Title: The Right Ventricular Response to Lung Resection

Authors: Dr Philip J. McCall (MBChB, MD)[1,2], Dr Alex Arthur (MBChB)[1,2], Dr Adam Glass (MB BCh)[1,2], Dr David S. Corcoran (MBChB)[3,4], Mr Alan Kirk (MBChB)[5], Dr Alistair Macfie (MBChB)[2], Dr John Payne (MBChB, MD)[6], Dr Martin Johnson (MBChB, MD)[7], Professor John Kinsella (MBChB, MD)[1], Dr Benjamin G. Shelley (MBChB, MD)[1,2]

Institutions:

[1]Academic unit of Anaesthesia, Pain and Critical Care, University of Glasgow, Glasgow, UK
[2]Department of Anaesthesia, Golden Jubilee National Hospital, Clydebank, UK
[3]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[4]Department of Cardiology, Golden Jubilee National Hospital, Clydebank, UK
[5]Department of Thoracic Surgery, Golden Jubilee National Hospital, Clydebank, UK
[6]National Advanced Heart Failure Service, Golden Jubilee National Hospital, Clydebank, UK
[7]Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Clydebank, UK

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Corresponding Author: Dr Philip McCall
Room 2.73
New Lister Building
Glasgow
G46 6JP
philipmccall@nhs.net

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GLOSSARY OF ABBREVIATIONS

BNP - B-type natriuretic peptide

CMR - Cardiovascular magnetic resonance

CV - Coefficient of variation

Ea - Arterial elastance

Emax - Maximal ventricular elastance

ESV - End systolic volume

hsTnT - High sensitivity Troponin T

LV - Left ventricle

PA - Pulmonary artery

PAAT - Pulmonary artery acceleration time

POD - Post-operative day

PVR - Pulmonary vascular resistance

RV - Right ventricle

RVEF - Right ventricular ejection fraction

SV - Stroke volume

CENTRAL PICTURE LEGEND

Right ventricular function deteriorates following lung resection and remains depressed two months postoperatively.

CENTRAL MESSAGE (200 characters - 186)

Right ventricular ejection fraction is reduced immediately following lung resection. These changes are still present at two months, suggesting peri-operative changes in RV function may have an influence long in to the recovery period.

PERSPECTIVE STATEMENT (405 characters - 371)

There is growing interest in the role of RV dysfunction in cardiorespiratory morbidity following lung resection. Using cardiovascular magnetic resonance, this study demonstrates postoperative RV dysfunction with increased pulsatile afterload, predominantly arising from the operative pulmonary artery. The deterioration in RV function may provide a therapeutic target for future interventions seeking to ameliorate the burden of morbidity in this population.

ABSTRACT

Objectives

Lung cancer is a leading cause of cancer death and in suitable cases the best chance of cure is offered by surgery. Lung resection however is associated with significant post-operative cardiorespiratory morbidity, with dyspnea and reduced functional capacity as dominant features. These changes are poorly associated with deterioration in pulmonary function and a potential role of right ventricular (RV) dysfunction has been hypothesized. Cardiovascular magnetic resonance (CMR) is a reference method for non-invasive assessment of RV function and has not previously been applied to this population.

Methods

We used CMR to assess the RV response to lung resection. CMR with volume and flow analysis was performed on 27 patients pre-operatively, on post-operative day (POD) 2 and at 2-months. Left and right ventricular ejection fraction (L- & RVEF), the ratio of Stroke Volume to End Systolic Volume (SV/ESV), pulmonary artery acceleration time (PAAT) and distensibility (of main and branch pulmonary arteries) were studied.

Results

Mean (Standard Deviation) RVEF deteriorated from 50.5% (6.9) pre-operatively, to 45.6% (4.5) on POD2 and remained depressed at 44.9% (7.7) by 2-months (p=0.003). SV/ESV deteriorated from 1.0 (0.9, 1.2) pre-operatively to 0.8 (0.7, 1.0) on POD2 (p=0.011). On

POD2 there was a decrease in PAAT and operative pulmonary artery distensibility ($p<0.030$ for both). There were no changes in LVEF during the study period ($p=0.621$).

Conclusions

These findings suggest RV dysfunction occurs following lung resection and persists 2-months after surgery. The deterioration in SV/ESV suggests a mismatch between afterload and contractility. There is an increase in indices of pulsatile afterload resulting from the operative pulmonary artery.

CLINICAL TRIALS REGISTRATION

ClinicalTrials.gov (NCT01892800)

INTRODUCTION

Lung resection is associated with high cardio-respiratory complication rates[1, 2] and significant long-term morbidity, with many patients experiencing disabling dyspnea and decreased functional capacity.[3, 4] These changes are poorly associated with lung function,[5, 6] and may be influenced by cardiac limitation.[7, 8] Given their close relationship, complex interaction and potential for disruption during lung resection, previous work has focussed on the right ventricular/pulmonary vascular unit.

Several studies have described a 15-25% *relative* reduction in right ventricular ejection fraction (RVEF) following lung resection;[9-14] patients experiencing a greater decline in RV function are more likely to suffer post-operative complications.[12-14] Lewis et al demonstrated that impaired RV function intra-operatively identified patients in whom late cardio-respiratory symptoms would develop,[11] suggesting peri-operative RV dysfunction has an impact long into the post-operative period.

