterload and increased contractility.

2. *Reduced deformation* (strain) due to increased afterload but maintained contractility.

3. *Reduced deformation* (strain) due to increased afterload and/or reduced contractility.

A further clinical example of load dependence is provided by Puwanant et al. who demonstrate RV strain is strongly associated with pulmonary artery pressure (increasing pressure was associated with reduced strain i.e. poorer RV function) when it would be expected that *contractility* would be increasing in this situation[112, 311]. In a swine model of repaired tetralogy of Fallot, Hodzic et al. demonstrated no association between conductance catheter determined E_{max} (the reference method for load independent contractility) and strain measurements. Furthermore strain was associated with RV end systolic pressure (used as a surrogate of afterload) and RV end diastolic volume (used as a surrogate of preload), confirming its load dependence[312].

Previous work has highlighted the potential benefit of strain parameters for assessment of RV function and has shown them to perform better than conventional parameters of RV function when compared to reference methods[121, 122, 150, 313, 314]. Focardi et al. demonstrated RV-FWPLS showed excellent predictive power for $RVEF_{CMR}$ ≤45% with an AUROCC of 0.92 in a heterogeneous population referred for CMR evaluation[121]. RV-GPLS did not perform as well in this population with an AUROCC of 0.78, although both strain parameters outperformed conventional echo parameters (AUROCC of 0.66 for TAPSE and 0.78 for FAC). Strain has also been shown to be predictive of RV dysfunction in other groups. In a population with ischaemic cardiomyopathy, Park et al. showed RV-GPLS had an AUROCC of 0.96 for detection of $RVEF_{CMR}$≤50%[150]. No study has attempted to validate RV-FWPLS or RV-GPLS in a lung resection cohort.

This study has demonstrated association between RV-GPLS, RV-FWPLS and $RVEF_{CMR}$ on pooled analysis. When taking account of within subject factors, RV-GPLS showed no association and RV-FWPLS only showed a *trend* towards

association (p=0.054). AUROCC analysis of the pooled results showed that both had good predictive power for RV dysfunction with AUROCC of 0.74 for RV-GPLS and 0.76 for RV-FWPLS. To assess the ability of the two parameters to predict RV dysfunction at each peri-operative stage, an individual analysis was performed at each time point which showed that RV-GPLS had predictive power at all time points (AUROCC 0.78-0.79) and that RV-FWPLS had predictive power pre-op and on POD 2 (AUROCC 0.79-0.86). Trend analysis demonstrated association between $\Delta RVEF_{CMR}$ and ΔRV-FWPLS, but no association with ΔRV-GPLS. Neither variable showed predictive power for a change in $RVEF_{CMR}$ of one standard deviation.

The poorer association between strain and $RVEF_{CMR}$ demonstrated within this investigation will also have been impacted by the factors that influence the conventional echo parameters described in section 6.4, pg 218. The tighter range of RV function in the current study, compared to the wide range of RV function in validation studies, mean association will be harder to demonstrate.

7.5.1 Strengths and limitations

The robust assessment of a novel echo parameter and its validation against a reference method in a representative population is a strength of this investigation. This includes dual reporting of anonymised scans with good agreement for dual reported images (signified by intraclass correlation coefficients >0.9).

A limitation of the STE technique is the dependence on image quality to obtain values. This was seen in the early period following lung resection when strain results were only available in 84.6% of participants on POD 2. The thin RV wall means it is difficult to define an accurate region of interest with the problem compounded when image quality is poor[76, 308]. These difficulties may have contributed to the discrepancy between observers, with 22.1% of scans requiring expert review and some of these yielding additional results.

The software utilised for strain analysis in this investigation had no specific RV tool, requiring use of an LV strain protocol applied to the RV. Software platforms specifically for RV strain analysis have now been developed. Additionally, there is

significant inter-vendor variability, meaning results may be influenced by the software used[315-317].

7.6 Conclusion

This investigation demonstrates that RV-FWPLS may have utility as a validated method for assessment of RV systolic function following lung resection. Strain has the potential to overcome some of the difficulties associated with standard echocardiographic assessment of the RV. Although not the *ideal* measure, it shows promise and performs better than the conventional methods discussed in chapter 6.

Further work in larger numbers will be required for confirmation of these findings. Additionally, investigations using RV *specific* speckle tracked echocardiography platforms may improve the predictive ability of strain for poor RV function in this population.

Chapter 8 Biomarkers of Myocardial Dysfunction

8.1 Introduction

This chapter describes the results of the biomarkers of myocardial dysfunction; B-type natriuretic peptide (BNP) and high sensitivity troponin T (hsTnT). Firstly it will describe changes in the biomarkers over time. Secondly, the association between these biomarkers and cardiac function will be assessed. Finally, on an exploratory basis, a comparison with post-op outcomes and functional capacity will be made.

Other than at 2-months post-op, BNP results were available for all 27 study participants at all time points. At 2-months, samples were available for 24 patients. Of the three participants without samples at 2-months, one declined venepuncture, one was unwell in another hospital and was unable to attend follow-up, and the third was as a result of administration error. Troponin results were available for 26 participants from pre-op to POD 2 and for 22 participants at 2-months. The reasons for unavailability of samples at 2-months were the same as for BNP, with an additional two not available as a result of laboratory administration error[X]. The troponin results unavailable at the other time points were as a result of laboratory administration error.

Coefficients of variation for BNP and hsTnT were 5.9% (calculated from frozen controls as described in section 4.6.2.2, pg 161) and <10% (report from biochemistry lab at Golden Jubilee National Hospital) respectively.

8.2 Changes in biomarkers over time

BNP increased over time, peaking on POD 2 and returning to baseline levels by 2-months (Figure 92, pg 244 and Table 47, pg 245). HsTnT showed a small but *statistically* significant post-op rise (Figure 93, pg 244 and Table 47, pg 245).

[X] BNP analysis was performed by the author and hsTnT analysis was performed by labs at the Golden Jubilee National Hospital.

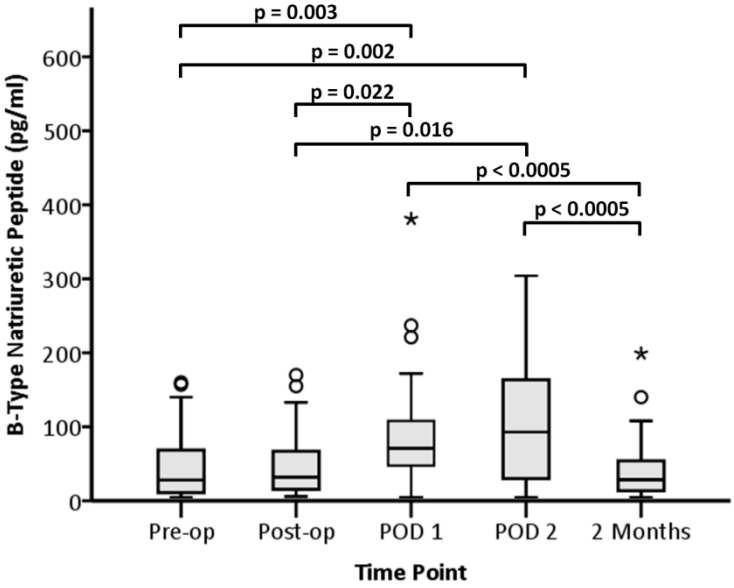


Figure 92. Changes in BNP over time
Box plots represent median, IQR and range. Changes over time assessed with Friedman's test, p<0.0005. Post-hoc comparisons with Wilcoxon rank sum test. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in the recovery area, POD = post-op day, BNP = B-type natriuretic peptide.

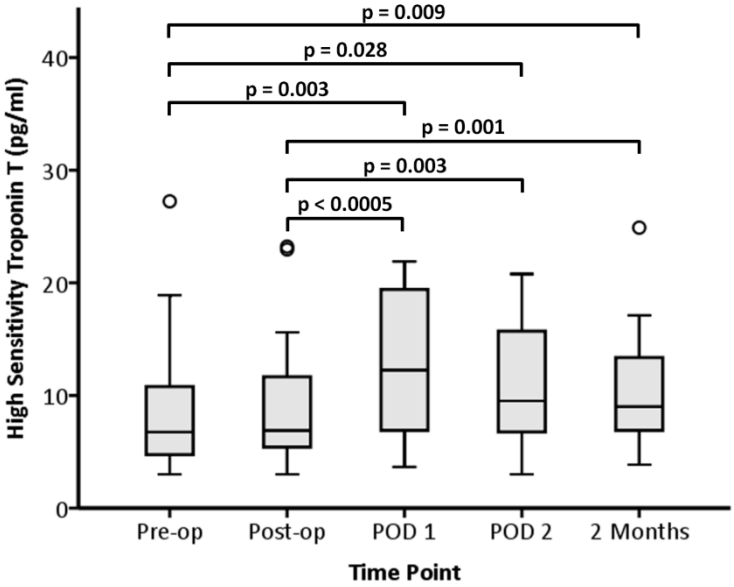


Figure 93. Changes in hsTnT over time
Box plots represent median, IQR and range. Changes over time assessed with Friedman's test, p<0.0005. Post-hoc comparisons with Wilcoxon rank sum test. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in the recovery area, POD = post-op day, hsTnT = high sensitivity troponin T.

Biomarkers of myocardial dysfunction						
	pre-op	**post-op**	**POD 1**	**POD 2**	**2-months**	**p-value**
	n=27	*n=27*	*n=27*	*n=27*	*n=24*	
BNP (pg/ml)	28.0 (5.0,160.0)	32.0 (6.0,170.0)	71.0 (5.0, 381.0)†‡	93.0 (5.0, 304.0)†‡	28.5 (5.0,199.0)§‖	<0.0005*
	n=26	*n=26*	*n=26*	*n=26*	*n=22*	
hsTnT (pg/ml)	6.8 (3.0, 27.2)	6.9 (3.0, 23.2)	12.3 (3.7, 21.9)†‡	9.5 (3, 20.7)†‡	9.0 (3.9, 24.9)†‡	<0.0005*

Table 47. Biomarkers of myocardial function over time

Data are presented as median (IQR), * = Friedman's Test, † = significant difference from pre-op, ‡ = significant difference from immediate post-op, § = significant difference from POD 1, ‖ = significant difference from POD 2, pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in the recovery area, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T.

8.3 Association of biomarkers with cardiac function by cardiovascular magnetic resonance

Association between the biomarkers and CMR determined cardiac function was assessed at each peri-operative time point. A summary is displayed in Table 48, pg 247. As evident in Table 48 (pg 247), there is moderate negative association between BNP_{POD2} and $RVEF_{POD2}$ (Figure 94).

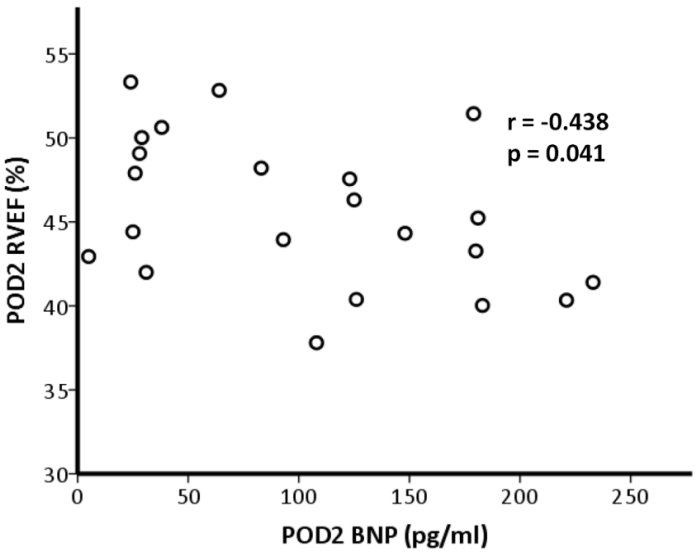


Figure 94. Association between $RVEF_{POD2}$ and BNP_{POD2}
Pearson's correlation coefficient, RVEF = right ventricular ejection fraction, BNP = B-type natriuretic peptide, POD = post-op day.

There is also evidence of negative association between both $RVEF_{2months}$, $LVEF_{2months}$ and; $hsTnT_{preop}$, $hsTnT_{postop}$ and $hsTnT_{2months}$. Visual inspection of these plots however, showed an outlier influencing the association (Figure 95).

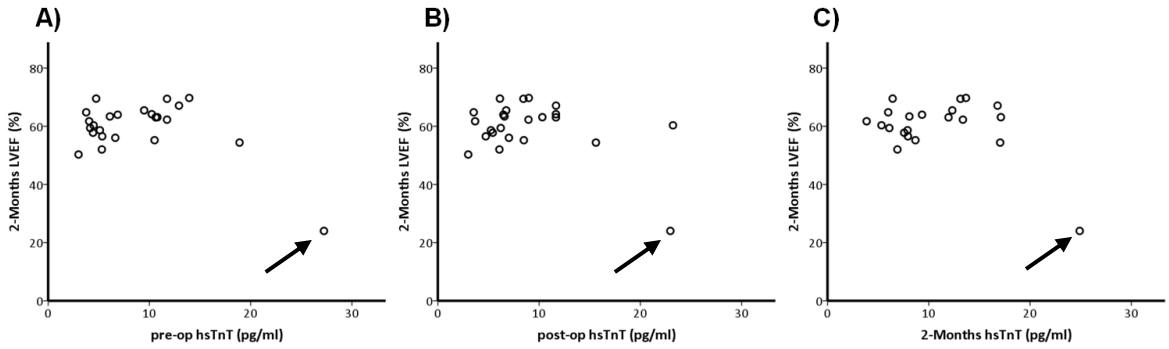


Figure 95. Association between LVEFCMR at 2-months and hsTnT at peri-op time points
A) pre-op hsTnT, B) post-op hsTnT, C) 2-months hsTnT. LVEF = Left ventricular ejection fraction, hsTnT = high sensitivity troponin T. Black arrows indicate outlier described in section 8.3, pg 246.

		$RVEF_{CMR}$			$LVEF_{CMR}$		
		pre-op	**POD 2**	**2months**	**pre-op**	**POD 2**	**2months**
BNP_{preop}	**r**	0.15	0.21	0.16	0.21	0.13	-0.20
	p	0.468	0.346	0.465	0.313	0.560	0.357
	n	26	22	24	26	22	24
BNP_{postop}	**r**		0.18	0.13		0.07	-0.18
	p		0.42	0.56		0.76	0.41
	n		22	24		22	24
BNP_{POD1}	**r**		-0.07	0.09		-0.28	-0.17
	p		0.749	0.693		0.202	0.428
	n		22	24		22	24
BNP_{POD2}	**r**		**-0.44**	-0.04		-0.06	-0.19
	p		**0.041**	0.867		0.782	0.371
	n		**22**	24		22	24
$BNP_{2months}$	**r**			0.12			-0.06
	p			0.601			0.777
	n			23			23
$hsTnT_{preop}$	**r**	0.01	-0.02	**-0.43**	-0.23	**-0.59**	**-0.47**
	p	0.973	0.932	**0.034**	0.280	**0.004**	**0.022**
	n	25	22	**24**	25	**22**	**24**
$hsTnT_{postop}$	**r**		0.16	**-0.41**		**-0.44**	**-0.41**
	p		0.480	**0.046**		**0.048**	**0.044**
	n		21	**24**		**21**	**24**
$hsTnT_{POD1}$	**r**		-0.09	-0.20		-0.26	-0.14
	p		0.696	0.349		0.264	0.516
	n		21	24		21	24
$hsTnT_{POD2}$	**r**		-0.08	0.12		-0.36	0.05
	p		0.734	0.601		0.110	0.823
	n		21	23		21	23
$hsTnT_{2months}$	**r**			**-0.49***			**-0.44**
	p			**0.025**			**0.045**
	n			**21**			**21**

Table 48. Association of biomarkers of myocardial dysfunction with $RVEF_{CMR}$ and $LVEF_{CMR}$
All associations are Pearson's correlation coefficient. Significant associations are highlighted in **BOLD**. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op extubated in the recovery area, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T.

This patient has been previously described as an outlier for cardiac function at 2-months (Footnote P, pg 180). Sensitivity analysis with this patient excluded resulted in loss of the linear relationship and no statistical significance (p>0.247 for all). This pattern was the same for association between $RVEF_{2months}$ and $hsTnT_{preop}$, $hsTnT_{postop}$ and $hsTnT_{2months}$. Again, sensitivity analysis with this patient excluded resulted in loss of the linear relationship and no statistical significance (p>0.304 for all, figures not shown). There is also moderate negative association between $hsTnT_{preop}$, $hsTnT_{postop}$ and $LVEF_{POD2}$ (Table 48, pg 247 and Figure 96). This suggests that those patients with higher troponin immediately before and immediately after lung resection had poorer LV function on POD 2 (signified by lower $LVEF_{POD2}$).

