Right to left ventricular volume ratio: A novel marker of disease severity in chronic thromboembolic pulmonary hypertension

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Background: Our objective was to define the relationship between structural changes in the heart and functional and haemodynamic changes, in subjects before and after pulmonary thromboarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH).

Methods: In this retrospective cohort study, 34 patients (40% men; age 55 +/- 15 years) diagnosed with CTEPH underwent PEA at The Prince Charles Hospital (TPCH) in Brisbane, Australia over a 7 year period. These patients underwent magnetic resonance imaging before and after surgery. We correlated the MRI derived ratio of right to left ventricular end-diastolic volumes (RV:LV) with a clinically relevant measure of functional capacity, the 6 minute walk distance (6MWD).

Results: Prior to PEA, increased RV:LV volume ratio was significantly and inversely associated with 6MWD ($r = -0.02$, $p = 0.490$). After PEA, there was also significant and positive association between RV:LV volume ratio and improvement in 6MWD ($r = 0.490$, $p = 0.02$). Postoperatively, the decrease in RV:LV volume ratio correlated significantly with improvement in 6MWD ($r = 0.490$, $p = 0.02$).

Conclusions: RV enlargement from high afterload and LV underfilling are important pathophysiological mechanisms in CTEPH. Our results highlight the relevance of a composite RV:LV volume ratio measurable on MRI as a correlate of baseline functional status, baseline PVR and of change in functional status after PEA surgery.

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1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), defined as a mean pulmonary artery pressure (mPAP) > 25 mm Hg with a pulmonary capillary wedge pressure (PCWP) < 15 mm Hg and at least one segmental perfusion defect following three months of adequate anticoagulation, is being increasingly recognized as an important cause of persistent pulmonary arterial hypertension [1,2]. Predominant mechanisms include recurrent pulmonary emboli, obliteration of central pulmonary arteries, pulmonary vascular remodeling and progressive small vessel arteriopathy. Consequences may include progressive right ventricular (RV) hypertrophy, dilatation and failure with progressive clinical decline [1–3].

In selected cases with centrally located anatomic obstructions in one or both branch pulmonary arteries, surgical pulmonary thromboarterectomy (PEA) can be performed often, but not always, with excellent clinical outcomes. Invasively determined increased pulmonary vascular resistance (PVR) has been found to be an important risk factor for perioperative mortality in this patient group [4–7]. Currently, however, non-invasive preoperative evaluation does not accurately or reliably predict postoperative haemodynamic or functional outcomes for PEA patients [1]. We sought to investigate the potential utility of cardiac MRI parameters in this regard. In particular, we hypothesised that the ratio of right to left ventricular end-diastolic volumes (RV:LV) might relate to haemodynamic and functional status and outcomes, as a large RV could indicate high afterload and a small left ventricle (LV) could indicate impaired preload from low pulmonary flow through the obstructed pulmonary vasculature. Thus, RV:LV volume ratio might provide a more relevant measure than either RV or LV volumes alone.
2. Methods

2.1. Patients

Over a 7 year period, 34 patients (40 men; age 55 +/− 15 years) diagnosed with CTEPH underwent PEA and cardiac MRI at The Prince Charles Hospital (TPCH) in Brisbane, Australia. All patients underwent PEA via a median sternotomy on cardiopulmonary bypass using the technique of Jamieson et al, from San Diego, U.S.A. [7], A Multidisciplinary Pulmonary Hypertension team at TPCH made the diagnosis and the decision to undergo surgery. Selection criteria included patients with significant pulmonary hypertension, surgically accessible chronic thromboembolic disease and an acceptable co-morbid status. The medical ethics committee at TPCH approved the study and all patients gave informed consent.

Of these 34 patients, 32 had MR image quality sufficient for preoperative analysis. Of these, 31 had functional assessment at baseline with 6 min walk distance measurement (6MWD), according to the American Thoracic Society Guidelines [8] and 29 patients had invasive measurement of cardiopulmonary haemodynamics at right heart catheterisation. Right heart catheterisation and haemodynamic assessment were performed with a 7-F balloon tipped, flow directed Sawn–Ganz catheter during continuous electrocardiography monitoring. PVR was calculated as (mPAP − PCWP)/CO (mPAP is mean pulmonary artery pressure, PCWP is pulmonary capillary wedge pressure and CO is cardiac output.)

4 patients died peri-operatively and 4 patients were lost to follow up or were followed up in a distant location. From those 26 patients who survived and attended TPCH for follow up, 21 had right heart studies on day 1 post operation and 26 had repeat MRI scans, of whom 23 had image quality sufficient for analysis. 19 of these 26 subjects had functional assessment with 6MWD at 6 months post operation. MRI was performed at a mean of 6 +/− 6 months post operatively and a mean of 9 +/− 5 months post operatively. This is summarised in Fig. 1.

2.2. Magnetic resonance imaging

2.2.1. Ventricular volumes and function

All imaging was performed using a 1.5 T MR scanner (GE medical system.) Retrospectively gated steady-state free precession (FIESTA) cine MR images of the heart were acquired in the vertical long axis, 4 chamber view and the short axis view covering the entirety of both ventricles (9–12 slices.) Image parameters – TR = 3.2 ms; TE = 1.6 ms; flip angle = 78°; slice thickness = 8 mm; matrix = 192 × 256; field of view = 300–380 mm; and temporal resolution = 40 ms, acquired during a single breath hold.