Assessing RV function is challenging because of the RV's complex geometry, retrosternal position and marked load dependence.[15-17] Previous studies in this population have been hampered by the limitations of the techniques used (mainly volumetric pulmonary artery catheters (vPAC's);[9, 11, 18] in many cases leading to conflicting results. The validity of vPAC's has been challenged, with the observation that their accuracy has never been convincingly demonstrated.[19, 20]

The primary mechanism of RV dysfunction following lung resection is hypothesized to result from increased afterload.[11, 12, 18] Though this seems intuitive, studies measuring pulmonary vascular resistance (PVR), as an index of RV afterload, have been unable to demonstrate sustained changes post-operatively. PVR rises intra-operatively, during one-lung ventilation and on pulmonary artery clamping, but returns to baseline by 24 hours.[10, 18, 21] Whilst PVR is

commonly used in clinical practice, this measure of opposition to *mean* flow (static afterload) ignores the pulsatile component of afterload.[17] 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; as such *true* RV afterload – the RV input impedance, is a composite of both static and pulsatile components.[16, 17]

Given the methodological concerns regarding the techniques used to assess RV function in previous studies and ongoing uncertainty about underlying mechanism, further work was required to understand the RV response to lung resection. Cardiovascular Magnetic Resonance (CMR) is the non-invasive gold standard method for assessing RV structure and function.[15, 16] In addition to accurate quantification of volumes, CMR allows pulmonary artery flow quantification,[15, 22] meaning pulsatile components of afterload can be explored.[23]

Although RVEF is a commonly used index of function, it is highly load dependent and doesn't fully reflect RV contractility.[16] Changes in RVEF can therefore result from alterations in the loading conditions, contractility or a combination. A more comprehensive assessment of RV and pulmonary vascular function can be provided by considering the matching between contractility and afterload. Maximal ventricular elastance (Emax) is a load-independent parameter used to characterize RV contractility. Arterial elastance (Ea) is an index of afterload faced by the ventricle. The ratio of these two elastances (Emax/Ea) reflects right ventricular-pulmonary artery coupling (coupling) and reflects matching between the ventricle and pulmonary circulation. An estimate of coupling can be obtained non-invasively with CMR, using a ratio of volume measurements (SV/ESV). [24]

The aim of this CMR imaging study was to provide a comprehensive understanding of changes in the RV/pulmonary vascular unit following lung resection.[24] Plasma biomarkers of myocardial dysfunction were measured contemporaneously.

METHODS

Subjects

Ethics approval was provided by the West of Scotland Research Ethics Committee (134/WS/0055) and all participants provided written informed consent. Patients attending for elective lung resection by thoracotomy and lobectomy were screened. Subjects who were pregnant, participating in any investigational research which could undermine the scientific basis of the study, had contraindications to CMR imaging or were undergoing; wedge/segmental/sub-lobar lung resection, pneumonectomy, isolated middle lobectomy or thoracoscopic/minimal access lung resection, were excluded. Surgical technique was standardized to a single surgeon performing a postero-lateral muscle sparing thoracotomy with anatomically appropriate lymph node clearance. Anesthetic technique was standardized and included volatile agents for anesthetic maintenance, intra-operative lung protective ventilatory strategies and thoracic epidural blockade.

Measurements

Cardiovascular Magnetic Resonance Imaging

CMR was performed within 24 hours pre-operatively, on post-operative day (POD) 2 and at 2-months (1.5 Tesla, Siemens Avanto, Siemens, Erlangen, Germany). ECG-gated fast imaging steady state free precession cines (TrueFISP, Siemens) were utilized throughout. Methodological details of importance include standardized 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 and propagated sequentially to the cardiac apex providing complete coverage of both ventricles. Analysis of randomized and anonymized images was performed by two

independent reporters using proprietary software (Argus, Siemens, Erlangen, Germany). RV and left ventricular (LV) volumes were determined by manual planimetry of short-axis images according to standard methods.[25] The ratio of RV stroke volume to end-systolic volume (RVSV/RVESV) was derived as an index of right ventriculo-arterial coupling.[24]

Flow imaging was performed with velocity encoded gradient sequencing of the main pulmonary artery (PA) and of both left and right pulmonary arteries. Mapping was set for the main PA perpendicular to the vessel and above the valve level with velocity encoding at 150cm/s. Mapping for the branch PA's was perpendicular to the vessel, proximal to 1st dividing vessel with velocity encoding at 150cm/s. Main and branch pulmonary artery contours were delineated by manual planimetry. Cubic splines with interpolation to 1ms temporal resolution were then fitted to flow and area versus time curves allowing calculation of pulmonary artery acceleration time (PAAT) and distensibility for the main and branch pulmonary arteries.[26] PAAT is the time to peak flow (ms) from the onset of the cardiac cycle, distensibility (%) was calculated as 100*(max-min PA area)/min PA area.

Biomarkers of myocardial function

Blood samples were collected pre-operatively, immediately post-operatively, on the morning of POD's 1 & 2 and at 2-months. B-type natriuretic peptide (BNP) was analysed immediately using the Alere Triage system (Alere, Stockport, UK). High sensitivity Troponin T (hsTnT) was analysed immediately using the Roche-cobas 6000e analyser (Roche, Basel, Switzerland).

Statistical Methods

Power analysis was carried out in consultation with the Robertson centre for biostatistics at the University of Glasgow. Primary outcome was change in RVEF on POD2. Although the

validity of previous work has been questioned, these studies suggested an *absolute* fall in RVEF of 6-9% by POD2[9, 10] and our study was powered to detect a change of at least this magnitude. They also suggest that mean RVEF is 45% and that the largest standard deviation is assumed to be 7%. Power analysis was based on a 2-sided, paired t-test and indicated that 19 patients would have 80% power to detect an absolute reduction in RVEF of 6%, with a significance level of 0.05. Allowing a margin of 30% for study withdrawal, 28 patients were recruited.

Data are presented as mean **(**Standard Deviation, SD) or median (Q1, Q3) as appropriate. Changes over time were assessed using one-way repeated measures ANOVA or Friedman's test with post-hoc pairwise comparisons using paired t-test or Wilcoxon signed rank test. Comparisons between independent groups were performed using the independent t test or Mann-Whitney U test. Association between continuous variables was assessed using Pearson's or Spearman's correlation coefficients. Bonferroni corrected p values are presented throughout.