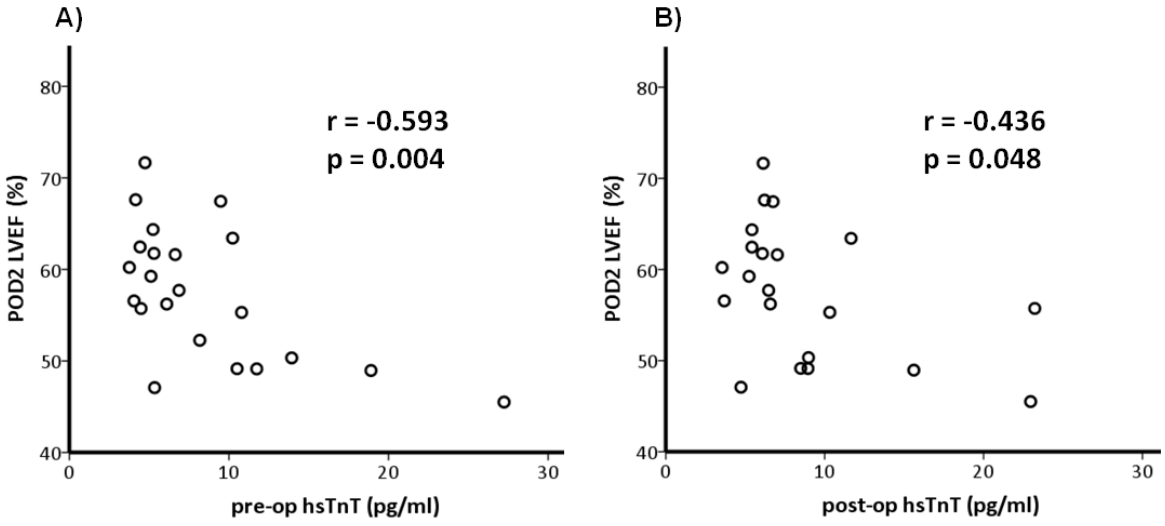


Figure 96. Association between $LVEF_{CMR}$ on POD 2 and hsTnT at peri-op time points
A) Immediately pre-op hsTnT, B) Immediately post-op hsTnT, associations are Spearman's correlation coefficient, LVEF = left ventricular ejection fraction, hsTnT = high sensitivity troponin T, POD = post-op day.

The association between the *absolute* biomarkers and *change* in cardiac function ($\Delta RVEF_{CMR}$ and $\Delta LVEF_{CMR}$) was assessed (Table 49, pg 249). Finally, to fully explore the potential role of the biomarkers in assessing post-op cardiac function, association between a *change* in the biomarkers (ΔBNP and ΔhsTnT) was compared with *absolute* cardiac function (Table 50, pg 250).

		ΔRVEF		ΔLVEF	
		POD2-preop	**2months-preop**	**POD2-preop**	**2months-preop**
BNP_{preop}	**r**	-0.03	0.06	-0.14	-0.34
	p	0.893	0.788	0.533	0.108
	n	22	23	22	23
BNP_{POD2}	**r**	**-0.52***	-0.06	-0.29	-0.38
	p	**0.014**	0.803	0.195	0.076
	n	**22**	23	22	23
$BNP_{2months}$	**r**		-0.11		-0.35
	p		0.643		0.116
	n		22		22
$hsTnT_{preop}$	**r**	0.06	**-0.43***	-0.36	-0.30
	p	0.805	**0.039**	0.098	0.158
	n	22	**23**	22	23
$hsTnT_{POD2}$	**r**	-0.27	-0.07	-0.32	0.09
	p	0.234	0.757	0.160	0.707
	n	21	22	21	22
$hsTnT_{2months}$	**r**		-0.34		-0.31
	p		0.142		0.188
	n		20		20

Table 49. Association of biomarkers of myocardial dysfunction with $\Delta RVEF_{CMR}$ and $\Delta LVEF_{CMR}$
All associations are Pearson's correlation coefficient. Significant associations are highlighted in **BOLD**. Pre-op = Immediately pre-op prior to induction of anaesthesia, Post-op = Immediately post-op extubated in recovery area, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T.

There was evidence of moderate negative association between BNP_{POD2} and $\Delta RVEF_{POD2\text{-}preop}$, this suggests that those patients with the highest BNP on POD2 were those with the largest change in $RVEF_{CMR}$ by the same time point (Table 49 and Figure 97, pg 250). There was also association between $\Delta RVEF_{2months\text{-}preop}$ and $hsTnT_{preop}$; this association was impacted by a single outlier (participant with largest drop in $RVEF_{CMR}$ by 2-months as previously described). Sensitivity analysis with this patient excluded resulted in loss of any linear association with no statistical significance (p=0.505, figure not shown).

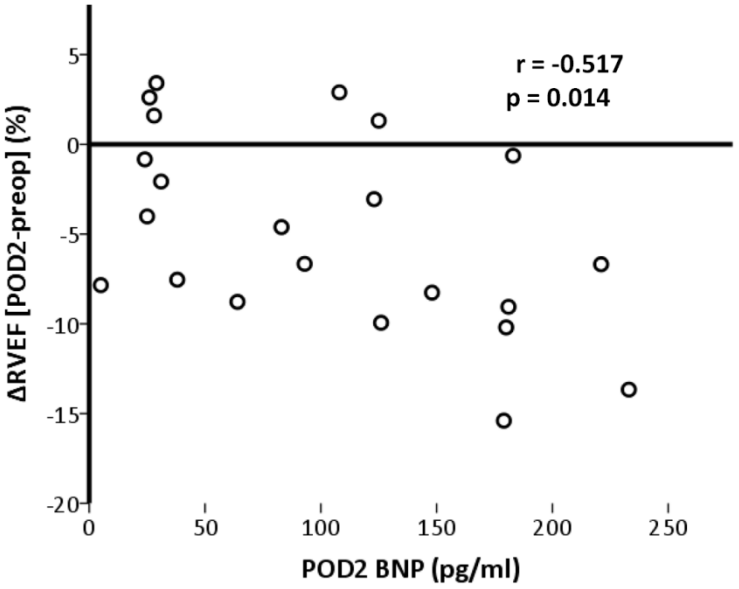


Figure 97. Association between $\Delta RVEF_{POD2\text{-}pre}$ and BNP_{POD2}
Associations is Pearson's correlation coefficient with p-value as illustrated, RVEF = right ventricular ejection fraction, BNP = B-type natriuretic peptide, POD = post-op day.

A moderate negative association between *RV* function on POD 2 and change in *both* biomarkers by this time point was demonstrated ($\Delta BNP_{POD2\text{-}preop}$ and $\Delta hsTnT_{POD2\text{-}preop}$). There was no association between LV function and the change in the biomarkers (Table 50 and Figure 98, pg 251).

			$RVEF_{POD2}$	$LVEF_{POD2}$
ΔBNP	**POD2-preop**	**r**	**-0.52**	-0.14
		p	**0.012**	0.535
		n	**22**	22
ΔhsTnT	**POD2-preop**	**r**	**-0.46**	0.07
		p	**0.035**	0.762
		n	**21**	21

Table 50. Association of $\Delta BNP_{POD2\text{-}preop}$ and $\Delta hsTnT_{POD2\text{-}preop}$ with cardiac function on POD 2
Associations are Pearson's correlation coefficient. Significant associations are highlighted in **BOLD**. Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T, RVEF = right ventricular ejection fraction, LVEF = left ventricular ejection fraction.

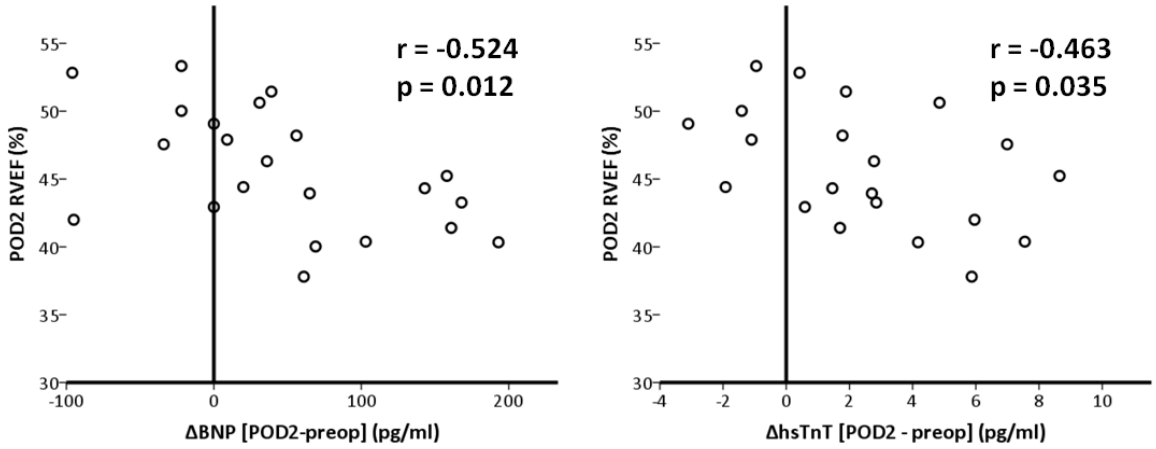


Figure 98. Association between $\Delta BNP_{POD2\text{-}preop}$, $\Delta hsTnT_{POD2\text{-}preop}$ and $RVEF_{POD2}$
Pearson's correlation coefficient. Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T, RVEF = right ventricular ejection fraction.

8.3.1 Prediction of right ventricular dysfunction

This study demonstrated moderate negative association between $RVEF_{POD2}$ and; BNP_{POD2}, $\Delta BNP_{POD2\text{-}preop}$ and $\Delta hsTnT_{POD2\text{-}preop}$. There is also moderate negative association between $\Delta RVEF_{POD2\text{-}preop}$ and BNP_{POD2}. The ability of these parameters to predict RV dysfunction on POD 2 (defined as $RVEF_{CMR} \leq 45\%$) were assessed.

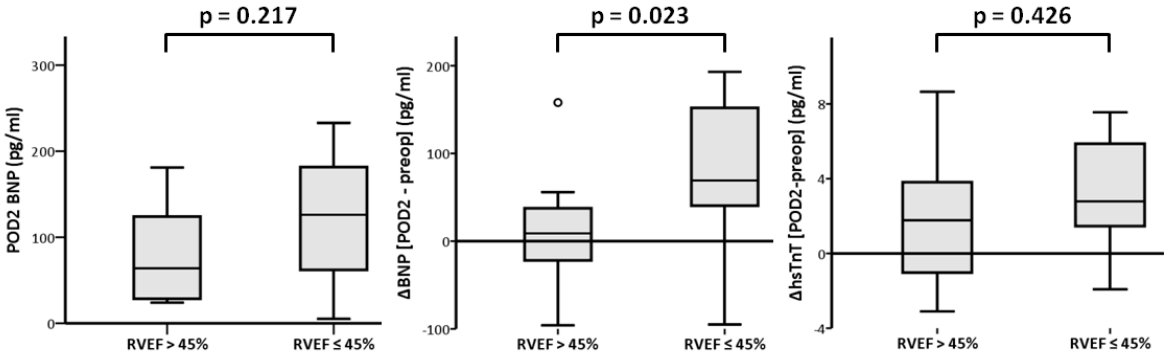


Figure 99. BNP_{POD2}, $\Delta BNP_{POD2\text{-}preop}$ and $\Delta hsTnT_{POD2\text{-}preop}$ versus $RVEF_{POD2}$>45% and $RVEF_{POD2} \leq 45\%$
Box plots represent median, IQR and range. All comparisons are Mann-Whitney U-Test, Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T, RVEF = right ventricular ejection fraction.

There was a difference in $\Delta BNP_{POD2\text{-}preop}$ between those with RVEF>45% and those with RVEF ≤45%. There was no difference in the other parameters between the two groups (Figure 99, above). Using area under the receiver operating characteristic curve (AUROCC) analysis, the predictive ability of $\Delta BNP_{POD2\text{-}preop}$ to detect $RVEF_{POD2}$ ≤45% was assessed. This demonstrated an AUROCC of 0.78 (Figure 100 and Table 51).

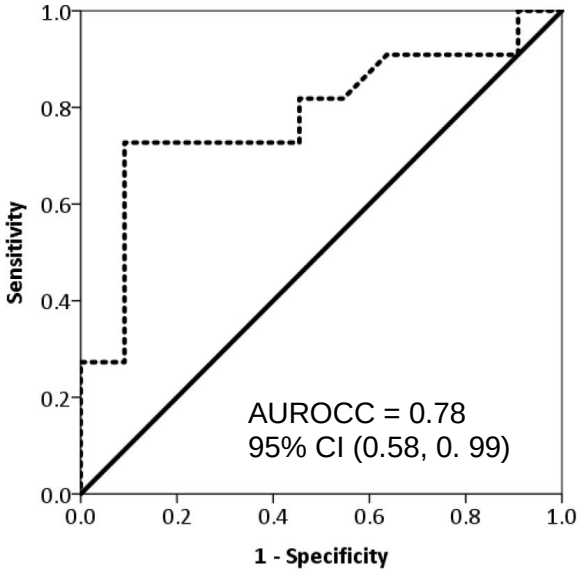


Figure 100. Receiver operating characteristic identifying $RVEF_{POD2}$ ≤45% with $\Delta BNP_{POD2\text{-}preop}$
Pre-op = Immediately pre-op prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, RVEF = right ventricular ejection fraction.

	$\Delta BNP_{POD2\text{-}preop}$
	$RVEF_{CMR}$ ≤45%
AUROCC (95%CI)	0.78(0.58, 0.99)
p	0.026
Cut-off value[Y]	58.5 pg/ml
Sensitivity	72.7%
Specificity	90.9%
PPV	88.8%
NPV	76.9%

Table 51. Predictive performance of a cut-off of $\Delta BNP_{POD2\text{-}preop}$ to detect $RVEF_{POD2}$ ≤45%
AUROCC = Area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value, Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, RVEF = right ventricular ejection fraction.

[Y] Defined by Youden's index (Maximum combination of sensitivity and specificity).

Given the association between $\Delta RVEF_{POD2\text{-}preop}$ and BNP_{POD2}, the ability of BNP_{POD2} to predict a *change* in RVEF by POD 2 was assessed. As no minimal clinically important difference for change in RVEF following lung resection exists, the standard deviation of $\Delta RVEF_{POD2\text{-}preop}$, 5.43%, was used as the minimal change that would be useful to determine and AUROCC analysis was performed.

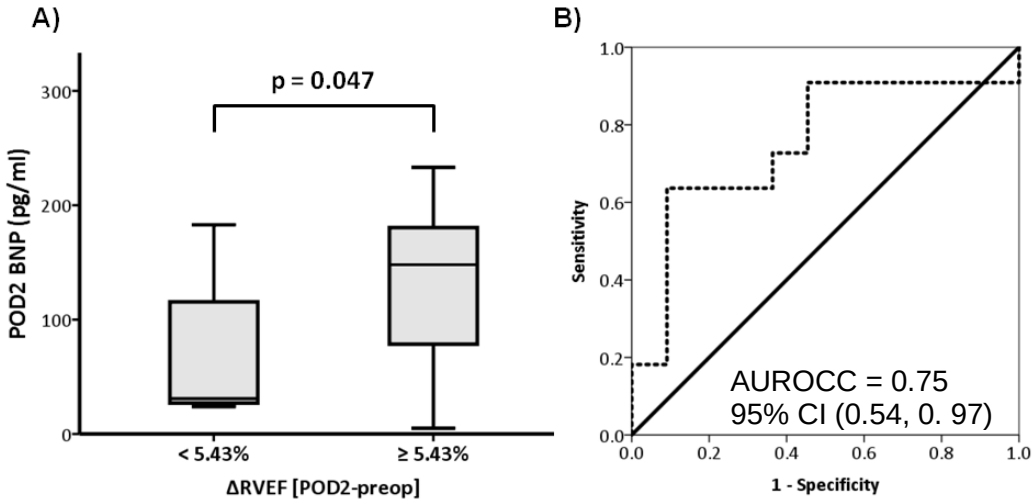


Figure 101. BNP_{POD2} and $\Delta RVEF_{POD2\text{-}preop}$ ≥5.43% and $\Delta RVEF_{POD2\text{-}preop}$ <5.43%.
Box plots represent median, IQR and range. A) Mann-Whitney U-Test. B) AUROCC to identify $\Delta RVEF_{POD2\text{-}preop}$ ≥5.43%. Pre-op = Immediately pre-op prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, RVEF =right ventricular ejection fraction.

As can be seen in Figure 101A there was a difference in BNP_{POD2} between $\Delta RVEF_{POD2\text{-}preop}$ ≥5.43% and $\Delta RVEF_{POD2\text{-}preop}$ <5.43%. BNP_{POD2} was able to predict $\Delta RVEF_{POD2\text{-}preop}$ ≥5.43% with an AUROCC of 0.75 (Figure 101B and Table 52).

	BNP_{POD2}
	$\Delta RVEF_{POD2\text{-}preop}$ ≥5.43%
AUROCC (95%CI)	0.75(0.54, 0.97)
p	0.045
Cut-off value[Z]	125.5 pg/ml
Sensitivity	63.6%
Specificity	90.9%
PPV	87.5%
NPV	71.4%

Table 52. Predictive performance of a cut-off of BNP_{POD2} for $\Delta RVEF_{POD2\text{-}preop}$ ≥5.43%
AUROCC = area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value, Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, RVEF = right ventricular ejection fraction.

[Z] Defined by Youden's index (Maximum combination of sensitivity and specificity).

8.4 Biomarkers and post-operative outcomes

As described in chapter 4, only two patients developed AF in the post-op period. Those patients were not outliers for BNP or hsTnT level at any time point (not shown). The association between the biomarkers and duration of stay (High dependency unit [HDU] and hospital) was explored. There was no relationship between hospital stay and the biomarkers, however there was a moderate positive association between BNP_{POD2} and duration of HDU stay (r=0.462, p=0.015, Pearson's correlation coefficient, figure not shown) which was strengthened when $\Delta BNP_{POD2\text{-}preop}$ was compared (Figure 102).