Short axis cine MR acquisitions were taken using a set of multi-slice cine acquisitions, with FIESTA images in a plane perpendicular to a line from the centre of the coronary veins to the apex of the RV [9].

2.2.2. Functional imaging

Ventricular volumetry and mass were assessed using a contrast-enhanced biplane transaortial volumetry with 4 chamber long axis, by one of two experienced (S.J.) OsiriX 64 bit, version 4.1.2, was used on an independent satellite console for contouring. If necessary, the window and level settings were adjusted to optimise myocardial and ventricular lumen contrast.

The endocardial and epicardial borders of the RV and LV were traced manually on the short-axis cine images. The end diastolic (LVEDV) and end systolic (LVESV) values were those where the chambers were the largest and smallest respectively, contours carefully excluded the right atrium (RA) and papillary muscles to avoid overestimation of the volumes and included the outflow tracts, mitral and aortic valves were excluded in the ventricular volumes and included the intraventricular septum. Ventricular volumes and mass were indexed to body surface area.

Calculation of stroke volume (SV) and ejection fraction (EF) followed the Simpson rule by summation of areas on each slice multiplied by the slice thickness and image gap. Mass was determined as the difference between end diastolic epicardial and endocardial volumes, including the trabeculations, multiplied by the specific gravity of myocardium.

Stroke volume was calculated as EDV − ESV. Ejection fraction (EF) was calculated as SV divided by EDV, and was expressed as a percentage. RV:LV was the ratio of the EDV of each respective chamber.

Atrial endocardial borders were delineated at ventricular end-systole in the 4 chamber view and the area calculated using the area-length method. Tricuspid regurgitation was calculated as RV SV − LV SV divided by RVSV, and expressed as a percentage.

2.3. Statistical analysis

Descriptive data are expressed as mean +/− SD. All analyses were performed with the SPSS statistical package (SPSS, version 21, SPSS Inc Chicago.). Paired sample t tests were used to analyse the changes associated with surgery for the relevant MRI functional and haemodynamic parameters. Linear regression analysis was used to assess correlations between MRI, haemodynamic parameters and functional status. Our prospectively defined primary endpoint was change in RVEDV to LVEDV ratio before versus after PEA and its correlation with 6MWD at baseline and change in 6MWD after successful surgery. A two tailed p-value < 0.05 was considered statistically significant.

3. Results

3.1. Preoperative assessment

Baseline clinical, haemodynamic and functional characteristics of the 32 patients are summarised in Table 1.

3.2. Relevance of the right to left ventricular end diastolic volume ratio

Pre-operative increase in RV:LV volume ratio was significantly and inversely associated with 6MWD (p = 0.04, Fig. 2) and significantly and positively associated with increased PVR (p = 0.004). Furthermore, the postoperative decrease in RV:LV volume ratio correlated significantly with the observed improvement in 6MWD (r = 0.490, p = 0.02), as shown in Fig. 3. Baseline functional status or change in functional parameters did not correlate with any other MRI parameters, nor did it correlate with change in mPAP or change in cardiac index.

3.3. Other preoperative parameters

A non-significant trend was noted towards decreased 6MWD with smaller LVEDVi (p = 0.09). Similarly but even less marked was the association between higher RVEDvi and 6MWD, as shown on Fig. 4 (p = 0.638). Smaller LV size was significantly associated with smaller left atrial (LA) size as shown in Fig. 5 (p = 0.011), suggesting that underfilling of the LV rather than LV compression by the enlarged RV was the cause of reduced LV size in these CTEPH patients.

3.4. Postoperative assessment

Significant RV remodeling was demonstrated after PEA (Table 2). There was also significant RA remodeling with a reduction in the degree of TR. LV structure and function did not significantly change post PEA, however, the change in the degree of TR was significantly associated with the change in LVEDVi. (r = 0.709, p = <0.0001).

Post-operative functional and haemodynamic changes are listed in Table 3 showing significant improvements.

There were no significant correlations between RV and LV MRI parameters and 6MWD post operatively. At 6 months post operation, peri-operative mPAP was not associated with 6MWD or MRI parameters.

4. Discussion

In this study, we have demonstrated the potential utility of a novel MRI measurement, RV:LV ratio, in severe CTEPH. Pre-operatively, the RV:LV ratio correlated significantly with functional status and PVR better than for RV or LV parameters alone. Furthermore, peri-operative change in the RV:LV ratio correlated with the change in functional capacity, again more so than for any right or left heart parameter considered alone. Neither change in mPAP and CI correlated significantly with change in 6MWD.
In patients with operable CTEPH, gas transfer and exercise capacity, as measured by the 6MWD, have been shown to be independently associated with outcomes in a multivariate analysis [4]. Additionally, RV function and remodeling post PEA, are an important determinant of outcomes [2]. However, common indices of resting RV function such as RVEF do not correlate with exercise capacity [10]. Furthermore, functional status in subjects with PAH does not correlate with changes in haemodynamics, nor has improvement in mPAP shown to be prognostic [2]. However, common indices of resting RV function and remodeling post PEA, are an important determinant of outcomes [4]. Additionally, RV function pressure has been shown to be independent of pulmonary artery pressure, PVR: Pulmonary vascular resistance. LV: Left ventricular ejection fraction, RVEF: Right ventricular ejection fraction, TR: tricuspid regurgitation, LA: Left atrial, RA: Right atrial, PA: Pulmonary artery, RV:LV, RVEDV:LVEDV, mPAP: Mean pulmonary artery pressure, PVR: Pulmonary vascular resistance.