Statistical analyses were performed using SPSS for Windows, version 22 (IBM Corp, Armonk, NY, USA). A p value <0.05 was considered significant.

RESULTS

Twenty-eight patients were recruited. One patient was excluded due to the unexpected discovery of an embedded piece of ferromagnetic material in their chest wall during pre-operative scanning, meaning no usable images could be obtained. There were no clinical sequelae but as this patient was unable to take any part in the main study, the patient was removed from all further analyses. Patient demographics are displayed in Table 1. Twenty-six patients underwent lobectomy or bilobectomy (incorporating the right middle lobe); one patient required unplanned intra-operative conversion to a pneumonectomy and is included in all analyses. Sensitivity analysis revealed this patient was not an outlier in any analysis (not shown).

CMR was well tolerated, with all patients completing the scan protocol pre-operatively. Due to an administration error, one participant did not have short axis images obtained meaning it was not possible to calculate ventricular volumes in this patient. Twenty-two (81.5%) patients completed the protocol on POD2 and 24 (88.9%) at 2-months. Time to final follow-up was 55.9 (13.1) days. Of the 5 patients unable to be scanned on POD2; three declined, one was unwell with persistent air-leak requiring additional inter-costal catheter drainage with CMR transfer deemed unsafe, and one patient had an epidural catheter in-situ that was not CMR compatible. Of the patients unable to complete the protocol at 2-months; one declined, one was an inpatient at another hospital and the third had a contraindication to CMR as a result of recent cataract surgery. The baseline characteristics of those completing and non completing follow-up are described in supplementary table 1.

CMR ventricular volumetric and flow velocity mapping

Coefficient of variation (SD/mean) for RVEF was 12.9% pre-operatively, 16.8% on POD2 and 15.9% at 2-months. Mean (SD) RVEF fell from 50.5% (6.9) pre-operatively, to 45.6%

(4.5) on POD2 and remained reduced at 44.9% (7.7) at 2-months (p=0.003, Table 2 and Figure 1A). There were no changes in left ventricular (LV) ejection fraction over the study period (p=0.621, Figure 1B). There was a deterioration in the ratio of RV stroke volume to RV end systolic volume (RVSV/RVESV) on POD2 which persisted at 2-months (p=0.011, Table 2 and Figure 1C).

RVESV increased on POD2, returning to baseline levels at 2-months. LV end diastolic volume, end systolic volume and stroke volume were unchanged on POD2. All other left and right ventricular volumes were reduced at 2-months (Table 2).

Main pulmonary artery flow increased from 6.6L/min (1.7) to 8.00L/min (1.6) on POD2, returning to baseline (6.52L/min (1.7)) by 2-months (p=0.004, Table 3 and Figure 2A). This increase in CO resulted from increased heart rate (Table 2). Pre-operatively there was an even distribution of CO between the left and right PA's (48.1% and 51.9%, p=0.055). This distribution was altered post-operatively with 66.3% and 60.9% of the CO travelling through the non-operative vessel on POD2 and at 2-months respectively (p<0.001, Table 3 and Figure 2B).

POD2 PAAT was reduced in all vessels with PAAT shorter in the operative versus non-operative vessel. At 2-months, PAAT remained shorter than pre-operative values in the main PA and operative vessel. At 2-months operative PAAT was again shorter than non-operative PAAT (Table 3 and Figures 3A & B).

Main PA distensibility was unchanged throughout the study. Non-operative PA distensibility increased in comparison to POD2 at 2-months, and was higher than the operative vessel at this time-point (Table 3 and Figure 3C). There were no consistent associations between PAAT, distensibility and RVEF at any time (Supplementary tables 2 and 3).

There is a moderate positive association between the transfer factor for carbon monoxide (TLCO) and the change in RVEF from pre-operative to POD2 ($\Delta RVEF_{POD2\text{-}pre}$, Pearson's r=0.517, p=0.014, supplementary figure 5).. There was no association between any of the *operative* variables described in Table 1 and any the CMR variables (RVEF, PAAT and distensibility). There was a strong negative association between RVEF on POD2 and the duration of critical care unit stay (Spearman's r=-0.653, p=0.001, supplementary figure 6). There was no association between RVEF at any timepoint and duration of hospital stay.

Biomarkers of myocardial function

Coefficients of variation for BNP and hsTnT were 5.9% and <10% respectively. BNP increased over time, peaking on POD2 and returning to baseline by 2-months (Table 4 and Figure 4A). HsTnT showed a small but significant post-operative rise (Table 4 and Figure 4B). There was moderate association between $\Delta RVEF_{POD2\text{-}pre}$ and BNP on POD2 (Pearson's r=-0.490, p=0.021, Figure 4C). There was no association between troponin and RVEF on POD2 (Figure 4D). Associations at other time points are detailed in supplementary table 4.

DISCUSSION

The main finding of this study (the first using CMR to describe changes in RV function following lung resection) is that RV function deteriorated by POD2 and remained depressed at 2-months. This is shown by a median *relative* decrease in RVEF of 10.9% from baseline on POD2, 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, meaning changes following lung resection primarily affect the right ventricular-pulmonary vascular unit. The association between pulmonary function and deterioration in RVEF by POD2 suggests those patients with poorer lung function are also likely to be those with a larger deterioration in RV function, meaning this group may be at particular risk.

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%. This is the first study to describe CMR in a lung resection cohort - CVs in this population have not been described. Work in normal subjects and those with cardiac pathology have shown CVs for RVEF between 8.0 and 10.7%.[27] Our study had higher CV's, however post-hoc analyses suggest surgical side was important to observed variability. Pre-operative CV's were similar for those having left or right sided resections (12.75% and 13.21% respectively). Post-operatively those patients with right sided resections had larger CVs (20.48% on POD2 and 16.92% at 2-months) than those having left sided surgery (11.53% and 13.81% respectively). Future studies using CMR in this population for mechanistic research, may wish to prioritise patients undergoing left sided resections.