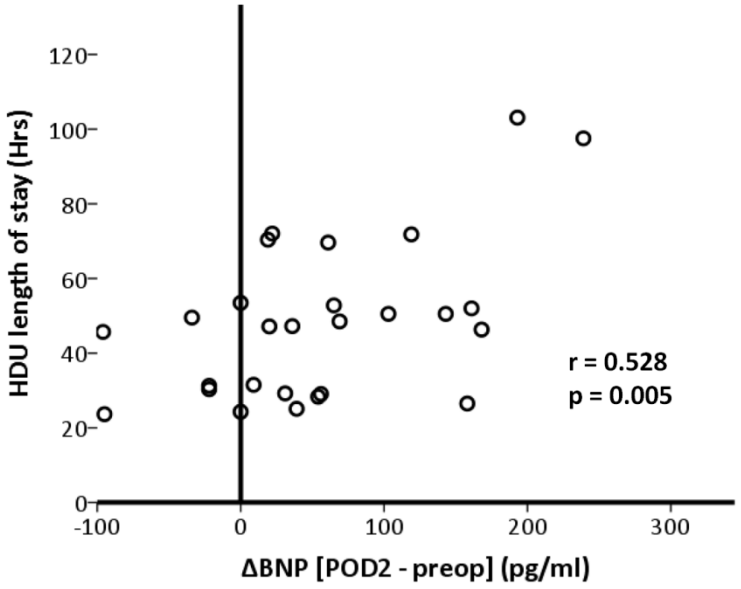


Figure 102. Association between $\Delta BNP_{POD2\text{-}preop}$ and HDU length of stay
Pearson's correlation coefficient. Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide, HDU = high dependency unit.

8.5 Biomarkers and functional capacity

The association between the biomarkers and functional capacity was explored. There was no evidence of association between BNP_{preop} or $hsTnT_{preop}$ and any of the measures of functional capacity pre-operatively (p>0.123 for all, Spearman's correlation coefficient, not shown). Association was examined between the biomarkers and functional capacity at both 2-months and at 1-year (Table 53, pg 255).

		2-months			1 year		
		WHO-PS	MRC	NYHA	WHO-PS	MRC	NYHA
BNP_{preop}	**r**	0.21	0.24	0.15	-0.28	-0.02	0.02
	p	0.321	0.248	0.489	0.228	0.929	0.929
	n	25	25	25	20	21	22
BNP_{postop}	**r**	0.30	0.35	0.16	-0.23	-0.11	0.03
	p	0.142	0.086	0.452	0.337	0.648	0.880
	n	25	25	25	20	21	22
BNP_{POD1}	**r**	**0.46**	**0.56**	0.22	-0.41	-0.05	0.19
	p	**0.020**	**0.003**	0.288	0.074	0.831	0.410
	n	**25**	**25**	25	20	21	22
BNP_{POD2}	**r**	**0.44**	0.33	0.28	-0.32	-0.03	0.07
	p	**0.027**	0.105	0.178	0.170	0.886	0.757
	n	**25**	25	25	20	21	22
$BNP_{2months}$	**r**	0.26	0.18	0.06	-0.26	0.15	0.10
	p	0.216	0.401	0.787	0.290	0.535	0.665
	n	24	24	24	18	19	20
$hsTnT_{preop}$	**r**	-0.28	-0.02	0.02	-0.16	-0.27	0.05
	p	0.228	0.929	0.929	0.504	0.251	0.836
	n	20	21	22	19	20	21
$hsTnT_{postop}$	**r**	-0.23	-0.11	0.03	-0.02	-0.19	0.08
	p	0.337	0.648	0.880	0.941	0.431	0.717
	n	20	21	22	19	20	21
$hsTnT_{POD1}$	**r**	-0.41	-0.05	0.19	-0.24	-0.12	0.12
	p	0.074	0.831	0.410	0.331	0.622	0.595
	n	20	21	22	19	20	21
$hsTnT_{POD2}$	**r**	-0.32	-0.03	0.07	-0.30	-0.16	-0.04
	p	0.170	0.886	0.757	0.201	0.500	0.872
	n	20	21	22	20	21	21
$hsTnT_{2months}$	**r**	-0.26	0.15	0.10	-0.42	-0.44	-0.20
	p	0.290	0.535	0.665	0.086	0.061	0.409
	n	18	19	20	18	19	20

Table 53. Association between biomarkers and functional capacity at 2-months and 1 year
All associations are Spearman's correlation coefficient. Significant associations are highlighted in **BOLD**. WHO-PS = World Health Organisation performance status. MRC = Medical Research Council dyspnoea scale. NYHA = New York Heart Association classification, Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in recovery area, POD = post-op day, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T.

There was moderate positive association between BNP_{POD1}, BNP_{POD2} and World Health Organisation performance status (WHO-PS) at 2-months. There was also moderate positive association between BNP_{POD1} and Medical Research Council dyspnoea scale (MRC-DS, Figure 103). There was no association between BNP and any of the measures of functional capacity at one year. There was no association between hsTnT with any of the measures of functional capacity at 2-months or one year.

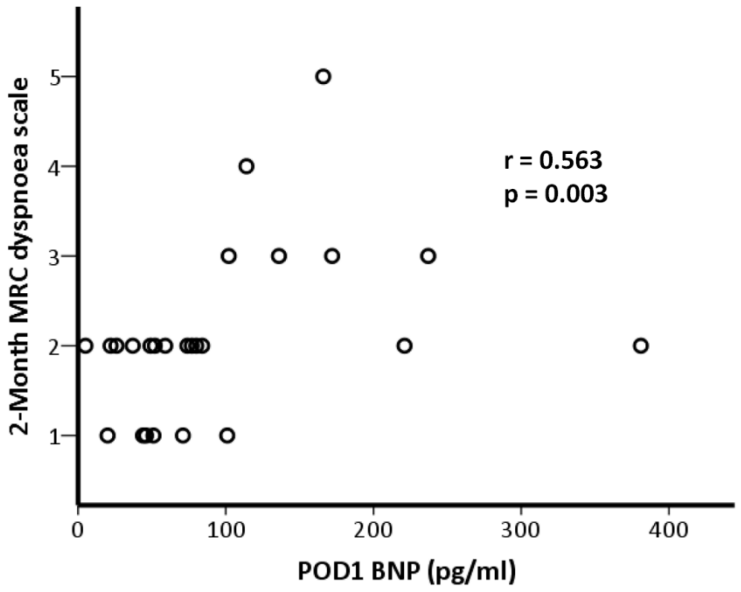


Figure 103. Association between 2-month MRC-DS and BNP_{POD1}
Spearman's correlation coefficient. MRC = Medical Research Council, POD = post-op day, BNP = B-type natriuretic peptide.

The association between the biomarkers and 6 minute walk test (6MWT) performance was explored. As can be seen in Figure 104 and Figure 105 (pg 257), BNP_{preop} and $hsTnT_{preop}$ were both higher in those participants who went on to have a deterioration in their 6MWT performance at 2-months[AA]. For the hsTnT group (Figure 105, pg 257) there *was* a change over time in the group with a deterioration in 6MWT performance (p=0.005, Friedman's test) but *not* in the group with unchanged 6MWT performance (p=0.062, Friedman's test).

[AA] Deterioration defined as a reduction in 6MWT by the minimal clinically important difference of 28m, see section 4.2.5.3, pg 130.

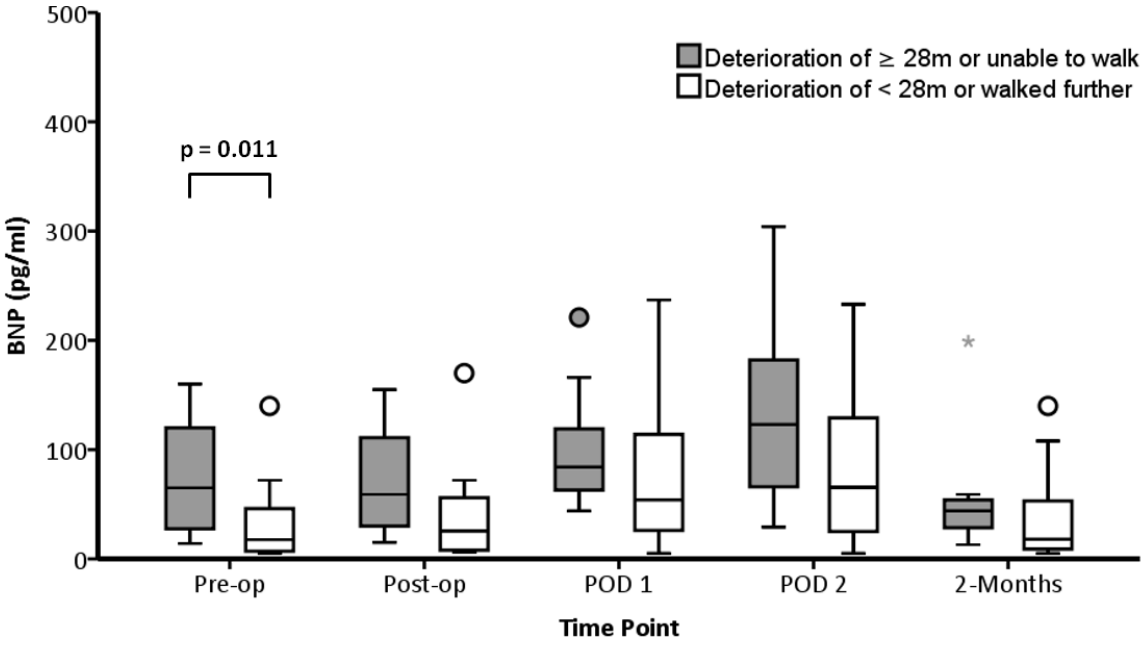


Figure 104. Changes in BNP over time by 6MWT group
Box plots represent median, IQR and range. Grey = deterioration of ≥28m from pre-op or unable to walk, White = deterioration <28m or walked further than pre-op. Changes over time assessed with Friedman's test (Grey p=0.020, White p=0.001). Pairwise comparisons between groups using Mann-Whitney U-Test, significant p-values as illustrated. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in recovery area, POD = post-op day, BNP = B-type natriuretic peptide.

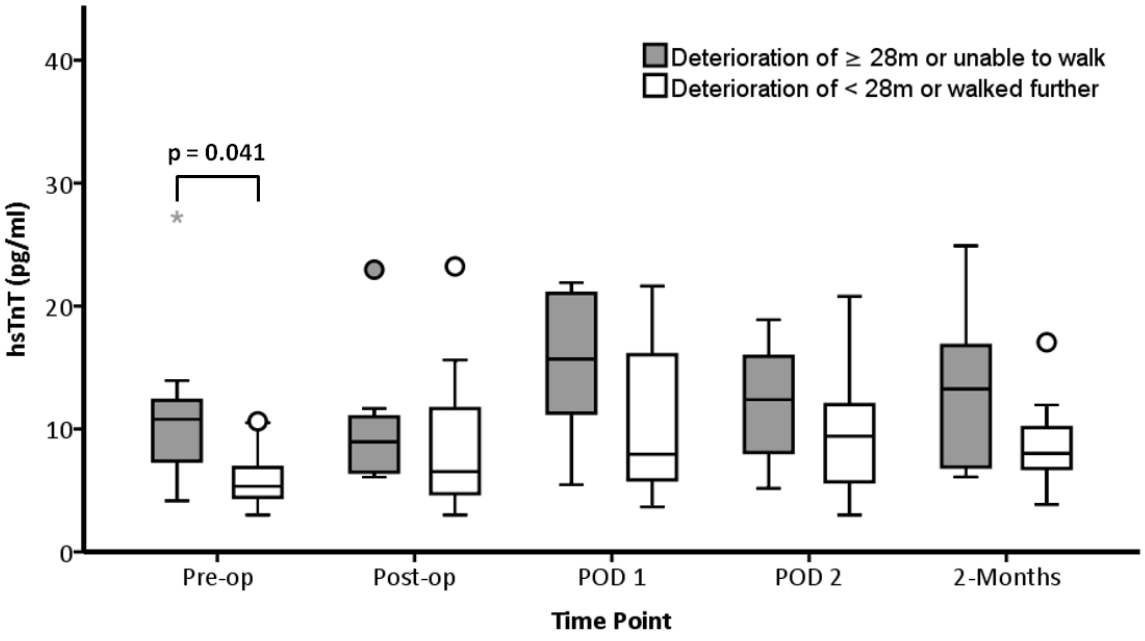


Figure 105. Changes in hsTnT over time by 6MWT group
Box plots represent median, IQR and range. Grey = deterioration of ≥28m from pre-op or unable to walk, White = deterioration <28m or walked further than pre-op. Changes over time assessed with Friedman's test (Grey, p=0.005, White p=0.062). Pairwise comparisons between groups using Mann-Whitney U-Test, significant p-values as illustrated. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in recovery area, POD = post-op day, hsTnT = high sensitivity troponin T.

The ability of BNP_{preop} and $hsTnT_{preop}$ to predict a deterioration in 6MWT performance at 2-months was assessed using AUROCC analysis (Figure 106 and Table 54).

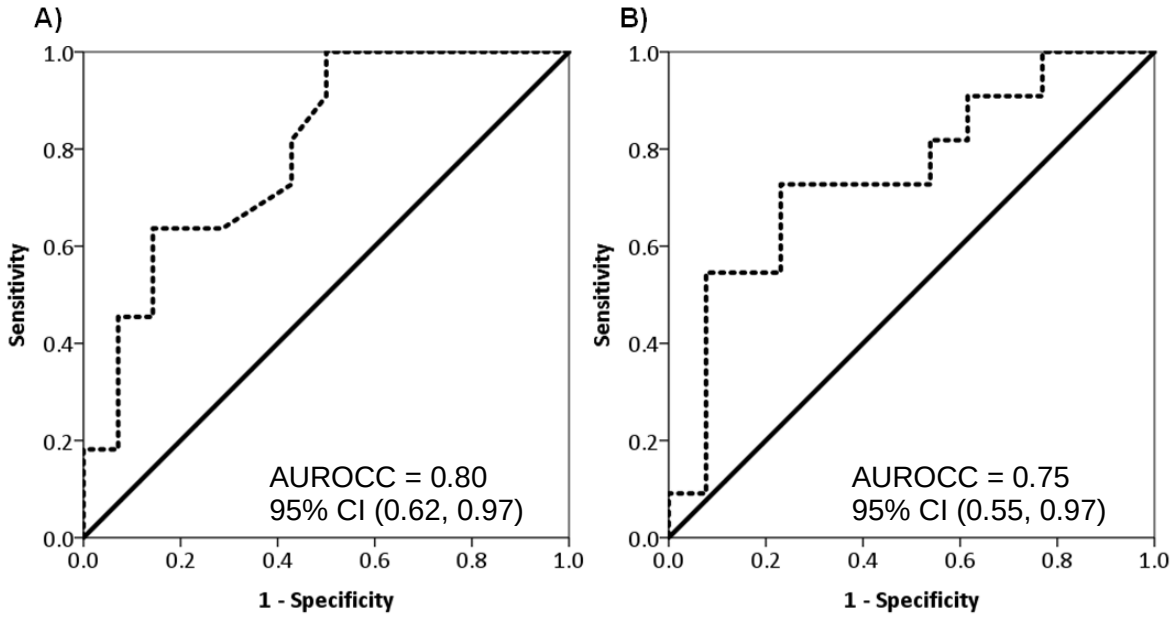


Figure 106. Receiver operating characteristic curve to identify a post-op deterioration in 6MWT using BNP_{preop} and $hsTnT_{preop}$
A) BNPpreop, AUROCC = 0.80 (0.62, 0.97) B) hsTnTpreop, AUROCC = 0.75 (0.55, 0.95). AUROCC = area under the receiver operating characteristic curve, Pre-op = Immediately pre-op, prior to induction of anaesthesia, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T, 6MWT = 6 minute walk test.

	BNP_{preop}	$hsTnT_{preop}$
	6MWT deterioration	
AUROCC (95%CI)	0.80 (0.62, 0.97)	0.75 (0.55, 0.97)
p	0.013	0.040
Cut-off value[BB]	13pg/ml	8.18pg/ml
Sensitivity	100%	72.7%
Specificity	50%	76.9%
PPV	61.1%	72.7%
NPV	100%	76.9%

Table 54. Predictive performance of BNP_{preop} and $hsTnT_{preop}$ for a deterioration in post-op 6MWT performance
AUROCC = area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value, Pre-op = immediately pre-op, prior to induction of anaesthesia, BNP = B-type natriuretic peptide, hsTnT = high sensitivity troponin T.

[BB] Defined by Youden's index (Maximum combination of sensitivity and specificity).

To explore association between the biomarkers and a *deterioration in functional capacity*, a composite endpoint was created. This composite consisted of *either* an increase in MRC dyspnoea scale *and/or* a deterioration in 6MWT performance. Comparison in the biomarkers was made between those participants with a deterioration in functional capacity, or those participants with unchanged functional capacity (Figure 107 and Figure 108, pg 260).