In our study, the significant correlation between reduced LA size and small LVEDV pre-operatively suggests that underfilling of the LV from a reduction in preload is a key contributing factor; hence the LV been small from compression by the enlarged RV would have expected to be larger rather than smaller. Moreover, larger RV size postoperatively correlated with a decrease in RV size, consistent with a smaller RV size leading to less functional TR, with an increase in forward flow through the right heart and pulmonary circulation and thereby better LV filling. This is consistent with another study, which showed that impaired LV filling is from a reduction in preload, rather than alteration in LV geometry from extrinsic compression [14–16]. Moreover, improvements in 6 min walk and 6MWD, have been shown to be independent of pulmonary artery pressure, PVR: Pulmonary vascular resistance.

Ventricular interdependence was first described in 1910 by Bernheim, who postulated that dilatation of the LV could affect geometry and hence function of the RV [12]. Subsequently, studies assessing the effect of increased LV volume and pressure on LV structure and function have shown that ventricular volume and pressure changes can alter diastolic and systolic functions of the ventricles [13]. Several mechanisms underlying normal LV size and/or function in this setting have been investigated, including reduced LV filling, LV compression, and RV-LV dyssynchrony.

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remodeling post PE has been demonstrated in several previous publications. Increased RVEF, decreased RV mass and volumes and normalization of septal bowing post PEA have been consistently demonstrated, with correlations between post-operative rise in RVEF and fall in PVR [25–27]. Our study confirms these findings by again demonstrating beneficial and significant RV remodeling post PEA, with significant reductions in RV size and mass, as well as RA size and the degree of TR.

RVEDVi:LVEDVi ratio, as assessed by MRI, reflects these pathophysiological processes. Previously, RV/LV has been demonstrated to be a better reflection of RV dilatation than RVEDVi in the setting of repaired Tetralogy of Fallot and quantification of pulmonary regurgitation [28]. Furthermore, it has been shown that RV-LV, measured by CT, correlates with pulmonary artery systolic pressure [29]. In CTEPH, we propose that the RV-LV ratio takes into account increased RV size and remodeling from pressure overload, but also the effects of reduced LV filling and decreased preload. In this study, RV-LV ratio correlated with both baseline functional status and PVR, and change in RV-LV ratio correlated significantly with change in functional status. As functional status and PVR are known to be prognostic indicators of outcome post PTE in CTEPH, RV-LV ratio could be a novel, non-invasive measure of prognosis in operable CTEPH.

4.1. Limitations

There are several limitations to our study. The size of our study was limited by relatively small numbers of patients with CTEPH undergoing PEA and the cost and availability of MRI pre and post surgery. Additionally, MRI image quality varied substantially in a small number of cases, and a small number of patients were lost to follow-up, limiting certain analyses. There was some variability in the timing of MRI, right heart catheterisation, and a subset of patients underwent follow-up to confirm certain analyses. There were some differences in the timing of MRI, right heart catheterisation, and a subset of patients underwent follow-up to confirm certain analyses. There were too few clinical events late after follow up to assess the relevance of RV-LV ratios to hard clinical outcomes.

### Table 2

| Parameter | Pre operative | Post operative | P value |
|-----------|---------------|----------------|---------|
| RVED Vi (mL) | 98 ± 24 | 72 ± 13 | <0.0001 |
| RVE S (mL) | 57 ± 21 | 33 ± 10 | <0.0001 |
| RV SV (mL) | 80 ± 19 | 73 ± 15 | 0.05 |
| RV EF (%) | 43 ± 10 | 53 ± 7 | 0.001 |
| RV mass index (mL/BSA) | 41 ± 16 | 33 ± 11 | 0.001 |
| RA size (mL) | 27 ± 9 | 23 ± 6 | 0.001 |
| TR fraction (%) | 11 ± 20 | −2 ± 17 | 0.005 |
| RV/LV | 1.7 ± 0.6 | 1.1 ± 0.2 | <0.0001 |

BSA: Body surface area.

### 5. Conclusions

RV to LV volume ratio, measurable on cardiac MRI, provides information concerning both RV enlargement from high afterload and LV underfilling as a consequence of impaired pulmonary flow, geometric alterations and ventricular remodeling. These are important pathophysiological mechanisms in CTEPH. We highlight the potential relevance of the RV:LV volume ratio on MRI as a clinically simple and convenient baseline functional status, baseline RV size and change in functional status, after successful PEA surgery in CTEPH patients.

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