As described in the introduction, a more complete assessment of RV and pulmonary vascular function can be provided by measuring the matching between contractility and afterload. The

CMR surrogate approximation used in this study has compared favourably to a combined pulmonary artery catheter and CMR determined coupling measurement in a pulmonary hypertension cohort.[24] This ratio however incorporates a number of assumptions; firstly that ventricular volume at time zero is negligible, and secondly it calculates end systolic elastance and not maximal elastance.[28-30] Our patients show a SV/ESV ratio of 1.0 which falls following surgery suggesting a deterioration in the matching of contractility and afterload which is still present 2-months following surgery.

Although widely hypothesized, increased afterload following lung resection has not been demonstrated.[10, 18, 21] PAAT and PA distensibility are indices of afterload that do not assume constant flow (as PVR assumes), providing some insight into the pulsatile nature of afterload. Reduced PAAT has been associated with abnormal wave reflections (increased pulsatile afterload) in pulmonary hypertension.[26] Reduced PA distensibility suggests decreased compliance of the pulmonary vessels, increasing afterload.[31, 32]

We observed a decrease in PAAT in all vessels on POD2, with the greatest decrease in the operative vessel. At 2-months, main PAAT remains reduced and although non-operative PAAT returns to pre-operative levels, operative PAAT remains lower. These findings suggest that post-operatively there is increased afterload in the operative vessel, potentially due to increased wave reflection.

There were no changes in main PA distensibility, however determination of distensibility in this vessel can be complicated by cardiac movement distorting the cross-sectional plane, compromising the measurement.[33] This was our experience, with diastolic increases in cross-sectional area not reflected in either changes in flow in the main PA, or area of the branch pulmonary vessels. Operative distensibility was lower than pre-operative at 2-months, again suggesting increased afterload on this side.

The changes in PAAT and distensibility, in addition to reduced operative PA blood flow, suggest changes in afterload mainly result from the operative PA. PAAT and distensibility are surrogate indices of pulsatile afterload but only partially reflect changes in overall pulmonary artery impedance; this may account for the lack of observed association between either of these measures and RVEF. In-depth analysis of pulsatile afterload is required to further explore any association between changes in afterload and RV function following lung resection. Additionally, it must be recognised that the observed changes in RVEF could also occur as a result of intrinsic changes in RV contractility which could not be fully accounted for in this study.

BNP and hsTnT are quantitative biomarkers of myocardial injury. BNP is released in response to myocardial stretch and has been measured in patients undergoing lung resection, with elevated peri-operative levels associated with early post-operative cardiopulmonary complications.[34] We observed association between POD2 BNP and both $RVEF_{POD2}$ and $\Delta RVEF_{POD2\text{-}pre}$. We found no association between LVEF and BNP (not shown) suggesting BNP is released in response to changes within the RV. We found no association with change in RV function and troponin at any time point.

Clinical Implications

This is the first study showing that RV function is impaired not just in the immediate peri-operative period following lung resection, but months later, long into the recovery period. In other clinical settings such as heart failure and pulmonary hypertension, RV dysfunction is associated with poor prognosis and reduced exercise capacity; we hypothesize that reduced RVEF following lung resection is likely to have clinical sequelae such as dyspnea and reduced functional capacity. The right ventricle and pulmonary vasculature may provide a

target for future peri-operative interventions, allowing amelioration of long-term cardiorespiratory morbidity.

Limitations

Although there is association between duration of critical care admission and post-operative RV function this does not suggest it is causative. The reasons for remaining in critical care are multi-factorial and some of the complications that may prolong stay, could in themselves cause RV dysfunction. This is a proof of concept study and its size means any clinical associations can only be hypothesis generating and do not allow robust clinical correlation; future work should fully assess the clinical implications of RV dysfunction.

We made no assessment of RV function during exercise, previous work in this patient group has consistently shown marked changes in pulmonary haemodynamics and RV function on exercise.[18, 35] While the deterioration in RVEF observed is modest, we suggest the changes observed at rest would be exacerbated during exercise.

CMR is a reference method for assessing RV volumes but its use in this group is limited, firstly by availability and secondly by suitability in the immediate post-operative patient. Although withdrawals were well within the number allowed by the study's power analysis, a group of participants were unable to undergo CMR assessment post-operatively. A validated bedside alternative to CMR for the assessment of RV structure and function, potentially utilising transthoracic echocardiography, biomarkers or a combination would have utility in this population.

CONCLUSIONS

Right ventricular function is impaired immediately post-operatively following lung resection and this persists at 2-months. There is a deterioration in the SV/ESV ratio with evidence of

increased afterload. There was moderate association between post-operative RV function and B-type natriuretic peptide. Future work should focus on assessing the mechanisms and clinical implications of post-operative RV dysfunction and on assessment of RV function during exercise.

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Contributors

All authors contributed significantly to the submitted work. PM led patient recruitment and acquisition of data, contributed to analysis and interpretation of data, and drafted the final manuscript. AA contributed to patient recruitment and analysis of CMR data. AA, AG and DC contributed to analysis and interpretation of data. AK was lead surgeon, contributed to study design and assisted in acquisition of data. AM was lead anesthetist and contributed to study design. JP contributed to study design and performed safety reporting of CMR imaging. MJ, and JK contributed to study design. BS conceived of the study, obtained funding and supervized all aspects of the study. All authors critically revized and approved the final manuscript.