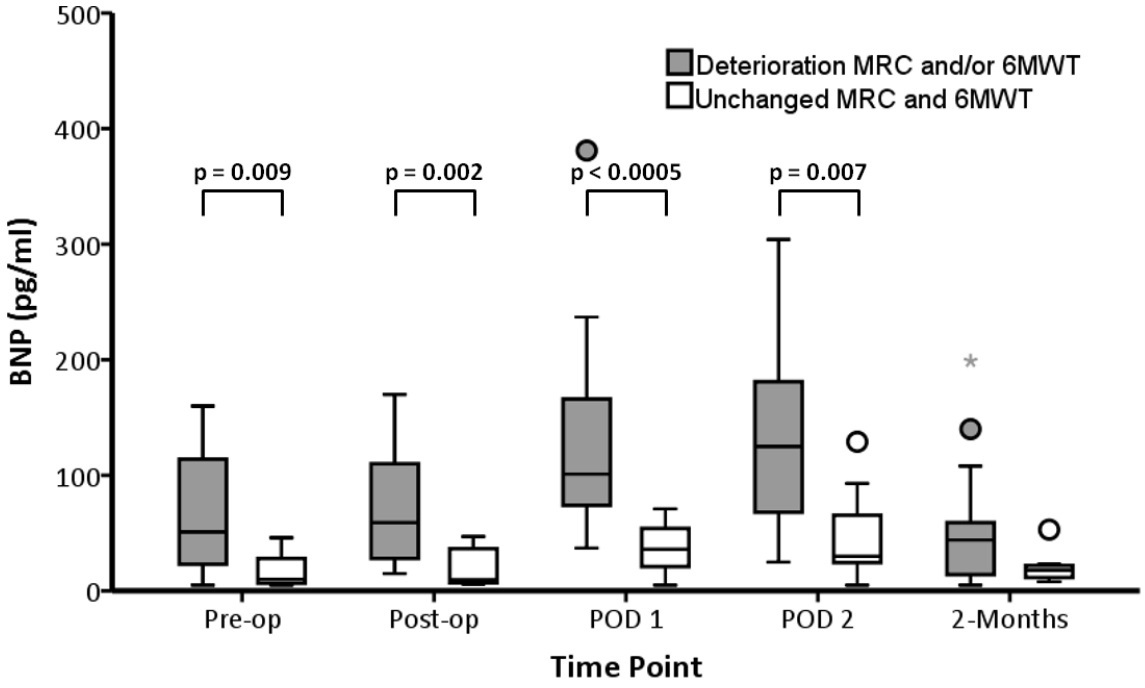


Figure 107. Changes in BNP over time by functional capacity group at 2-months
Box plots represent median, IQR and range. Grey = deterioration MRC and/or 6MWT, White = unchanged MRC and 6MWT. Changes over time assessed with Friedman's test (Grey p<0.0005), (White p=0.339). Pairwise comparisons between groups using Mann-Whitney U-Test, significant p-values as illustrated. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in recovery area, POD = post-op day, BNP = B-type natriuretic peptide, MRC = Medical Research Council dyspnoea scale, 6MWT = 6 Minute walk test.

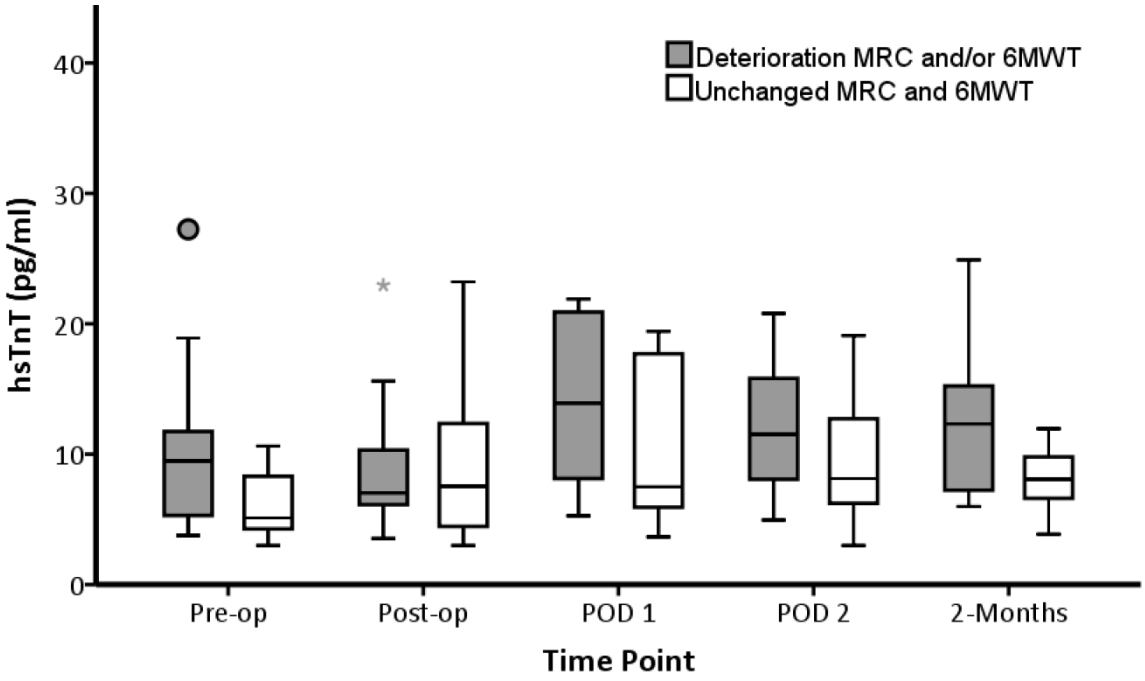


Figure 108. Changes in hsTnT over time by functional capacity group at 2-months
Box plots represent median, IQR and range. Grey = deterioration MRC and/or 6MWT, White = unchanged MRC and 6MWT. Changes over time assessed with Friedman's test (Grey p<0.0005), (White p=0.711). Pairwise comparisons between groups using Mann-Whitney U-Test revealed no significant results. Pre-op = immediately pre-op, prior to induction of anaesthesia, Post-op = immediately post-op, extubated in the recovery area, POD = post-op day, hsTnT = high sensitivity troponin T, MRC = Medical Research Council dyspnoea scale, 6MWT = 6 Minute walk test.

As can be seen in Figure 107 there was an increase in BNP over time for the group who had a deterioration in post-op functional capacity (p<0.0005, Friedman's test) but not in the group who had unchanged functional capacity (p=0.339, Friedman's test). BNP was also higher at every peri-operative time point in those patients who went on to have a deterioration in post-op functional capacity. For the group with a deterioration in post-op functional capacity, hsTnT changed over the duration of the study (p<0.0005, Friedman's test) but not for those with unchanged functional capacity (p=0.711, Friedman's test). There was no difference between the groups for peri-operative hsTnT at each time point (Figure 108).

To assess the predictive ability of BNP_{preop} to determine a change in post-op functional capacity, AUROCC analysis was performed (Figure 109 and Table 55, pg 261).

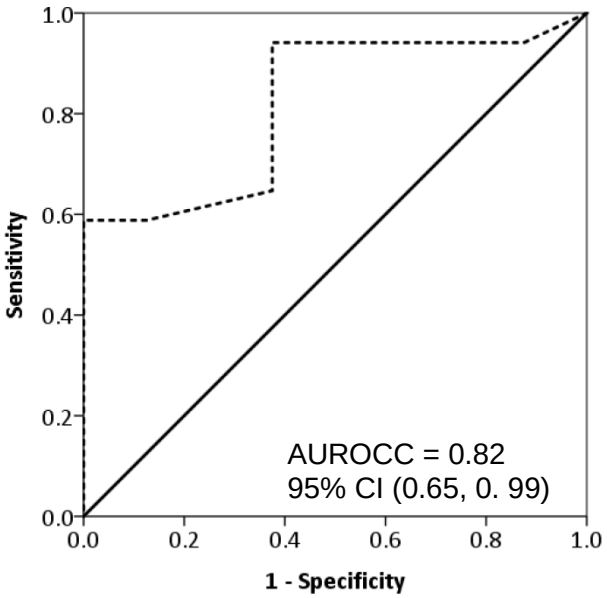


Figure 109. Receiver operating characteristic curve to identify deterioration in functional capacity using BNP_{preop}
AUROCC = 0.82 (0.65, 0.99). AUROCC = area under the receiver operating characteristic curve, Pre-op = immediately pre-op, prior to induction of anaesthesia, POD = post-op day, BNP = B-type natriuretic peptide.

	BNP_{preop}
	Functional capacity deterioration
AUROCC (95%CI)	0.82 (0.65, 0.99)
p	0.011
Cut-off value[CC]	46.5pg/ml
Sensitivity	58.8%
Specificity	100%
PPV	100%
NPV	53.3%

Table 55. Predictive performance of BNP_{preop} for a deterioration in functional capacity
AUROCC = Area under the receiver operating characteristic curve, PPV = positive predictive value, NPV = negative predictive value, Pre-op = immediately pre-op, prior to induction of anaesthesia, BNP = B-type natriuretic peptide.

[CC] Defined by Youden's index (Maximum combination of sensitivity and specificity).

8.6 Discussion

The main findings of this investigation are that BNP and hsTnT are elevated following lung resection and that they are associated with both; post-op RVEF and functional outcomes.

Peri-operative changes in BNP have previously been described in patients undergoing lung resection and the data in this investigation follows a similar pattern[318]. In the largest study published to date in this cohort, Cagini et al. measured BNP in 294 participants[DD]; pre-op, on PODs 1, 2, 4 and 7 (Figure 110)[318]. They demonstrated BNP peaked on POD 1, was falling by POD 2, but was not yet back to base line by POD 7. A smaller study (n=25) showed BNP peaked on POD 3 and was still elevated from base line at POD 7[278]. For the pattern of change in BNP following lung resection, the results of the current investigation confirm these previous findings.

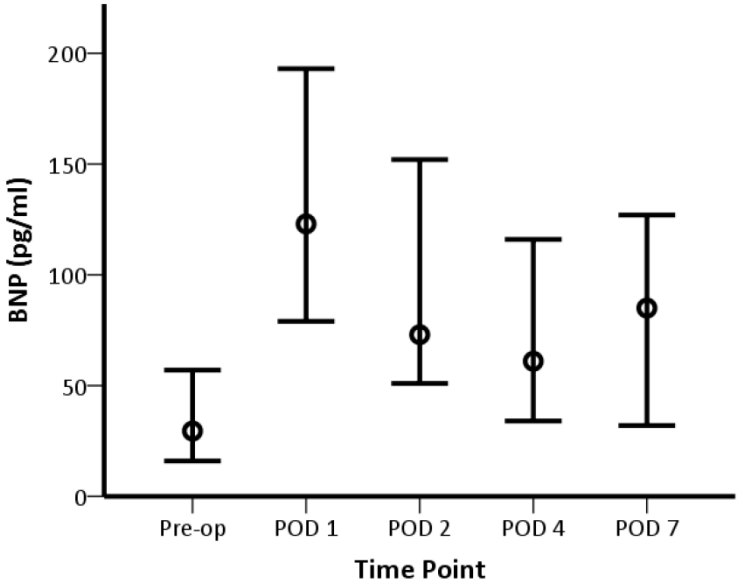


Figure 110. BNP over time, redrawn from Cagini et al.[318].
Plots represent median, IQR. BNP = B-type natriuretic peptide, POD = post-op day

The peri-operative changes in troponin demonstrated in this investigation have not previously been described beyond 24 hours. Muley et al. established troponin (TnI) is elevated in the first 24 hours following both lobectomy and

[DD] 178 lobectomy, 68 wedge/segmentectomy, 24 pneumonectomy, 13 bilobectomy and 11 sleeve lobectomy in a mixed thoracotomy / VATS population.

pneumonectomy, with a larger rise occurring in the pneumonectomy group[319]. In a third group undergoing wedge resection there was no rise. The current study demonstrates hsTnT is elevated following lung resection and peaks on POD 1 with a median (IQR) concentration of 12.3pg/ml (3.7, 21.9) at that time. Despite a small absolute change in values over the duration of the study, there is an increase in the *proportion* with an *abnormal* value. An upper normal range (99th percentile) for hsTnT has been described at 14pg/ml[156] and this study demonstrates two patients (7.7%) have levels above this pre-operatively, three (11.5%) immediately post-op, 11 (42.3%) on POD 1, seven (26.9%) on POD 2 and four (18.2%) at 2-months. None of the patients had any other criteria for diagnosis of myocardial infarction during the study[152].

In other studies of patients undergoing high risk *non-thoracic* surgery, abnormal hsTnT (>14pg/ml) was present in 31% of patients pre-op[280]. Levels were higher in those with advancing age, poorer renal function and higher ASA status. With only two patients having a level >14pg/ml in the current cohort, there is no ability to perform assessment of the factors associated with raised pre-op troponin. It is worth noting that the patient who has been identified as an outlier at a number of times in this thesis as a result of his poor cardiac function on CMR at 2-months (footnote P, pg 180), was one of only two patients to have hsTnT >14pg/ml at *all* peri-operative time points. This patient had a history of ischaemic heart disease (IHD) and the author hypothesises that the elevated hsTnT is a result of *sub-clinical* myocardial ischaemia in the context of his lung resection which ultimately decompensated by 2-month follow-up. The two patients who developed AF peri-operatively had abnormal hsTnT on POD 1, POD 2 and at 2-months, making up 50% of the patients with an abnormal level at long-term follow-up.

Troponin release is common following non-cardiac surgery[281]. In an observational study of 203 patients undergoing major *non-thoracic* surgery, Noordzij et al. demonstrated an elevated hsTnT (>14pg/ml) in 52.2% of patients between POD 1-3[280]. In non cardiac surgery elevated peri-operative troponin has been shown to be associated with increased complications (both cardiac and non-cardiac) and mortality[152, 275, 280, 281, 320]. Devereaux et al. measured troponin (TnT) in 15,133 patients following surgery (282 [1.9%] of which were *"major thoracic"*), and found a positive association between post-op troponin and 30-day mortality[282]. A similar pattern is found in lung resection where peri-operative troponin rise is associated

with early mortality[279]. No patients from the current investigation died within the first year following surgery and the small numbers mean any *attempt* to seek association between mortality and hsTnT levels would be meaningless. On an exploratory basis there was no association between peri-operative hsTnT and duration of hospital or critical care stay. The clinicians involved in patient care were blinded to hsTnT results, meaning hsTnT levels would not have impacted decision making unless ordered independently as a result of clinical suspicion.

In a non cardiac surgery cohort, Gibson et al.[283] demonstrated *pre-op* BNP predicted those with post-op cardiac complications[EE]. BNP has also been shown to predict long-term mortality following non-cardiac surgery[321]. Following lung resection, elevated peri-operative BNP is associated with post-op AF and (both respiratory and cardiovascular) complications[FF] (Figure 111)[276, 318]. In patients undergoing lung resection, elevated *pre-op* BNP has been shown to be associated with increased risk of post-op atrial fibrillation and complications[275-277].

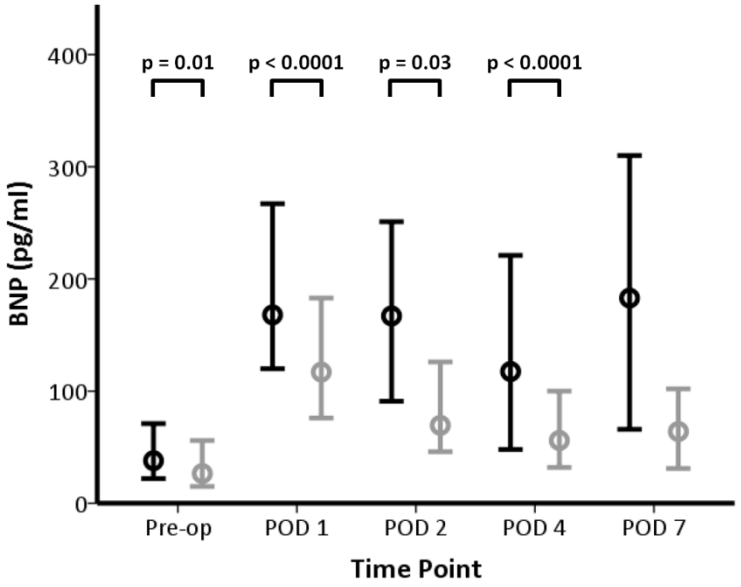


Figure 111. BNP over time in those with (black) and those without (grey) complications, redrawn from Cagini et al.[318].
Plots represent median, IQR. Black bars represent those participants with complications, Grey bars represent those without complications. Comparisons between groups using Mann-Whitney U-Test, significant p-values as illustrated. BNP = B-type natriuretic peptide, POD = post-op day.

[EE] Non-fatal myocardial infarction and cardiac death.

[FF] Pulmonary complications were diagnosed when four or more of the following were present: radiological evidence of consolidation, temp >38°C, SaO_2 <90% on air, abnormal sputum production, sputum culture indicating infection, ↑WCC, abnormal examination, physician's diagnosis or administration of antibiotics. Cardiovascular complications included: arrhythmias (AF, SVT and VT), angina pectoris, MI, CHF, thromboembolic events, DVT, acute renal failure and TIA.

In this investigation, as only two patients developed AF, it is difficult to make any meaningful comparisons with BNP. The study has demonstrated an association between duration of critical care stay and the magnitude of BNP rise on POD 2. There are multiple heterogeneous reasons for prolonged duration of HDU stay but this association suggests a role of cardiac dysfunction. As with hsTnT, the clinicians involved in the peri-operative care of these patients were blinded to BNP results.

