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

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ABSTRACT

Background: Our objective was to determine 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 (MRI) 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 min walk distance (6MWD).

Results: Prior to PEA, increased RV:LV volume ratio was significantly and inversely associated with 6MWD ($p = 0.04$) and significantly and positively associated with increased pulmonary vascular resistance (PVR) ($p =$ [illegible]). Small LV volumes were associated with small left atrial (LA) size, suggesting LV underfilling rather than compression of the LV by the enlarged RV. Postoperatively, the decrease in RV:LV volume ratio correlated significantly with improvement in 6MWD ($r = 0.490$, $p = 0.02$). After PEA, there was also significant [illegible] the RV and right atrium (RA) and in the severity of tricuspid regurgitation (TR).

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.

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 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.

☆ **Conflicts of interest**: None.

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[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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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 TCPH 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 catherisation 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 operatively 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 operatively. MRI was performed at a mean of 6 +/− 6 months pre 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; [illegible] view = 300–380 mm; and temporal resolution = 40 ms, acquired during a single [illegible] hold.

Short axis cine MR acquisitions were taken using a set of multi-slice cine acquisi[illegible] FIESTA images in a plane perpendicular to a line from the centre of th[illegible]monary val[illegible] to the apex of the RV [9].

2.2.2. Functional imaging

Ventricular volumetry and mass were assessed wi[illegible]hort a[illegible]e imaging [illegible] atrial volumetry with 4 chamber long axis, by one [illegible]rienced ob[illegible] (S.J.) OsiriX 64 bit, version 4.1.2, was used on an independent s[illegible] console for con[illegible]acing. If necessary, the window and level settings were o[illegible] best myocardial [illegible]entricular lumen contrast.

The endocardial and epicardial bor[illegible] of the RV and [illegible]e traced manually on the short-axis cine images. The end dias[illegible] (EDV) and end syst[illegible]SV) values were those where the chambers were the lar[illegible]nd smallest respectively. [illegible] contours carefully excluded the right atrium (RA) [illegible]icuspid [illegible] to avoid overestimation of the volumes and included the outflow tra[illegible]illar[illegible]scles and trabeculae were excluded in the ventricular volumes and include[illegible]ntricular [illegible]. Ventricular volumes and mass were indexed to bod[illegible] area [illegible]

Calculation of[illegible]DV and [illegible]h the Simpson rule by summation of areas on each [illegible]ultipli[illegible]y the sum [illegible] thickness and image gap. Mass was determined as [illegible]ifference [illegible]ween end diastolic epicardial and endocardial volumes, including the s[illegible]wall[illegible]ulations, multiplied by the specific gravity of myocardium.

Stroke volume [illegible]as calculated as EDV − ESV. Ejection fraction (EF) was calculated as SV divided by E[illegible] was expressed as a percentage. RV:LV was the ratio of the EDV of each respective ch[illegible]er.

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.

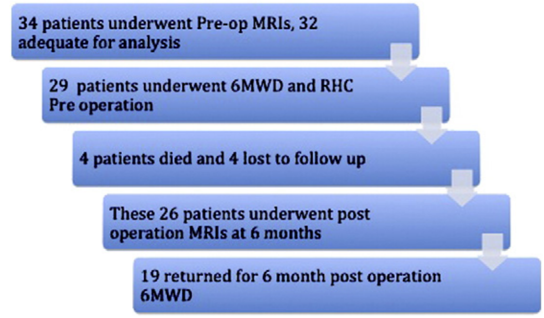

Fig. 1. Flow chart outlining patient fol[illegible]udy.

3. Results

3.1. Preoperative assessment

Baseline clinical, haem[illegible]amic[illegible] functional [illegible]haracteristics of the 32 patients are summ[illegible]ized [illegible] 1.

3.2. Relevance [illegible]ht to left ven[illegible] end diastolic volume ratio

Pre-operative incre[illegible] RV:LV volume ratio was significantly and inver[illegible]ociated with [illegible]VD ($p = 0.04$, Fig. 2) and significantly an[illegible]ositively associated with increased PVR ($p = 0.004$). Furtherm[illegible], the postop[illegible]ative decrease in RV:LV volume ratio correlated sig[illegible]cantly wit[illegible]e observed improvement in 6MWD ($r = 0.490$, $p =$ [illegible]2), as sh[illegible] in Fig. 3. Baseline functional status or change in functio[illegible]d not correlate with any other MRI parameters, nor did it correlate with change in mPAP or change in cardiac index.