Other Contributions

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FIGURE LEGENDS

Figure 1 (A-C). Ventricular ejection fraction and coupling over time

For box plots, the middle horizontal line represents the median, the boxes represent the interquartile range (IQR) and the whiskers represent the range of values no greater than 1.5 times the IQR. Circles represent outliers and are values 1.5-3 times IQR.

(A) Decrease in right ventricular ejection fraction (RVEF) on post-operative day (POD) 2, remaining reduced at 2-months. (B) No changes in left ventricular ejection fraction (LVEF) over time. (C) Deterioration in the stroke volume/end systolic volume ratio (SV/ESV) over study period.

Figure 2 (A-B). Pulmonary artery flow over time

For box plots, the middle horizontal line represents the median, the boxes represent the IQR and the whiskers represent the range of values no greater than 1.5 times the IQR. Circles represent outliers and are values 1.5-3 times IQR. *Blue bars* represent the Main pulmonary artery (MPA), *green bars* represent the operative pulmonary artery (OPA) and *white bars* represent the non-operative pulmonary artery (NPA)

(A) Flow in the MPA increases on POD2 before returning to pre-op levels by 2-months. (B) Post-operative distribution of CO between the two pulmonary arteries is altered, with reduced flow through the OPA on POD2 and at 2-months.

Figure 3 (A-C). Pulmonary artery acceleration time (PAAT) and distensibility over time

For box plots, the middle horizontal line represents the median, the boxes represent the IQR and the whiskers represent the range of values no greater than 1.5 times the IQR. Circles and

positive symbols (+) represent outliers and are values 1.5-3 and >3 times IQR respectively. *Blue bars* represent the Main pulmonary artery (MPA), *green bars* represent the operative pulmonary artery (OPA) and *white bars* represent the Non-operative pulmonary artery (NPA).

(A) PAAT in the MPA is reduced post-operatively, remaining reduced from pre-op levels at 2-months. (B) PAAT in the OPA is reduced on POD2 and despite partial recovery, remains reduced at 2-months. PAAT in the NPA is reduced on POD2 but recovers by 2-months. PAAT is lower in the OPA on POD2 and at 2-months. (C) Distensibility in the OPA is reduced on POD2 and at 2-months. Distensibility in the OPA is lower than the NPA at 2-months.

Figure 4 (A-D). Biomarkers of myocardial function

For box plots, the middle horizontal line represents the median, the boxes represent the IQR and the whiskers represent the range of values no greater than 1.5 times the IQR. Circles and positive symbols (+) represent outliers and are values 1.5-3 and >3 times IQR respectively.

(A) Changes in B-type natriuretic peptide (BNP) over time, peaking on post-operative day (POD) 2. (B) Changes in High sensitivity troponin T (hsTnT) over time, peaking on POD1. (C) Moderate association of change in right ventricular ejection fraction from pre-op to POD2 (ΔRVEF [POD2-Pre]) and BNP on POD2 (D) No association with ΔRVEF [POD2-Pre] and hsTnT on POD2.

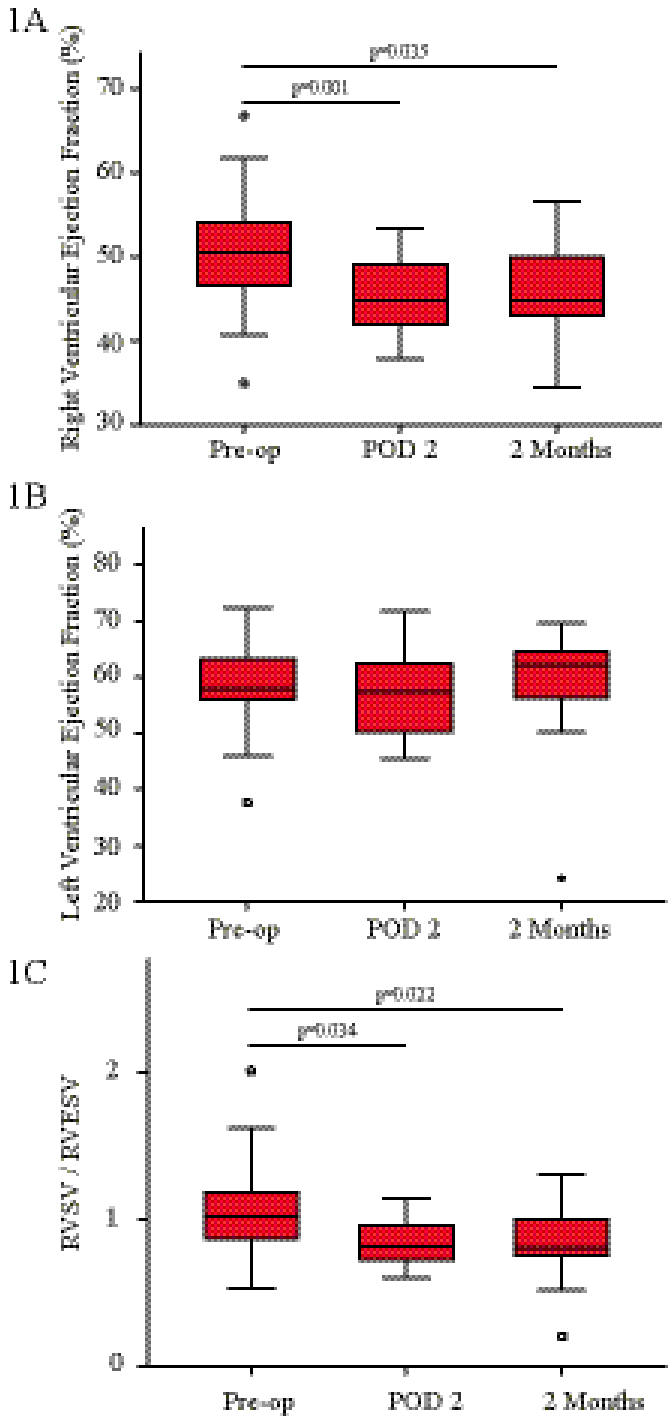

1A
Right Ventricular Ejection Fraction (%)
p=0.035
p=0.001
70
60
50
40
30
Pre-op
POD 2
2 Months
1B
Left Ventricular Ejection Fraction (%)
80
70
60
50
40
30
20
Pre-op
POD 2
2 Months
1C
RVSV / RVESV
p=0.022
p=0.034
2
1
0
Pre-op
POD 2
2 Months