BNP and hsTnT are associated with myocardial injury but are not specific to either the LV or RV. In the absence of left sided disease, hsTnT or BNP elevation can indicate RV dysfunction[158]. This investigation demonstrated *consistent* association between BNP and RV function on POD 2. This included BNP and RVEF, ΔBNP and RVEF, BNP and ΔRVEF. There was also association between ΔhsTnT and RVEF on POD 2. The consistent association between biomarkers and RV function on POD 2 is in contrast to that of LV function. There was no change in $LVEF_{CMR}$ over the duration of the study and the study was unable to find association between any of the biomarkers in the post-op period (or magnitude of change in biomarkers) and LVEF. This adds support to the hypothesis that BNP and hsTnT are released in response to changes affecting the right ventricular-pulmonary vascular unit.

There was moderate positive association between $hsTnT_{preop}$, $hsTnT_{postop}$ and LVEF on POD 2. Other than one outlier who had a hsTnT rise during surgery of 18.73 pg/ml, hsTnT pre-op is very similar to hsTnT immediately post-op (Pearson's correlation coefficient, $r=0.867$, $p<0.0005$) meaning it's largely the same patients with a higher troponin level. As can be seen from Figure 112 (pg 266), there was a tendency for those patients with a pre-op diagnosis of ischaemic heart disease (IHD) to have a lower LVEF (57.1% of those with LVEF <55% had a pre-op diagnosis of IHD in contrast to 6.7% of those with LVEF >55%). Similarly those with IHD were more likely to have higher hsTnT pre-op and the author hypothesises the association between hsTnT and LVEF is as a result of this relationship. Those patients with IHD are more likely to have elevated troponin and are more likely to have lower LVEF.

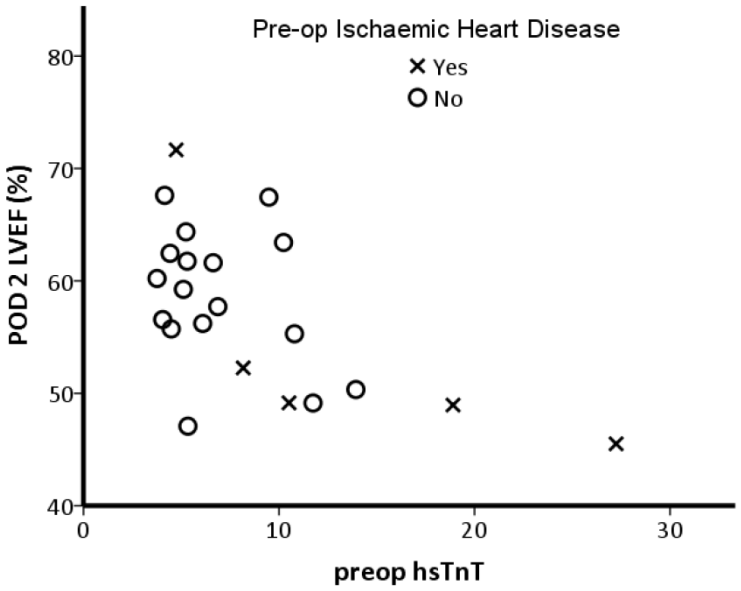


Figure 112. HsTnT and POD 2 LVEF by diagnosis of ischaemic heart disease
Crosses = pre-op diagnosis of IHD, Circles = no pre-op diagnosis of IHD, LVEF = left ventricular ejection fraction, hsTnT = hsTnT = high sensitivity troponin T, IHD = ischaemic heart disease.

Association between biomarkers and RV dysfunction has not been established in a lung resection population but has been demonstrated in other clinical conditions. In acute pulmonary embolism (hypothetically, a clinical situation analogous to lung resection with a sudden increase in RV afterload), BNP[271], NT-pro-BNP[272] and troponin-t[272] have all been shown to be predictive of RV dysfunction[GG] on echocardiography with AUROCC of 0.78, 0.91 and 0.80 respectively. Another study by Kline et al. demonstrated BNP and troponin-I levels at the time of "*submassive*" pulmonary embolism was associated with RV hypokinesis (signified by AUROCCs of 0.71 for both biomarkers)[273]. Kline et al. also demonstrated an additional association between elevated BNP and mortality at 6-months. In a pulmonary hypertension population, NT-pro-BNP has been shown to predict RV systolic dysfunction (defined as an RVEF <42%) with 100% sensitivity and 94 specificity[155].

Following lung resection Tayama et al.[278] demonstrated association between BNP and extent of resection, with levels higher on POD 3 and POD 7 in pneumonectomy patients compared with lobectomy patients. The same authors

[GG] Kruger et al. defined RV dysfunction as one or more of; RV dilation, RV/LV ratio>1, abnormal motion of interventricular septum and pulmonary hypertension. Choi et al. defined RV dysfunction as RV free wall hypokinesia/akinesia or RV/LV ratio>1 and pulmonary hypertension

also demonstrated association between BNP and pulmonary vascular resistance on POD 3 (n=10, r=0.56, p<0.01), caution must be used when interpreting this result though as visual inspection of the scatter plot demonstrates the significant impact of an outlier on the correlation coefficient. This association suggests biomarkers of myocardial dysfunction may be influenced by changes in the right ventricular-pulmonary vascular unit. Consistent with the findings in other populations, this study has demonstrated BNP has the ability to predict RV dysfunction, with the magnitude of change in BNP between pre-op and POD 2 ($BNP_{POD2\text{-}preop}$) predictive of an RVEF≤45% with an AUROCC of 0.78.

As described above, peri-operative BNP has been shown to be associated with post-op complications in the lung resection population. There has been no work examining the association of peri-operative BNP and *longer term functional outcomes* following lung resection. BNP at the time of pulmonary embolism is associated with exercise intolerance (signified by 6MWT <330m) at 6-months[273]. The current study has shown association between peri-operative BNP and; 6MWT performance at 2-months and MRC dyspnoea scale at the same time. To further explore this association, these parameters were combined using 6MWT as an *objective* measure of functional capacity and MRC dyspnoea scale as a *subjective* measure. There was association at all peri-operative time points between BNP and this composite endpoint. Although there was no difference in hsTnT between functional capacity groups, there was evidence of an increase over time in the group with a deterioration in functional capacity, but no change in the group with unchanged functional capacity.

Calculation of predicted post-op (PPO) pulmonary function is currently recommended as a method to predict those at higher risk of dyspnoea following lung resection[15, 27, 228]. As described in chapter 1, pulmonary function is poorly associated with post-op functional outcomes and a post-hoc analysis in this cohort demonstrated no association between pulmonary function and the composite functional capacity outcome (Figure 113, pg 268). BNP is a quantitative biomarker of cardiac function and its association with functional capacity strengthens the hypothesis that *cardiac function* has an impact on post-op functional outcomes.

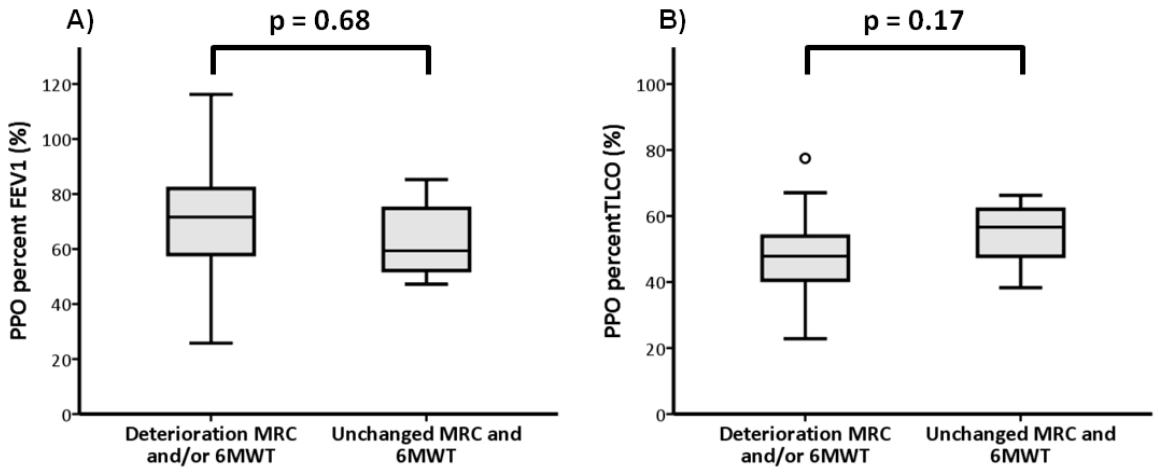


Figure 113. Predicted post-op pulmonary function and functional capacity
Box plots represent median, IQR and range. A) = PPO percentFEV_1, B) = PPO percent TLCO. Comparisons between groups using Mann-Whitney U-Test. MRC = Medical Research Council dyspnoea scale, 6MWT = 6 Minute walk test. PPO = predicted post-op , FEV_1 = forced expiratory volume in 1 second, TLCO = transfer factor for carbon monoxide.

The finding that *pre-op* biomarkers are predictive of post-op functional capacity is interesting. As described above, pre-op BNP has been shown to be associated with post-op complications following thoracic surgery. In non-cardiac surgery BNP has also been shown to be associated with long-term mortality[321]. The finding that it is *also* predictive of functional capacity suggests pre-op biomarkers may be useful in the assessment and pre-op planning of patients undergoing lung resection.

Current guidelines, for assessment of the lung resection candidate, advocate the use of PPO lung function as a method to predict those patients at higher risk of post-op complications and dyspnoea. Inclusion of biomarkers may improve the ability to accurately predict risk (of complications and functional deterioration) and would allow improvement of the consent process. Additionally, the ability to identify an at risk population would give a group in who interventions could be targeted to try and ameliorate post-op complications and dyspnoea. The use of BNP to predict post-op outcome in this population would fit with combined guidelines by the European Society of Cardiology and the European Association of Anaesthesiology (2014) which advocate the use of BNP measurement for obtaining prognostic information for peri-operative and late cardiac events in high-risk non-cardiac surgery patients[322].

8.6.1 Strengths and limitations

Despite being an *a-priori* secondary endpoint, the study had a modest sample size and no power analysis was performed. The results therefore are at high risk of type 1 error meaning that the findings should be considered hypothesis generating and require validation in larger cohorts. There was a small amount of missing data for the biomarker samples. The majority of missing samples were at 2-months and there were no relevant significant comparisons at this time, meaning missing data probably didn't impact reported results.

As discussed above, peak BNP following lung resection has been described as occurring from POD 1 to POD 3. This peak is for all patients considered together however, and in those patients developing complications following lung resection there is a suggestion that BNP levels continue to rise peaking later compared to those patients that don't develop complications[276, 323]. The current study measured BNP until POD 2 and it cannot be certain that BNP wouldn't continue to rise beyond this time. Biomarkers at this later time may have better predictive power for poor RV function. Additionally there was no continuous method of assessing RV function, meaning comparison was made between biomarkers on *POD 1* and RVEF on *POD 2*. Continuous assessment would not have been possible using CMR but a validated bedside alternative may allow association with paired biomarker results.

8.7 Conclusion

BNP and troponin increase following lung resection and return to base line levels by 2-months. Association between the biomarkers and RVEF (and not LVEF) suggests the cardiac biomarkers are released in response to changes in the right heart. BNP shows promise in its ability to predict RV dysfunction following lung resection and this needs to be further explored. Given the difficulties of echocardiographic assessment of RV function in the post-op period, biomarkers (by themselves *or* in combination with imaging) may have clinical utility.

Peri-operative changes in BNP and troponin are associated with a decrease in functional capacity following lung resection. The lack of any association between predicted post-op pulmonary function and changes in functional capacity, supports

the hypothesis that cardiac dysfunction has a role in post-op limitation. BNP and troponin need to be studied further, but may be incorporated in to future risk stratification protocols.

Chapter 9 Mechanisms of Right Ventricular Dysfunction

This chapter describes a number of exploratory analyses performed to examine potential mechanisms of post-op RV dysfunction. Echocardiographic measures of pulmonary heaemodynamics are described followed by changes in a cardiovascular magnetic resonance imaging derived surrogate of right ventriculo-pulmonary artery (RV-PA) coupling.

9.1 Pulmonary artery acceleration time and pulmonary artery systolic pressure

9.1.1 Reproducibility

A summary of the inter-observer and intra-observer variability for trans thoracic echocardiographic measurement of pulmonary artery systolic pressure (PASP) and pulmonary artery acceleration time (PAAT) is provided in Table 56. Both measures showed good agreement with intraclass correlation coefficients for absolute agreement ≥0.78.

Inter-Observer Variability			
	Paired Measures	**CV (%)**	**ICC Agreement (95% CI)**
PASP (mmHg)	n=32	4.78%	0.96 (0.92, 0.98) p<0.0005
PAAT (ms)	n=72	10.97%	0.78 (0.59, 0.87) p<0.0005

Intra-Observer Variability			
	Paired Measures	**CV (%)**	**ICC Agreement (95% CI)**
PASP (mmHg)	n=10	5.27%	0.91 (0.63, 0.98) p<0.0005
PAAT (ms)	n=10	8.78%	0.85 (0.23, 0.97) p<0.0005

Table 56. Inter and intra-observer variability for PASP and PAAT
Coefficient of Variation (CV) calculated as per Equation 8, pg 138, intraclass Correlation coefficient (ICC) calculated as mixed effect, absolute agreement. PASP = pulmonary artery systolic pressure, PAAT = pulmonary artery acceleration time, POD = post-op day.

There was no disparity in availability[HH] of PASP and PAAT between the author and the echocardiography technicians (ET's). There were however changes in availability of PASP and PAAT over the duration of the study. PASP could only be determined in 44.% of patients pre-operatively, 53.8% on POD 2 and 25% at 2-months. PAAT was available in all patients pre-operatively and on 95.8% of patients post-operatively (Table 57).

	Pre-op (n = 27)		POD 2 (n = 26)		2-Months (n = 24)	
	ET	**Author**	**ET**	**Author**	**ET**	**Author**
PASP	12 (44.4%)	12 (44.4%)	14 (53.8%)	14 (53.8%)	6 (25.0%)	6 (25.0%)
PAAT	27 (100%)	26 (96.3%)	23 (88.5%)	23 (88.5%)	24 (100%)	23 (95.8%)

Table 57. Availability of PASP and PAAT at each time point
POD = post-op day, ET = echocardiography technician, PASP = pulmonary artery systolic pressure, PAAT = pulmonary artery acceleration time.

[HH] Availability in this context refers to the ability to obtain a result from the echocardiographic image provided. Availability will have been affected by the quality of the image and by the interpretation by the observer.

9.1.2 Bland Altman Analysis

Bland Altman analysis between the author and ETs of the tricuspid regurgitant pressure gradient and PAAT showed minimal bias with acceptable limits of agreement (Figure 114 and Figure 115).

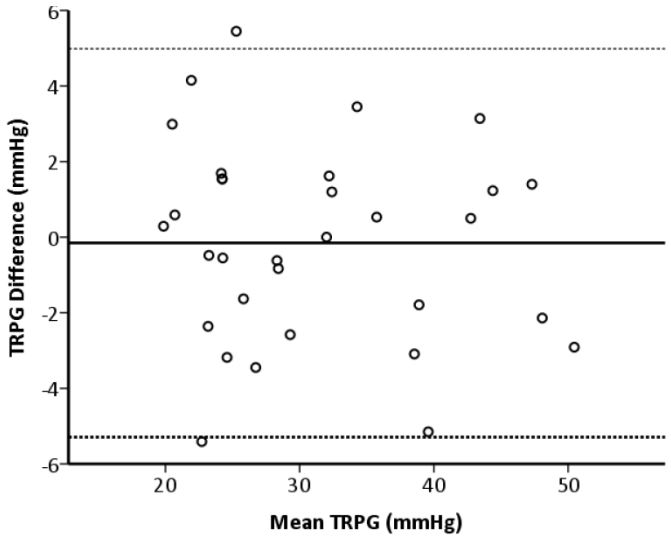


Figure 114. Bland Altman analysis of Tricuspid Regurgitation Pressure Gradient (TRPG*) measurements (n = 32)
Solid line represents mean bias (-0.15mmHg) and dashed lines represent 95% limits of agreement (-5.29, 4.99 mmHg). *TRPG used to calculate pulmonary artery systolic pressure (see Equation 14, pg 154)

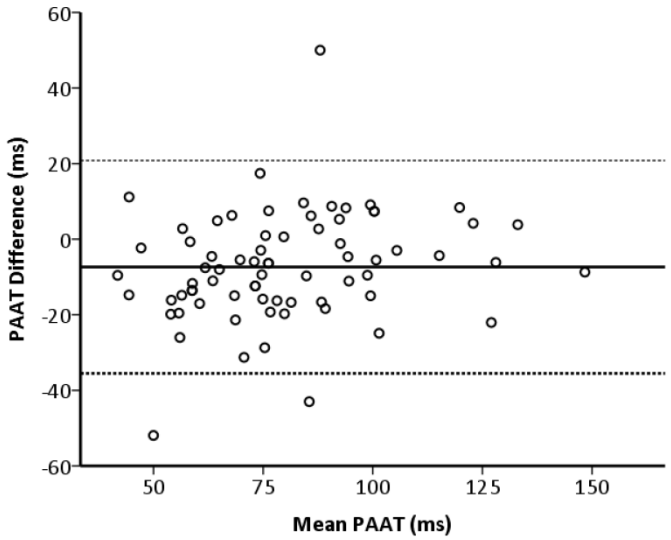


Figure 115. Bland Altman analysis of PAAT measurements (n = 72)
Solid line represents mean bias (-7.35ms) and dashed lines represent 95% limits of agreement (-35.52, 20.82ms). PAAT = pulmonary artery acceleration time.