[illegible]. 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.

Table 1
Baseline pre operative characteristics.

Characteristic	$N = 32$
Age, years	55 +/− 15
Male Sex, %	41
NYHA	3 +/− 0.7
LVEDV index, mL/m^2	64 +/− 15
RVEDV index, mL/m^2	110 +/− 34
LVEF, %	59 +/− 9
RVEF, %	41 +/− 11
LV mass index (g/m^2)	66 +/− 18
RV mass index (g/m^2)	45 +/− 18
TR fraction, %	12 +/− 18
LA size, cm^2	19 +/− 6
RA size, cm^2	27 +/− 9
PA size, mm^2	11 +/− 2
RV:LV	1.8 +/− 0.6
6MWD, metres	417 +/− 112
mPAP, mm Hg	41 +/− 15
PVR, dynes	542 +/− 387
Cardiac index L/min/m^2	2.3 +/− 0.7

NYHA: New York Heart Association Class, LVEDV: Left ventricular end diastolic volume, RVEDV: Right ventricular end diastolic volume, LVEF: 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 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 [11]. In our study, we confirmed that resting RV function and changes in RV function post PEA, do not correlate with functional capacity, however, the RV:LV ratio does. This ratio is an intuitively appealing measurement, as it combines non-invasive relevant information about RV loading conditions and LV under filling into a "composite" value that appears to have potential as a novel marker of disease severity and outcomes in this group.

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 RV volume and pressure on LV structure and function have shown that ventricular volume and pressure changes can alter diastolic and systolic function of the contralateral ventricle [13]. Several mechanisms underlying abnormal LV size and/or function in this setting have been investigated, including reduced LV filling, LV compression and RV/LV dyssynchrony.

In our study, the significant correlation between reduced LA size and small LVEDV preoperatively suggests that underfilling of the LV from a

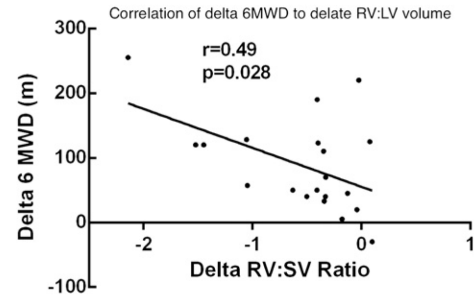

Fig. 3. Correlation of delta 6 min walk distance to delta RV:LV volume ratio.

reduction in preload is a key contributing factor; had the LV been small from compression by the enlarged RV, LA size would have expected to be larger rather than smaller. Moreover, larger LV size postoperatively correlated with a decrease in TR severity, 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 other studies, which have shown that impaired LV filling is from a reduction in preload, rather than alteration in LV geometry from extrinsic compression [14–16]. Moreover, improvements in LV strain and strain rate post PTE, shown by Olsen et al, may reflect an improvement in LV function from an increase in preload after successful relief of pulmonary circulatory obstruction [17]. Hardziyenka et al. demonstrated left ventricular free wall atrophy from myocyte shrinkage in a rat model of CTEPH and this was reversible after PEA in a clinical arm of their study [18,19]. Our study did not show significant changes in LV mass and size post operatively, however this may be because the interventricular septum was included in LV mass calculations.

LV geometric alteration by compression from an enlarged RV and LV septal bowing has been shown to impair early diastolic LV filling in the presence of a pressure-loaded RV [20–22]. Lurz et al showed that in patients with RV to PA conduit obstruction, relief of the obstruction led to improvement in early LV diastolic filling which best correlated with favourable septal motion and an improvement in exercise capacity [23]. In our study, there was a significant positive correlation between RV stroke volume and increased LV size, highlighting the importance of impaired LV filling from reduced preload, rather than LV compression from an enlarged RV, in CTEPH. One possible explanation for this involves pericardial adaptation. Diastolic ventricular interdependence with septal shift and a reduction in LV dimensions has been shown to be stronger with an intact, rather than absent, pericardium [13]. However, while the pericardium is intact in CTEPH, the disease process occurs chronically, giving the pericardium time to adapt to an enlarged RV [24].