Figure 1.2

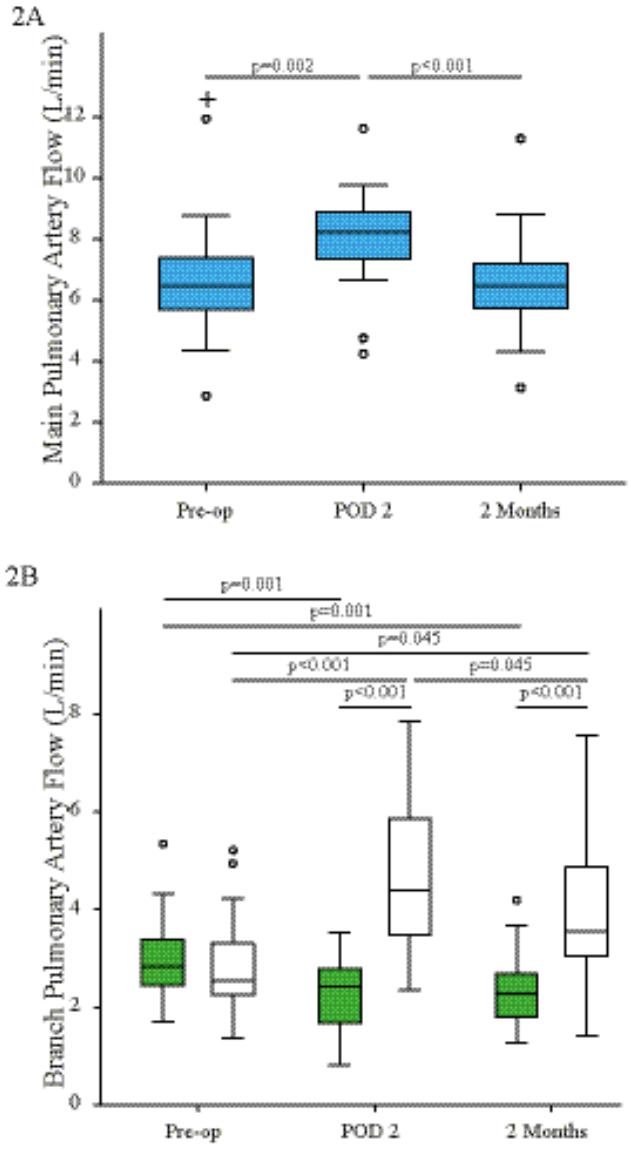
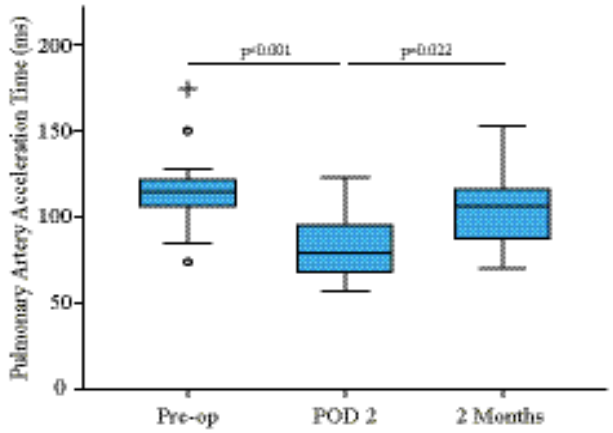
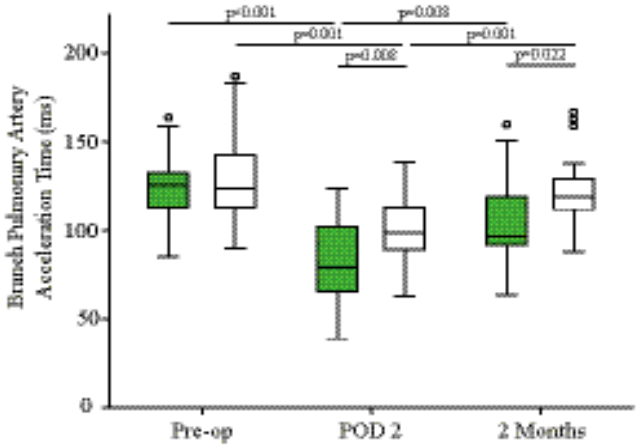

2A
Main Pulmonary Artery Flow (L/min)
p=0.002
p<0.001
0
2
4
6
8
10
12
Pre-op
POD 2
2 Months
2B
Branch Pulmonary Artery Flow (L/min)
p=0.001
p=0.001
p=0.045
p<0.001
p=0.045
p<0.001
p<0.001
0
2
4
6
8
Pre-op
POD 2
2 Months