9.1.3 Change over time

As displayed in Figure 116 and Table 58 there was no significant change in PASP or PAAT over the duration of the study (Friedman's test and one-way repeated measures ANOVA respectively, p>0.074 for both).

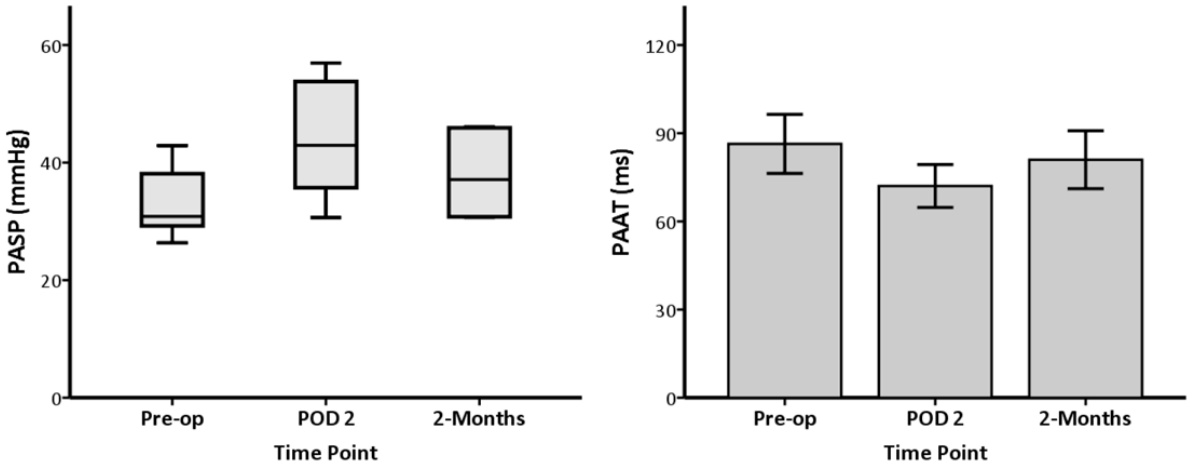


Figure 116. PASP and PAAT over time
Box plots represent median, IQR and range. Bar (error bars) represent mean (95% CI). PAAT = pulmonary artery acceleration time, PASP = pulmonary artery systolic pressure, POD = post-op day.

	Pre-op	POD 2	2-Months	p-value
PASP (mmHg)	n=12	n=10	n=5	0.074†
	30.8 (29.2, 39.8)	42.9 (34.9, 54.0)	37.1 (30.8, 46.0)	
PAAT (ms)	n=26	n=23	n=23	0.350*
	86.4 (24.9)	72.0 (16.9)	81.0 (22.8)	

Table 58. PASP and PAAT over time
Values are mean (SD) or Median (IQR). * = one-way repeated measures ANOVA. † = Friedman's test. PAAT = pulmonary artery acceleration time, PASP = pulmonary artery systolic pressure, POD = post-op day.

9.1.4 Comparison of pulmonary artery systolic pressure and pulmonary artery acceleration time with right ventricular ejection fraction

Pooled analysis revealed weak positive association between $RVEF_{CMR}$ and PAAT (Figure 117 and Table 59, pg 275). The presence of an outlier appeared to influence this association. This outlier has previously been described (footnote P,

pg 180). Sensitivity analysis with the outlier excluded revealed a stronger positive association (r=0.410, p=0.001). There was no association between PASP and $RVEF_{CMR}$ (Figure 117 and Table 59).

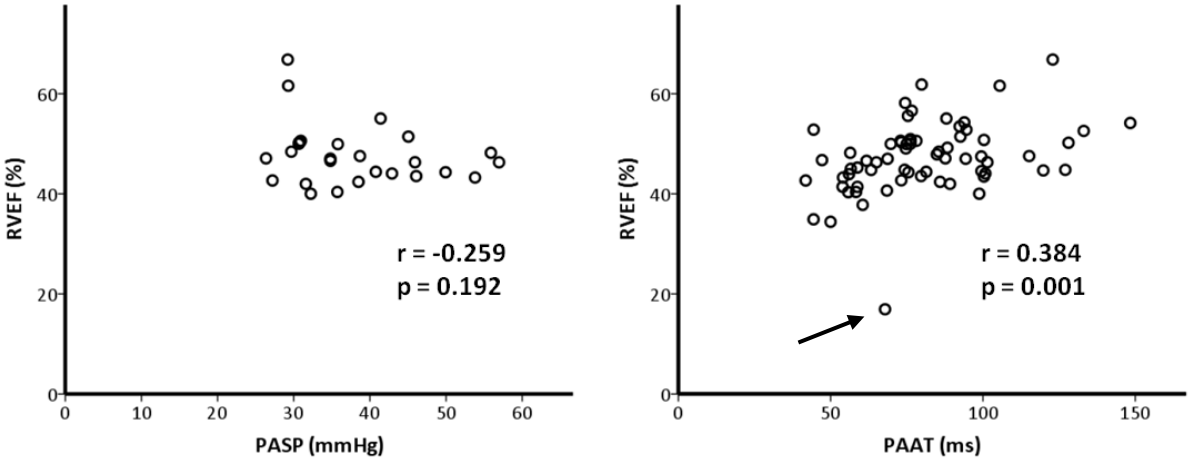


Figure 117. Relationship between PASP and PAAT with $RVEF_{CMR}$
p-value for pooled association (Pearson's) as illustrated. PAAT = pulmonary artery acceleration time, PASP = pulmonary artery systolic pressure, RVEF = right ventricular ejection fraction. Black arrow indicates outlier described in section 9.1.4.

Within subject (ANCOVA) analysis was performed and this strengthened the positive association between $RVEF_{CMR}$ and PAAT (Table 59). ANCOVA analysis confirmed no association between PASP and $RVEF_{CMR}$.

Pooled analysis (Pearson's)			
		PASP	**PAAT**
$RVEF_{CMR}$	r	-0.259	0.384
	p	0.192	0.001

Within-subject analysis (ANCOVA)			
		PASP	**PAAT**
$RVEF_{CMR}$	r	0.473	0.468
	p	0.198	0.002

Table 59. Association between PASP, PAAT and $RVEF_{CMR}$
PAAT = pulmonary artery acceleration time, PASP = pulmonary artery systolic pressure, RVEF = right ventricular ejection fraction. ANCOVA = analysis of covariance.

9.2 Right ventricular stroke volume / end systolic volume

The ratio of RV stroke volume (RVSV) to RV end systolic volume (RVESV) has been described as a volumetric surrogate of RV-PA coupling. Inter and intra-observer variability data for RVSV and RVESV is provided in chapter 5. There was a significant change in the median (IQR) RV SV/ESV ratio over time from 1.0 (0.9, 1,.2) pre-op to 0.8 (0.7, 1.0) on POD 2 and 0.8 (0.1, 1.0) at 2-months (Figure 118, p=0.011, Friedman's test).

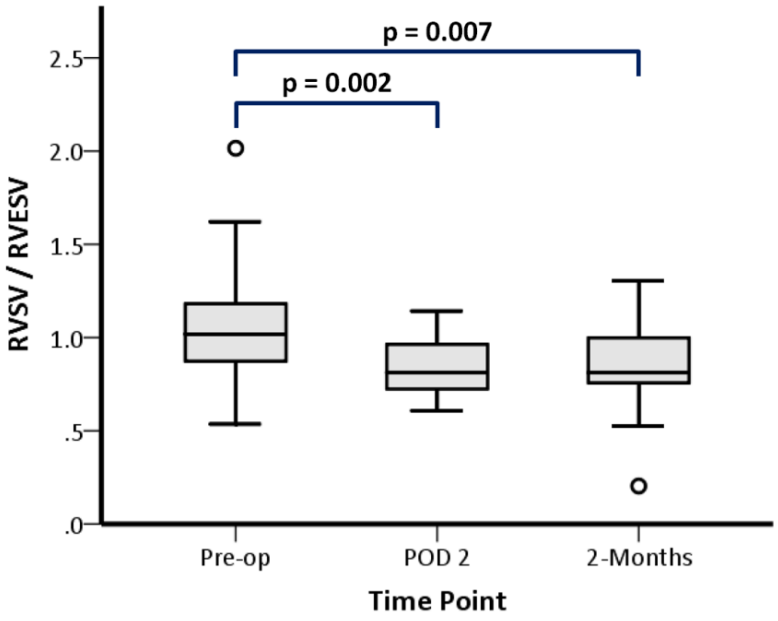


Figure 118. Change in RVSV / RVESV over time
Box plots represent median, IQR and range. Pairwise comparisons with Wilcoxon rank sum test. RVSV = RV stroke volume, RVESV = RV end systolic volume.

9.3 Discussion

This investigation explored potential mechanisms of RV dysfunction following lung resection. The main finding is that increased afterload (lower PAAT) is associated with poor RV function (lower RVEF). There is also suggestion of a deterioration in RV-PA coupling with the ratio of RV SV/ESV decreasing on POD 2 and remaining depressed at 2-months.

Although widely hypothesised, increased afterload following lung resection has not been consistently demonstrated[170, 174, 176]. Previous studies have utilised PVR as a measure of afterload and have been unable to demonstrate sustained changes (see section 2.4, pg 104). As described in chapter 2, whilst commonly used in clinical practice, PVR measures opposition to mean flow and ignores the pulsatile component. Up to half of the hydraulic power in the main pulmonary artery is contained in the *pulsatile* components of flow; comprising resistance, capacitance, inertia and pulse wave reflection. The true opposition to pulsatile flow, the RV impedance, is a composite of both s*tatic and pulsatile* components.

> *Acceleration time is an indicator of constraint to ejection; shortened times have been associated with increased pulmonary vascular resistance and pressure.*
>
> Tousignant et al. (2015)[324]

PAAT is an *index* of afterload that does not assume constant flow in the pulmonary artery (as PVR does) and can provide insight into the pulsatile nature of pulmonary afterload. Despite an apparent trend towards reduced PAAT on POD 2, there was no significant change in PAAT in the post-op period (p=0.350, Table 58 and Figure 116, pg 274). Reduced PAAT has been associated with abnormal wave reflections (increased pulsatile afterload) in pulmonary hypertension. In a swine model, acceleration time was associated (r=-0.65) with increasing RV impedance (from banding of the pulmonary artery)[II][325]. PAAT is also associated with pulmonary artery pressures and pulmonary vascular resistance in pulmonary hypertension[70, 139, 140].

[II] PAAT was assessed in 15 pigs (7 open pericardium, 8 closed pericardium). RV impedance was not specifically measured and PA banding was used as a method of *increased impedance*. Association was made between PAAT and *resistance* over the banding.

The relationship between PAAT and $RVEF_{CMR}$ in this cohort demonstrates association between higher afterload and poorer RV function. On an exploratory basis the association between *change* in RVEF by POD 2 ($\Delta RVEF_{POD\text{-}preop}$) and change in PAAT by the same time ($\Delta PAAT_{POD2\text{-}preop}$) was assessed and this demonstrated a strong positive association (Figure 119). This suggests that change in afterload (as measured by PAAT) is associated with deterioration in RV function following lung resection.

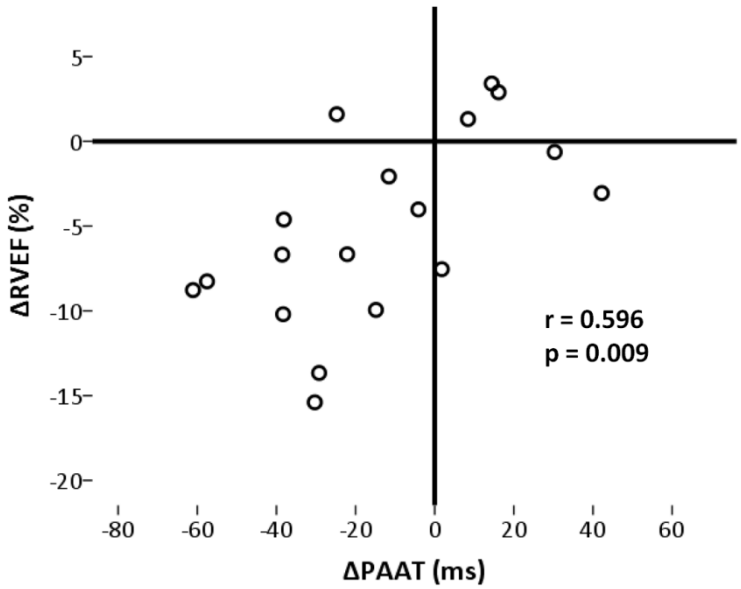


Figure 119. Changes in PAAT against corresponding changes in $RVEF_{CMR}$ by POD 2
Pearson's correlation coefficient. RVEF = Right ventricular ejection fraction, PAAT = Pulmonary artery acceleration time.

Although there was no significant change in PASP, there was an apparent trend towards increased PASP on POD 2 (compared to pre-op, p=0.09, Wilcoxon Signed Rank test, Figure 116, pg 274). There was also an increase in the *proportion* of patients who had tricuspid regurgitant jets (TRJ's) visible on POD 2. This may suggest that PASP is increasing in some participants (meaning they now have visible TRJ's).

It was not possible to determine PASP in a large proportion of patients in this study, with TRJ's measurable in approximately half of patients pre- and post-operatively and a quarter of patients at 2-months. There was no discrepancy between the author and the echocardiography technicians with regards to result availability from provided images. Difficulties in obtaining adequate tricuspid

regurgitant jets have previously been described following lung resection. Amar et al. described a deterioration in the number of patients with available TRJ's following lung resection, though they had much better availability than the current study[198]. In their cohort RVSP availability was 88% pre-operatively, 74% on POD 1 and 82% at POD 2-6. Backlund et al.[176] observed TRJ's in 33.3% pre-operatively and only 16.7% on POD 1. Six months following lobectomy, Foroulis et al.[201] obtained reliable TRJ's in 58.8% of participants.

On reviewing the images in this study where TRJ's were not available, there were some patients with evidence of *trace* tricuspid regurgitation. Guidelines on echocardiographic assessment of the right heart by Rudski et al. only recommend reporting of values in those with *"reliable"* regurgitant jets[128]. Qualitative review indicated that those patients with trace TRJ tended to have lower velocities (<2m/sec, <16mmHg). As the TRJ's had been obtained (although analysed at a later date) at the time of echocardiographic imaging, it is not possible to know from the current investigation if further interrogation would have provided more (or better) images for analysis. The non-invasive assessment of PASP following lung resection is therefore not reliable.

Pulmonary artery pressure is an often used parameter of RV function and provides some information on RV afterload. In an oscillatory system (one without constant flow), the pressure generated is equal to the product of impedance (opposition to flow) and flow itself (Equation 15)[324].

$$P = Z \; x \; Q$$

Equation 15. Relationship of pulmonary artery pressure, impedance and flow
P = pulmonary artery pressure, Z = pulmonary artery impedance, Q = pulmonary artery flow

As can be seen from the above equation, PA pressure is dependent on both; the *opposition* to pulmonary artery flow (pulmonary artery impedance or afterload) and pulmonary artery flow itself (cardiac output). As afterload increases, if cardiac output remains constant, pressure will increase. If cardiac output were to drop in response to higher afterload however, there would be a drop in PA pressure. This can be observed clinically the later stages of pulmonary hypertension, when PA pressures start to fall as the RV has maximally compensated and cannot increase

cardiac output in response to increasing afterload. This is illustrated in Figure 120[160].

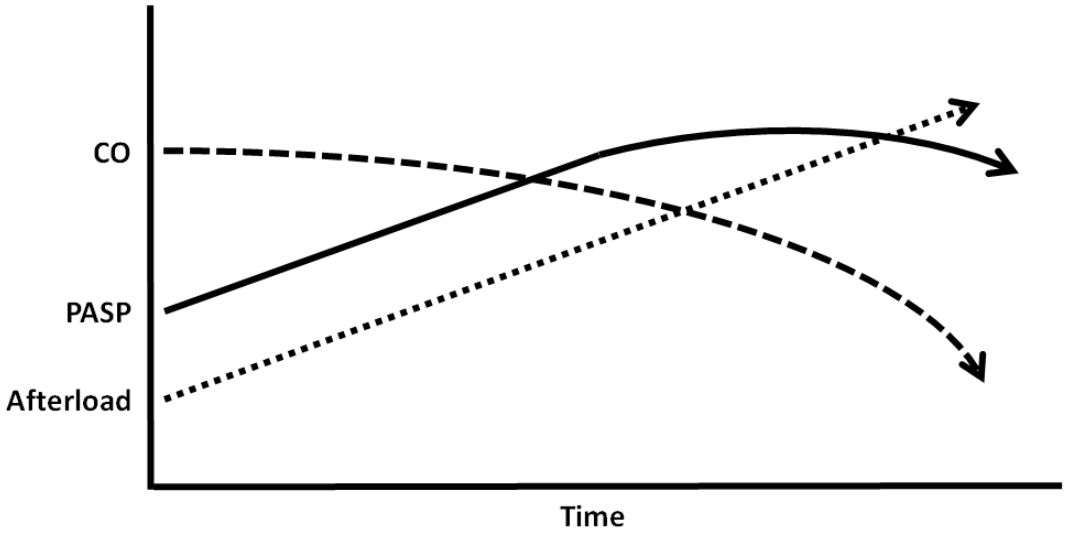


Figure 120. Relationship of CO, PASP and afterload in progressive pulmonary vascular disease
Adapted from Haddad et al.[160] CO = cardiac output, PASP = pulmonary artery systolic pressure.

Figure 120 shows that PASP can be influenced by both the afterload experienced by the RV and by RV function itself. When interpreting PA pressures, it is important that RV function is taken in to account. As described in chapter 1, effective RV function relies on haemodynamically efficient interaction with the pulmonary circulation[81]. The ideal assessment of RV and pulmonary vasculature would incorporate both afterload and RV function along with their matching.

The changes in RVEF observed in chapter 5 may result from alterations in the loading conditions, contractility or a combination. Although RVEF is the most commonly used index of function, it is described as highly load dependent and doesn't solely reflect RV contractility[46]. As described in Section 1.2.3.4.2, pg 34, maximal ventricular elastance (E_{max}) is a load-independent parameter for assessing RV contractility. Arterial elastance (E_a) is an index of afterload faced by the ventricle. The ratio of these two elastances (E_{max}/E_a) reflects RV-PA coupling (coupling) and is a measure of matching between the ventricle and pulmonary circulation (Section 1.2.3.7, pg 38).

The reference method for determining coupling involves simultaneous measurement of pressure and volumes. Given common terms within the

calculation of E_{max}/E_a, an estimation of coupling can be made from volume measurements using CMR (Equation 16):

E_{es} is the elastance at end systole. It is typically calculated as described below, where ESP = end systolic pressure, ESV = end systolic volume and V_0 = the theoretical volume of an unstressed or unloaded ventricle:

$$E_{es} = ESP/(ESV - V_0)$$

A common assumption is that V_0 is negligible and can be excluded from calculations:

$$E_{es} = ESP/(ESV)$$

Ea can be represented by the slope of the arterial ESP versus stroke volume (SV) relationship:

$$Ea = ESP/SV$$

Coupling is the ratio of E_{es}/E_a

$$\frac{E_{es}}{E_a} = \frac{(ESP/ESV)}{(ESP/SV)}$$

Cancelling out ESP:

$$\frac{E_{es}}{E_a} = \frac{SV}{ESV}$$

Equation 16. Derivation of volume method for assessment of coupling from Sanz et al.[83].
E_{es} = end systolic elastance, ESP = end systolic pressure, ESV = end systolic volume, V_0 = theoretical volume of unloaded ventricle, SV = stroke volume.

This surrogate approximation has a number of assumptions, firstly it assumes ventricular volume at time zero is negligible and secondly it calculates end-systolic elastance and not *maximal elastance* which is a better measure of RV contractility[326-328]. This measurement contains the same information as required to calculate RVEF and they have a non-linear relationship (Figure 121 [pg 282])

meaning there is uncertainty about the additional information that it may provide, but there is a suggestion it provides information on RVEF in a "*less preload dependent manner*" [326].

The SV/ESV estimation of coupling has been shown to be predictive of outcome in patients with pulmonary hypertension[329] including a group where RVEF was shown *not* to be predictive (but SV/ESV was)[330]. SV/ESV has been compared to a combined pulmonary artery catheter and CMR determined measure of coupling with good association ($r=0.93$, $p<0.001$)[83]. As V_0 is assumed to be zero, E_{es} is underestimated, meaning the SV/ESV ratio would be expected to underestimate invasively determined E_{es}/E_a[326].

The non-linear relationship observed in Figure 121 may be responsible for why SV/ESV *may* be a better predictor than RVEF. The range of RVEF is 0.17 to 0.67[JJ] and the range of SV/ESV is 0.2 to 2.2. This results in over a 3 times wider range with SV/ESV for the same patients, which may improve the predictive ability of the constituent parameters[328].

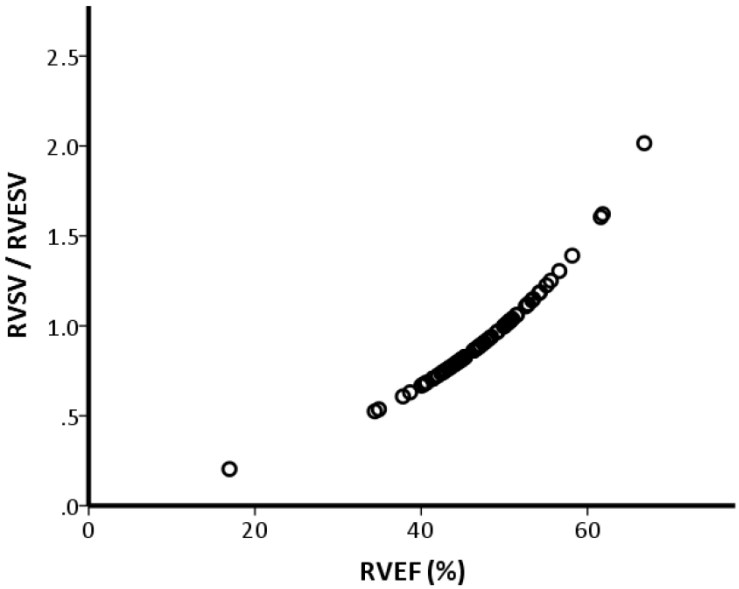


Figure 121. Relationship of RVSV/RVESV and RVEF
RVSV= RV stroke volume, RVESV = RV end systolic volume, RVEF = right ventricular ejection fraction.

[JJ] RVEF in this context is reported as an actual *fraction*. e.g. RVEF of 55% = 0.55

Coupling values in awake humans (control patients without pulmonary hypertension) using SV/ESV are reported from 1.5-2.0[83, 113, 331] with values in patients with 'early pulmonary hypertension' reported as 1.1[113]. The patients in the current investigation show a ratio of 1.0 which falls following surgery. The majority of the patients in this study had underlying health conditions e.g. smoking history, older age, pulmonary malignancy etc (Table 17, pg 164). As these conditions can impact on both ventricular function and pulmonary afterload, they may partly explain the lower baseline value. A study by Wink et al.[85] using the conductance catheter intra-operatively in patients undergoing lung resection demonstrated a similar percentage deterioration in coupling at time of PA clamping, as seen with the change in SV/ESV in the current study (a more complete description of the Wink et al. study is provided in section 2.3.4, pg 102). The current investigation has shown this decrease is still present on POD 2 and more interestingly that it persists at 2-months.

The change in SV/ESV *suggests* a deterioration in RV-PA coupling. This may be as a result of increased afterload (increased E_a), a deterioration in contractility (E_{es}) or a combination.

9.3.1 Strengths and limitations

The dual analysis of anonymised images by blinded observers is a strength of this investigation. Additionally, the availability of PAAT in the majority of patients (93.5%) means this may provide a reliable method for assessing RV afterload in this patient population.

The lack of availability of tricuspid regurgitant jets mean reliable assessment of PASP was not possible. This difficulty has been previously reported in similar cohorts.

Full RV assessment, including loading conditions, requires the use of the conductance catheter. Although this gold standard technique offers high fidelity data and is able to assess rapid changes in RV function, non- invasive modalities are favoured in clinical practice[76]. The SV/ESV volumetric approximation of RV-PA coupling has been used in pulmonary hypertension, but has not yet been compared to a reference method such as the conductance catheter.

9.4 Conclusion

This study is the first to describe a convincing association between afterload and RV function in patients undergoing lung resection. It also demonstrates association between an *increase* in afterload (as measured by PAAT) following lung resection and *deterioration* in RV function. These results provide some confirmation for the underlying hypothesis that increased RV afterload results in RV dysfunction following lung resection.

The change in SV/ESV suggests a deterioration in coupling that is still present 2-months following surgery. Although the changes in PAAT suggest an association of increased afterload with RV function, it is not clear from the current results if there are also changes in RV contractility.

Future work fully analysing contractility and the RV input impedance (along with its components) is required to fully explore the changes in afterload and RV function following lung resection.

Chapter 10 Major Findings, Conclusions and Future Directions

This thesis initially provides a review of RV physiology and its assessment. It then presents a comprehensive assessment of the RV response to lung resection. A summary of each investigations' major findings is presented here.

10.1 Major findings

10.1.1 Chapter 2

The literature review describes the studies to date examining the RV response to lung resection. Although there is concern about the methodology used (based on the validity of the volumetric pulmonary artery catheter), there appears to be a deterioration in RV function, that is associated with post-op morbidity. Although widely hypothesised, an elevation in afterload (most commonly measured as pulmonary vascular resistance) has not been consistently demonstrated. There are consistent changes in RV haemodynamics on exercise.

10.1.2 Chapter 3

The results of this investigation demonstrate an unplanned intensive care unit admission rate of 2.6% following lung resection. It also shows an incidence of RV dysfunction in this cohort of at least 25% and that RV dysfunction is associated with high mortality.

10.1.3 Chapter 4

Chapter 4 describes the methodology for future studies (Chapters 5-9) and provides generic outcome results. Lung resection is associated with decreased functional capacity, increased dyspnoea and poorer quality of life.

10.1.4 Chapter 5

Using an established reference method, this investigation demonstrated that RV function (CMR determined RV ejection fraction - $RVEF_{CMR}$) deteriorates immediately following lung resection and that it continues to be impaired long in to

the recovery period. This occurs despite no change in LV function during the same time period.

10.1.5 Chapter 6

Fractional area change (FAC), Tricuspid Annular Plane Systolic Excursion (TAPSE) and S'Wave velocity at the tricuspid annulus (S'Wave) are established echocardiographic methods for assessment of RV function. These were compared to $RVEF_{CMR}$ and were found not to be useful for assessment of RV function in this population.

10.1.6 Chapter 7

The novel technique of speckle tracked echo strain was compared to $RVEF_{CMR}$. Although strain does not change over time, RV free wall strain shows promise as an echocardiographic measure of RV function following lung resection.

10.1.7 Chapter 8

The biomarkers of myocardial dysfunction, Troponin (hsTnT) and B-type natriuretic peptide (BNP), increase following lung resection and are both associated with RV dysfunction in the immediate post-op period (but not LV function). This investigation also demonstrates these biomarkers are associated with functional capacity in the post-op period.

10.1.8 Chapter 9

This investigation demonstrates an association between increased afterload (as measured by echo determined pulmonary artery acceleration time [PAAT]) and RV dysfunction following lung resection. It also suggests (using a volumetric surrogate) that RV-PA coupling deteriorates in the immediate post-op period and that this deterioration is still present at 2-months.

10.2 Conclusion

The main finding of this thesis is the confirmation that RV function deteriorates in the immediate post-op period following lung resection. It also demonstrates a novel finding that RV function is impaired 2-months in to the recovery period.

Cardiovascular Magnetic Resonance is a reference method for assessment of RV function, but is not suitable for use in the immediate post-op period. Alternative non-invasive options include echocardiography or biomarkers.

Although technically challenging, echocardiography is the most widely utilised method for assessment of RV function and could potentially be suitable for use in this population. The difficulties with this modality however, are compounded following lung resection surgery, with image quality and availability impacting on interpretation, especially in the immediate post-op period. Conventional echocardiographic methods were found to be inadequate in this population and not suitable for prediction of poor RV function. Speckle tracked strain echocardiography of the RV, has been shown to overcome some of the difficulties associated with these conventional methods in other populations. Although RV global strain (RV-GPLS) was unable to provide information on RV function, RV free wall strain (RV-FWPLS) showed promise. As can be seen from Table 60, pg 288, RV-FWPLS performed better than global strain and the conventional methods in multiple domains.

RV-FWPLS was available in the majority of patients on POD 2 (84.6%). This was comparable to S'Wave, the parameter that was available in most patients at this time point (88.5%). RV-FWPLS performs best on pooled analysis and is the only parameter to even *approach* significance when within subject factors are accounted for (p=0.054). Using an area under the receiver operating characteristic curve of 0.75 or above as providing *"good diagnostic value"*, only RV-FWPLS reaches this level on pooled analysis[332]. RV-FWPLS was the only variable to achieve significance on trend analysis.

The author considers the immediate post-op period as a time when determination of RV dysfunction is perhaps most clinically important. Identification at this time would allow management targeted to specific pathology. In future *intervention* studies, accurate identification of RV dysfunction (or its absence) at this time may be useful as an end-point. There was moderate negative association between RV-FWPLS and $RVEF_{CMR}$ on POD 2, with RV-FWPLS demonstrating good diagnostic value at this time with an AUROCC of 0.86 (Table 60, pg 288).

		Conventional Parameters			Strain	
		FAC	**TAPSE**	**S'Wave**	**RV-GPLS**	**RV-FWPLS**
Pooled imaging availability		61.0%	**93.5%**	**96.1%**	**94.8%**	**94.8%**
Pooled association (Pearson's coefficient)		-	**0.34**	**0.29**	**-0.41**	**-0.48**
Pooled prediction (AUROCC)		-	0.65	-	0.74	**0.76**
Within subject association (ANCOVA)		-	-	-	-	***-0.31****
Trend association		-	-	-	-	**-0.32**
Trend prediction		-	-	-	-	-
Time point association	**Pre-op**	-	-	-	**-0.41**	**-0.53**
	POD 2	-	-	-	**-0.54**	**-0.51**
	2-Months	-	-	-	**-0.52**	**-0.55**
Time point prediction (AUROCC)	**Pre-op**	-	-	-	**0.79**	**0.79**
	POD 2	-	-	-	**0.78**	**0.86**
	2-Months	-	-	-	**0.79**	-

Table 60. Summary of conventional parameters and speckle tracked strain echocardiography in comparison to $RVEF_{CMR}$
Only statistically significant results are displayed. * = p-value approached significance (p=0.054). Results highlighted in **bold** are considered to be at a level considered clinically useful. AUROCC are for prediction of RVEF <45%. RVEF = right ventricular ejection fraction, FAC = fractional area change, TAPSE = tricuspid annular plane systolic excursion, S'Wave = S' Wave velocity at the tricuspid annulus. ANCOVA = analysis of covariance, RV-GPLS = RV global peak longitudinal strain, RV-FWPLS = RV free wall peak longitudinal strain, AUROCC = area under the receiver operating characteristic curve.

In other clinical settings the diagnostic accuracy of imaging parameters can be complemented by the use of biomarkers. In this investigation the magnitude of change in BNP by POD 2 ($\Delta BNP_{POD2\text{-}preop}$) demonstrated good diagnostic value for RV dysfunction at this time with an AUROCC of 0.78. The size of the current study does not allow *robust* multivariate analysis with a combination of imaging and biomarkers. On an *exploratory* basis a binary logistic regression model was created to ascertain the effect of RV-FWPLS on POD 2 and $\Delta BNP_{POD2\text{-}preop}$ on the likelihood of having RV dysfunction on POD 2 (RVEF<45%). The model was statistically significant (p<0.0005) and explained 88.2% (Nagelkerke R^2) of the variance, correctly classifying 94.4% of the cases of RV function. The combined model corresponded to an AUROCC of 0.98 (95% CI 0.91,1.00 and p=0.001).

This is the first investigation to demonstrate a consistent association between RV afterload (pulmonary artery acceleration time [PAAT]) and RV function in a cohort undergoing lung resection. It has also shown association between an *increase* in afterload and a *deterioration* in RV function by POD 2. An increase in the RV SV/ESV ratio suggests a deterioration in RV-PA coupling with an imbalance in RV contractility and afterload.

In summary, RV function deteriorates following lung resection. Surgery is associated with a favourable admission rate to intensive care. Those patients admitted to intensive care have a high incidence of RV dysfunction and this is associated with higher mortality. Conventional echocardiographic methods for assessment of RV function are not suitable in this population but speckle tracked RV free wall strain shows promise. Biomarkers of myocardial dysfunction increase following lung resection and are associated with functional outcomes and RV function, but not LV function. RV dysfunction is associated with an increase in RV afterload, with the suggestion of a deterioration in the coupling of RV contractility and afterload.

10.3 Future directions

Future work building on this thesis needs to further explore the mechanisms of RV dysfunction following lung resection, assess the clinical impact of these changes and assess the RV on exercise. Improved understanding should lead to targeted interventions, trying to reduce post-operative morbidity in this population and ultimately benefiting patients.

10.3.1 Explore mechanisms

Although an association has been demonstrated between increased PAAT and RV dysfunction following lung resection, this only provides *some insight* in to RV afterload. Further exploration of the RV input impedance (comprising pulsatile and static afterload) is required to fully explain the relationship between RV function and afterload following lung resection.

Utilising imaging already performed, indices of afterload can be obtained non-invasively using CMR flow analysis and include; PAAT, pulmonary artery distensibility and wave intensity analysis. Pulmonary artery acceleration time is

associated with increased wave reflections in pulmonary hypertension[333]. Pulmonary artery distensibility is a measure of the compliance of the pulmonary vessels, with reduced levels suggesting increased afterload[334, 335]. Wave intensity analysis combines changes in area and flow through the pulmonary vessels during the cardiac cycle in to *wave intensity*. This wave can be separated into compression waves that drive blood *away from*, or *towards* the heart. With decreased vessel compliance, a forward wave will be partial reflected back towards the heart, causing increased afterload[333]. In preliminary work assessing these parameters, Dr Adam Glass (clinical research fellow in anaesthesia) has demonstrated an increase in pulsatile afterload following lung resection[338]. This increase results from the operative pulmonary artery and there is also association between wave intensity and RV function following lung resection[339].

In pulmonary embolism, a clinical situation analogous to lung resection with an acute occlusion (in contrast to clamping in lung resection) of a pulmonary artery, there is evidence of RV inflammation with neutrophil infiltration of RV myocardium[254]. CMR T1 mapping (section 1.3.2.1, pg 44) is a method of assessing inflammation/fibrosis in the RV myocardium and could provide insight in to the role of inflammation in post-op RV dysfunction[KK].