Figure 2.2

3A



3B



3C

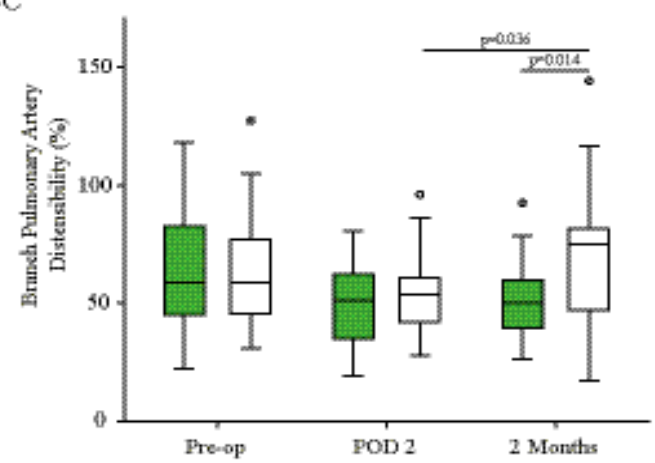


Figure 3.2

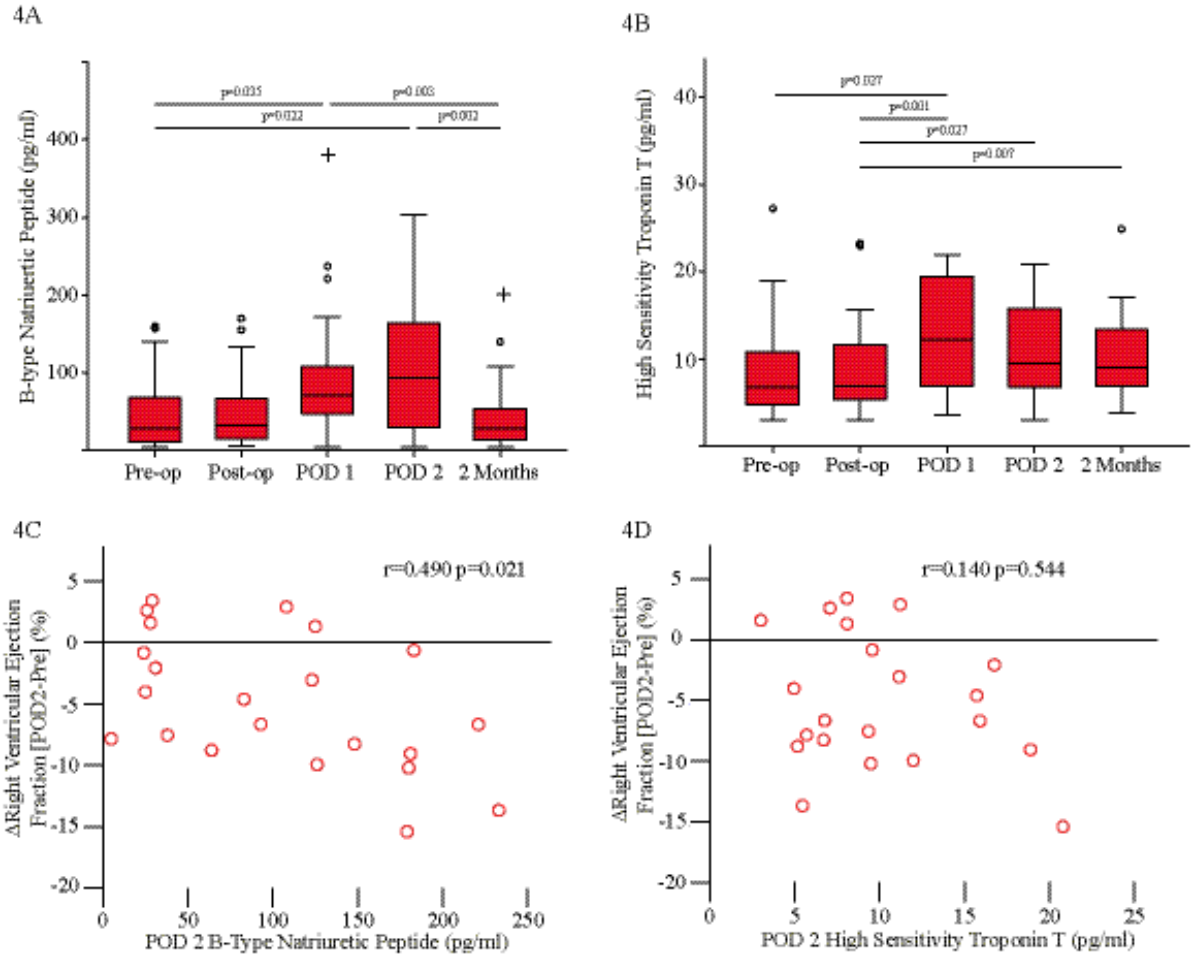

4A
B-type Natriuretic Peptide (pg/ml)
Pre-op
Post-op
POD 1
POD 2
2 Months
4B
High Sensitivity Troponin T (pg/ml)
Pre-op
Post-op
POD 1
POD 2
2 Months
4C
r=0.490 p=0.021
ΔRight Ventricular Ejection Fraction [POD2-Pre] (%)
POD 2 B-Type Natriuretic Peptide (pg/ml)
4D
r=0.140 p=0.544
ΔRight Ventricular Ejection Fraction [POD2-Pre] (%)
POD 2 High Sensitivity Troponin T (pg/ml)

Figure 4.2

Table 1. Patient characteristics

Patient characteristics	**n = 27**
Age, yr	67.0 (59.0, 74.0)
Sex, n Female	17 (63.0%)
Smoking	
None, n (%)	2 (7.4%)
Former, n (%)	12 (44.4%)
Active, n (%)	13 (48.1%)
Pre-operative pulmonary function	
SaO_2 on air, %	96.4 (1.7)
FEV_1, L	1.9 (1.6, 2.4)
% Predicted FEV_1, %	87.5 (25.1)
FEV_1/FVC ratio, %	64.1 (14.8)
TLCO, mmol/kPa/min	5.2 (1.7)
% Predicted TLCO, %	66.6 (15.2)
Operative Variables	
Pneumonectomy, n (%)	1 (3.7%)
Lobectomy, n (%)	22 (81.5%)
Bilobectomy, n (%)	4 (14.8%)
Right sided procedure, n (%)	17 (63.0%)
Segments resected, n	5 (3, 5)
Duration of surgery, mins	146.0 (116.0, 169.0)
Duration of OLV, mins	56.0 (48.0, 84.0)
Intra-op fluid administration, mls	933.3 (402.9)
Pathology	