10.3.2 Further assess the clinical impact

This thesis demonstrates association between biomarkers of RV dysfunction and functional capacity. A larger study would be required to definitively assess the impact of post-op RV dysfunction on functional and quality of life outcomes. Speckle tracked RV free wall strain and BNP (individually or in combination) could be used to identify those with RV dysfunction.

10.3.3 Assess right ventricular function on exercise

Previous work examining RV function in this population has demonstrated inconsistent results. When function is assessed on exercise there are consistent changes in RV and pulmonary vascular parameters (Table 5, pg 82)[169, 171, 172, 174, 177]. Although the changes observed in the current investigation are modest, the

[KK] The author is a co-applicant on this successful 2016 ACTACC Project Grant - 'Right ventricular inflammation after lung resection'. Recruitment commencing April 2018.

author hypothesises that the changes observed at rest would be exacerbated with exercise, limiting functional capacity.

There is growing appreciation of the importance of the right ventricles capacity to respond to exercise, with its ability to accommodate termed *'reserve.'* Ventricular reserve is the *"extent of increase or change in ventricular function that occurs during exercise*[336]*."* D*ecreased* reserve means the ventricle is unable to increase function at times of increased demand and this parameter has prognostic value in pulmonary hypertension[337].

Assessment of the ventricular reserve following lung resection would provide insight in to the ability of the RV to cope during exercise and determine if the modest changes observed in this population are exacerbated on exercise[LL].

[LL] The author is a co-applicant on the successful 2016 Ernest Leach Research Fund - 'Assessment of RV contractile reserve on exercise following lung resection - a pilot study '. Recruitment commenced Dec 2017.

Appendices

Appendix 1 - CALoR Article

Appendix 2 - Case report form 1

Appendix 3 - Case report form 2

Appendix 4 - Functional outcomes and RV function

Right side of heart function after lung resection.
CRF 1 – Baseline demographics

Patient ID number in this study:	**RV** |__|__|

1. Sex: □□male □□female

2. Age: |__|__|__| years

3. Date of birth: |__|__| |__|__| |__|__|__|__| d d m m y y y y

4. Height: |__|__|__| cm

5. Weight: |__|__|.|__| kg

6. Ever smoked?: □□yes □□no

6.2 If yes, □□Current smoker* □□Past-smoker*

6.3 If yes, No. of pack years smoked*: |__|__| years

**See footnote for definitions*

6.4. If current smoker, No. of cigarettes per day: |__|__|

6.5. If past smoker, When stopped: |__|__| |__|__|__|__| [mm/yyyy]

7. Ever drink alcohol?: □□yes □□no

7.1 Currently Drinking?: □□yes □□no

7.2 If yes, Units per week: |__|__|__|

8. Chronic co-morbidity: □□yes □□no

8.2 If yes, *tick all that apply*

□□History of cancer*
□□COPD*
□□Arterial hypertension*
□□Heart disease*
□□Diabetes mellitus*
□□Peripheral vascular disease*
□□Obesity*
□□Alcoholism*

**See footnote for definitions*

9. Pulmonary function test results:

9.1 Oxygen saturation on air: |__|__|__| %

9.2 FEV1: Pre-bronchodilator |__|.|__|__| L |__|__|__| % predicted

9.3 FEV1: Post-bronchodilator (if applicable) □N/A

|__|.|__|__| L |__|__|__| % predicted

9.4 FVC: |__|.|__|__| L |__|__|__| % predicted

9.5 FEV1/FVC: |__|__| %

9.6 DLCO: |__|__|.|__|__| mmol $kPa^{-1}min^{-1}$ |__|__|__| % predicted

10. Baseline laboratory values:

10.1 Hb: |__|__|__| g/L

10.2. Albumin: |__|__|__|__|__| *g/L*

10.3. Creatinine: |__|__|__| µmol/L

10.4 eGFR: |__|__|__| ml/min

10.5 CRP: |__|__|__| *mg/L*

11. Pre-operative neo-adjuvent therapy:

11.1 Pre-operative chemo-therapy? □ □□yes □□no

11.2 Pre-operative radio-therapy? □ □□yes □□no

12. Medication History:

For coding: □

□□Beta blockers
□□Ace inhibitor
□□Angiotensin receptor antagonist
□□Calcium channel antagonist
□□Inhaled bronchodilator
□□Inhaled steroid
□□Oral steroid
□□Antiplatelet
□□Statin

Please record all medications (including those above and those purchased over the counter):

Medication	***Dose***	***Frequency***

Explanatory notes:
6. Smoking History
Past Smoker (stopped > 1 month prior to operation
Current Smoker should be selected if the patient stopped smoking <1 month prior to the surgical procedure.

Pack Years:
One 'Pack Year' is 20 cigarettes smoked/day for one year

$$\frac{\text{No. of cigarettes/day x number of years}}{20} = \text{No. of pack years}$$

Loos tobacco: ounces per week x 2/7 x number of years = pack years

Info taken from: "Pack year" smoking histories: what about patients who use loose tobacco? doi: 10.1136/tc.2004.009977

8.2 Chronic co-morbidity:

[These co-morbidities are being collected to allow calculation of the Thoracoscore (Ref: http://www.sfar.org/scores2/thoracoscore2.php)].

History of cancer	Includes cancers treated many years previously. But does not include non-melanoma skin cancer or premalignant conditions such as cervical dysplasia or Barrett's disease.
COPD	FEV1/FVC ration <0.7 after bronchodilator therapy
Arterial hypertension	Treated, or higher than 140/90 on more than one occasion
Heart disease	Either ischaemic heart disease (documentation of angina, myocardial infarction (MI), CABG, PCI) or congestive cardiac failure (documentation of symptomatic cardiac failure, asymptomatic low ejection fraction does not count), or symptomatic valvular heart disease.
Diabetes mellitus	Presence and/or history of diabetes mellitus, regardless of duration of disease or need for anti-diabetic agents diagnosed prior to surgical intervention.
Peripheral vascular Disease	Claudication either with exertion or rest; carotid occlusion or > 50% stenosis; previous or planned surgery on abdominal aorta, limb arteries or carotids; documented abdominal (below the diaphragm) aortic aneurysm with or without repair; positive non-invasive or invasive testing documented ankle brachial index ≤

	0.9, angiography, ultrasound, MRI or CT imaging of > 50% stenosis in any peripheral artery. .
Obesity	Body mass index ≥ 30.
Alcoholism	Current alcohol intake > 14 units/week for Women and >21 units/week for men. Previous treatment for alcohol dependence.

Right side of heart function after lung resection.
CRF 2 – Self-report of functional status / quality of life

Patient ID number in this study:	**RV |__|__|**

Pre-op ❑ **2 months** ❑ **1 year** ❑

We would like to ask you some questions about how your health / symptoms effect your day to day life. Please read the instructions and tick the appropriate box. Though, some of the scoring systems overlap it is important that you answer each one individually. This should take no longer than 10 minutes.

Thank you for your time!

World Health Organization Performance status:

Please tick the ONE box that best describes you:

Fully active, able to carry on all pre-disease performance without restriction ❑

Restricted in physically strenuous activity but ambulatory (able to walk) and able to carry out work of a light or sedentary nature, e.g., light house work, office work ❑

Ambulatory (able to walk) and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours ❑

Capable of only limited self-care, confined to bed or chair more than 50% of waking hours ❑

Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair ❑

MRC Breathlessness Scale:

Please tick the ONE box that best describes you:

No breathlessness except with strenuous exercise ❑

Breathless when walking up an incline or hurrying on the level ❑

Walks slower than most people on the level, or stops after 15 minutes of walking on the level ❑

Stops after a few minutes of walking on the level ❑

Breathless with minimal activity such as getting dressed, to breathless to leave the house ❑

New York Heart Association classification:

Please tick the ONE box that best describes you:

No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc. ❑

Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. ❑

Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). ❑

Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound. ❑

Quality of Life

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

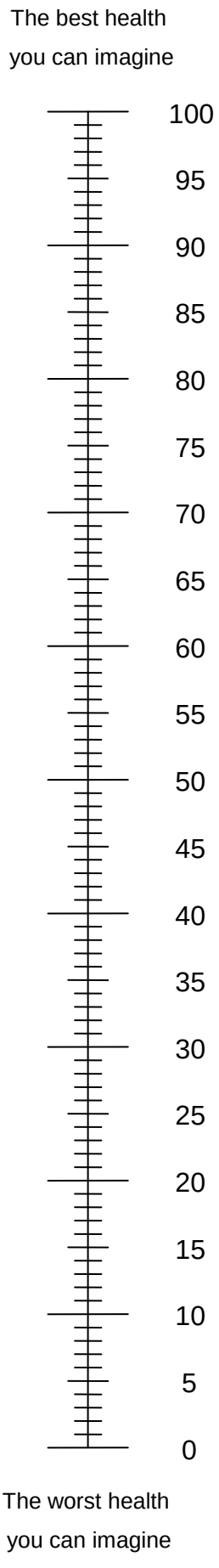
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Pre-op		
		$RVEF_{preop}$
WHO-PS	**r**	-0.108
	p	0.598
WHO-PS any*	**p**	0.586
MRC-DS	**r**	0.157
	p	0.443
MRC-DS any*	**r**	0.597
NYHA class	**r**	0.201
	p	0.326
NYHA any*	**r**	0.367
Global Health Score	**r**	-0.57
	p	0.782
EQ5D		
Mobility	**r**	-0.149
	p	0.468
Self care	**r**	0.093
	p	0.650
Usual activities	**r**	0.153
	p	0.457
Pain / discomfort	**r**	0.049
	p	0.813
Anxiety / depression	**r**	-0.039
	p	0.849
Health Utility Score	**r**	-0.052
	p	0.799

Association between pre-op RV function and pre-op functional and quality of life scores
All comparisons are Spearman's correlation coefficient. RVEF = right ventricular ejection fraction, ΔRVEF = change in right ventricular ejection fraction, WHO-PS = World Health Organisation performance status. MRC-DS = Medical Research Council dyspnoea scale. NYHA = New York Heart Association, EQ5D = EuroQol 5 domain.

		2-Months			
		RVEF		ΔRVEF	
		POD 2	2months	POD2-preop	2months-preop
WHO-PS	**r**	-0.230	-0.162	-0.091	-0.189
	p	0.329	0.448	0.703	0.387
WHO-PS any*	**p**	0.275	0.815	0.311	0.477
MRC-DS	**r**	-0.323	0.055	-0.105	-0.109
	p	0.165	0.799	0.659	0.622
MRC-DS any	**r**	>0.999	0.673	0.437	0.812
NYHA class	**r**	-0.233	-0.145	-0.091	-0.175
	p	0.323	0.498	0.703	0.423
NYHA any	**r**	0.445	0.804	0.349	0.671
Global Health Score	**r**	-0.029	0.351	-0.011	**.438***
	p	0.903	0.093	0.962	**0.037**
EQ5D					
Mobility	**r**	0.005	-0.151	0.359	-0.144
	p	0.983	0.481	0.120	0.511
Self care	**r**	-0.043	-0.339	0.412	-0.225
	p	0.856	0.105	0.071	0.302
Usual activities	**r**	-0.427	-0.230	0.137	-0.164
	p	0.061	0.280	0.563	0.453
Pain / discomfort	**r**	0.086	0.220	0.203	0.295
	p	0.718	0.303	0.391	0.172
Anxiety / depression	**r**	-0.010	-0.078	-0.112	-0.025
	p	0.968	0.718	0.638	0.912
Health Utility Score	**r**	0.078	.452*	-0.316	0.263
	p	0.744	0.027	0.175	0.225

Association between post-op RV function and functional and quality of life scores at 2-months

All comparisons are Spearman's correlation coefficient. RVEF = right ventricular ejection fraction, ΔRVEF = change in right ventricular ejection fraction, WHO-PS = World Health Organisation performance status. MRC-DS = Medical Research Council dyspnoea scale. NYHA = New York Heart Association, EQ5D = EuroQol 5 domain.

		1 Year			
		RVEF		ΔRVEF	
		POD2	2months	POD2-preop	2months-preop
WHO-PS	**r**	-0.109	-0.195	0.326	0.075
	p	0.688	0.438	0.217	0.767
WHO-PS any	**p**	0.562	0.536	0.313	0.930
MRC-DS	**r**	0.043	0.083	-0.001	-0.045
	p	0.869	0.736	0.996	0.856
MRC-DS any	**r**	<0.999	0.831	0.660	0.966
NYHA class	**r**	0.030	0.126	-0.278	-0.145
	p	0.907	0.596	0.265	0.542
NYHA any	**r**	0.645	0.933	0.505	0.445
Global Health Score	**r**	-0.242	-0.033	0.053	0.279
	p	0.333	0.890	0.835	0.233
EQ5D					
Mobility	**r**	0.078	0.056	0.078	-0.086
	p	0.760	0.813	0.760	0.717
Self care	**r**	0.204	0.246	0.273	0.132
	p	0.416	0.296	0.274	0.578
Usual activities	**r**	0.129	-0.123	0.184	-0.174
	p	0.611	0.606	0.465	0.464
Pain / discomfort	**r**	0.417	0.322	0.096	0.113
	p	0.085	0.166	0.705	0.634
Anxiety / depression	**r**	-0.143	0.012	0.117	-0.097
	p	0.571	0.960	0.645	0.684
Health Utility Score	**r**	-0.335	-0.076	-0.233	0.148
	p	0.174	0.751	0.352	0.533

Association of post-op RV function with functional and quality of life scores at 1 year
All comparisons are Spearman's correlation coefficient. RVEF = right ventricular ejection fraction, ΔRVEF = change in right ventricular ejection fraction, WHO-PS = World Health Organisation performance status. MRC-DS = Medical Research Council dyspnoea scale. NYHA = New York Heart Association, EQ5D = EuroQol 5 domain.

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List of Presentations and Publications

Presentations

Oral presentations

Peri-operative BNP changes and functional capacity following lung resection
Glasgow and West of Scotland Society of Anaesthetists, Joint Meeting with Glasgow Anaesthetic Research Club 2014

Speckle tracked strain assessment of right ventricular function following lung resection
British Journal of Anaesthesia Research Forum (York) 2015

Right Ventricular Response to lung resection
Association of Cardiothoracic Anaesthetists and Critical Care Annual Scientific Meeting (Belfast) 2016

Right Ventricular Response to lung resection
European Association of Cardiothoracic Anaesthetists Annual Congress (Basel) 2016

Peri-operative BNP changes and functional capacity following lung resection
European Association of Cardiothoracic Anaesthetists Annual Congress (Basel) 2016

Echocardiographic assessment of right ventricular systolic function following lung resection
Association of Cardiothoracic Anaesthetists and Critical Care Annual Scientific Meeting (Bristol) 2018

Echocardiographic assessment of right ventricular systolic function following lung resection
European Association of Cardiothoracic Anaesthetists Annual Congress (Manchester) 2018

Poster presentations

Critical care after lung resection (CALoR 1)
Association of Anaesthetists Great Britain and Ireland Annual Congress. Poster presentation (Edinburgh) 2015

Utility of speckle tracked strain assessment of the right ventricle following lung resection
Euroecho imaging (Liepzig) 2016

Publications

Abstracts / letters

McCall P, Steven M, Shelley B. Magnetic resonance imaging safety of epilong soft epidural catheters (Letter). Anaesthesia 2014; 69 (10) 1180

McCall P, Corcoran D, Arthur A, Payne J, Kirk A, Macfie A, Kinsella J, Shelley B. The right ventricular response to lung resection. In submission

McCall P, Sonecki P, Kirk A, Kinsella J, Shelley B. Speckle tracked strain assessment of right ventricular function following lung resection (Abstract). British Journal of Anaesthesia. 2016;116(6):E932-E3.

McCall P, Arthur A, Kirk A, Macfie A, Kinsella J, Shelley B. Peri-operative BNP changes and functional capacity following lung resection (Abstract). Journal of Cardiothoracic and Vascular Anesthesia 2016; 30: S26-S7.

McCall P, Corcoran D, Arthur A, Payne J, Kirk A, Macfie A, Kinsella J, Shelley B. The right ventricular response to lung resection (Abstract). Journal of Cardiothoracic and Vascular Anesthesia 2016; 30: S23-S4.

McCall P, Sonecki P, Kinsella J, Shelley B. Utility of speckle tracked strain assessment of the right ventricle following lung resection (Abstract). European Heart Journal. In Press.

Full publications

McCall P, Macfie A, Kinsella J, Shelley B. Critical Care After Lung Resection: CALoR 1, a single-centre pilot study. Anaesthesia 2015; 70 (12): 1382-1389

McCall P, Corcoran D, Arthur A, Payne J, Kirk A, Macfie A, Kinsella J, Shelley B. The right ventricular response to lung resection. In submission.

Teng W, McCall P, Kinsella J, Shelley B. Validation of Transthoracic Echocardiographic Determined Eccentricity Index in a Lung Resection Cohort. In submission.

Young D. McCall P, Arthur A, Kirk A, Macfie A, Kinsella J, Shelley B. Pre-operative BNP predicts deterioration in functional capacity in patients undergoing lung resection. In submission.

McCall P, Soosay A, Sonecki P, Kinsella J, Shelley B. The utility of trans thoracic echocardiographic measures of right ventricular systolic function in a lung resection cohort. In submission.