Primary lung cancer	24 (88.9%)
Metastatic malignancy	1 (3.7%)
Benign	2 (7.4%)
Comorbidities*	
History of Cancer, n (%)	7 (25.9%)
COPD, n (%)	6 (22.2%)
Hypertension, n (%)	9 (33.3%)
Ischemic Heart Disease, n (%)	6 (22.2%)
Diabetes Mellitus, n (%)	0
Peripheral Vascular Disease, n (%)	5 (18.5%)
Obesity, n (%)	2 (7.4%)
Alcoholism, n (%)	0
Thoracoscore (%)	0.7 (0.5, 0.8)
Critical Care Unit Length of Stay (Days)	2.0 (1.2, 2.2)
Hospital Length of Stay (Days)	8 (7, 11)

***As per Thoracoscore definition of comorbidities.**

Data are presented as mean (SD) or median (Q1, Q3).

SaO_2, oxygen saturation; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLCO, transfer factor for carbon monoxide; OLV, one lung ventilation; COPD, chronic obstructive pulmonary disease.

Table2. Ventricular Volumes and Function over Time

	Pre-op	**POD2**	**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*
Right ventricle volume measurements				
RVEF (%)	50.5 (6.9)	45.6 (4.5)‡	44.9 (7.7)‡	0.003*
RVEDV (ml)	119.1 (25.4)	125.9 (22.5)	109.4 (31.6)	0.019*
RVESV (ml)	59.8 (17.1)	68.6 (14.5)‡	59.8 (17.6)	0.040*
RVSV (ml)	59.3 (12.0)	57.3 (10.7)	49.6 (16.5)‡	0.002*
RVSV/RVESV	1.0 (0.9, 1.2)	0.8 (0.7, 1.0)**§**	0.8 (0.8, 1.0)**§**	0.011†
Left ventricle volume measurements				
LVEF (%)	58.4 (7.1)	57.4 (7.3)	59.7 (9.3)	0.621*
LVEDV (ml)	109.2 (19.5)	106.3 (19.2)	93.6 (28.2)‡	0.001*
LVESV (ml)	46.0 (13.2)	46.0 (14.2)	37.7 (13.1)	0.019*
LVSV (ml)	63.2 (11.7)	60.3 (9.0)	55.9 (18.0)‡	0.004*

Data are presented as mean (SD) or median (Q1, Q3).

***One-way repeated measures ANOVA.**

†Friedman's test.

‡ Significant difference from Pre-op (paired t-test, p<0.05).

§ Significant difference from Pre-op (Wilcoxon signed rank test, p<0.05).

§ Significant difference from POD2 (paired t-test, p<0.05).

POD, post-operative day; HR, heart rate; bpm, beats per minute; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end diastolic volume; RVESV,

right ventricular end systolic volume; RVSV, right ventricular stroke volume; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVSV, left ventricular stroke volume.

Table3. PAAT and Distensibility Index

	Pre-op	**POD2**	**2-months**	**p-value**
	n = 26	**n = 22**	**n = 24**	
Pulmonary artery flow (L/min)				
Main PA flow	6.6 (1.7)	8.0 (1.6) ‡	6.5 (1.7) §	0.004*
Operative PA flow	3.0 (0.8)	2.3 (0.7) ‡	2.3 (0.8) ‡	0.004*
Non-operative PA flow	2.8 (1.0)	4.7 (1.4) ‡ ll	3.8 (1.5) ‡ § ll	<0.001*
Pulmonary Artery Acceleration Time (PAAT, ms)				
Main PA	115.9 (20.7)	82.7 (18.9) ‡	104.0 (19.5) §	<0.001*
Operative PA	124.7 (19.3)	82.1 (23.0) ‡	106.0 (23.9) ‡§	<0.001*
Non-operative PA	128.0 (24.8)	100.5 (18.8) ‡ll	121.4 (20.4) §ll	<0.001*
Distensibility (%)				
Main PA	32.0 (26.9, 46.0)	29.8 (22.3, 38.8)	28.4 (25.8, 39.6)	0.818†
Operative PA	65.2 (25.5)	50.7 (16.9)	51.8 (16.2)	0.027*
Non-operative PA	62.6 (23.2)	54.4 (17.7)	69.2 (28.0) §ll	0.120*

Data are presented as mean (SD) or median (Q1, Q3).

***One-way repeated measures ANOVA.**

† Friedman's test.

‡ Significant difference from pre-op (paired t-test, p<0.05).

§ Significant difference from POD2 (paired t-test, p<0.05).

ll Significant difference from operative vessel at given timepoint (independent samples t-test, p<0.05).

POD, post-operative day; PA, pulmonary artery.

Table 4. Biomarkers of myocardial function

	Immediate Pre-op	**Immediate Post-op**	**POD1**	**POD2**	**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)	71.0 (5.0, 381.0)†	93.0 (5.0, 304.0)†	28.5 (5.0, 199.0) § ll	<0.001*
	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)‡	<0.001*

Data are presented as median (Q1, Q3).

***Friedman's test.**

† Significant difference from Pre-op (Wilcoxon signed rank test, p<0.05).

‡ Significant difference from Immediate Post-op (Wilcoxon signed rank test, p<0.05).

§ Significant difference from POD1 (Wilcoxon signed rank test, p<0.05).

ll Significant difference from POD2 (Wilcoxon signed rank test, p<0.05).

POD, post-operative day; BNP, B-type natriuretic peptide; hsTnT, high sensitivity troponin T.