Increased PVR, decreased compliance and increased pulmonary artery wave reflection contribute to increased right ventricular afterload in CTEPH, leading to increased RV mass and eventually RV dilatation and failure [2]. Patient outcomes are predominantly determined by the response of the RV to this increased load and successful RV

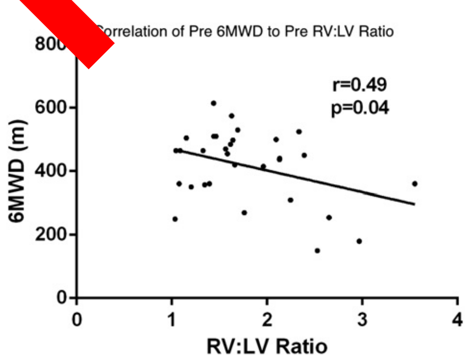

Fig. 2. Correlation of pre 6 min walk distance to pre RV:LV volume ratio.

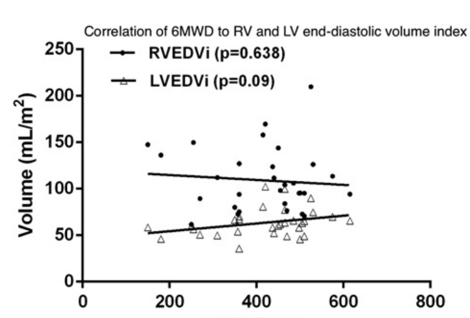

Fig. 4. Correlation of 6 min walk distance to RV and LV end-diastolic volume index.

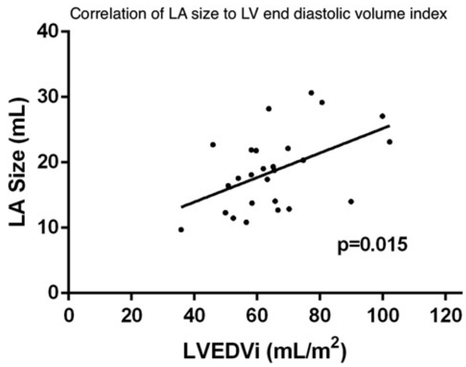

Fig. 5. Correlation of LA size to LV end-diastolic volume.

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.

RVEDV:LVEDV 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 [illegible] decreased preload. In this study, RV:LV ratio correlated with [illegible] baseline functional status and PVR, and change in RV:LV ratio correla[illegible] significantly with change in functional status. As functio[illegible] status a[illegible] PVR are known to be prognostic indicators of outc[illegible] PTE i[illegible] CTEPH, RV:LV ratio could be a novel, non-invasive [illegible]sure o[illegible]ognosis in operable CTEPH.

4.1. Limitations

There are several limitations [illegible] our study. [illegible]size of our study was limited by relatively small nu[illegible]rs of patients [illegible]TEPH undergoing PEA and the cost and avail[illegible]ty of M[illegible]I pre and pos[illegible]surgery. Additionally, MRI image quality [illegible]subopt[illegible] in a small number of cases, and a small number of patients [illegible] to follo[illegible]up, limiting certain analyses. There was [illegible] varia[illegible] in th[illegible]ming of MRI, right heart catherisation [illegible]D asses[illegible] relation to the performance of PEA, but [illegible]e were[illegible]latively [illegible] and we believe it would be unlikely to [illegible]antial[illegible] correlations observed between MRI, functional a[illegible]odyna[illegible] parameters after surgery. There were too few clinica[illegible]nts late after follow up to assess the relevance of RV:LV ratios to ha[illegible]nical outcomes.

Table 2
Right ventricular geometry pre and post PEA.

Parameter	Pre operative value	Post operative value	P value
RVEDVi (mL)	98 +/− 24	72 +/− 13	<0.0001
RVESVi (mL)	57 +/− 21	33 +/− 10	<0.0001
RVSV (mL)	80 +/− 19	73 +/− 15	0.05
RVEF (%)	43 +/− 10	53 +/− 7	<0.0001
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.

Table 3
Functional and haemodynamic changes.

Parameter	Pre operative	Post operative	P value
NYHA	2.8 +/− 0.7	1.1 +/− 0.4	<0.0001
6MWD (m)	431 +/− 98	520 +/− 83	<0.0001
mPAP (mm Hg)	40 +/− 14	23 +/− 5	0.001
Cardiac index (L/min/m²)	2.3 +/− 0.7	3.1 +/− 0.5	<0.0001

5. Conclusions

RV to LV volume ratio, measurable on cardi[illegible] provides information concerning both RV enlargement f[illegible]terload and LV underfilling as a consequence of impai[illegible] pulmonar[illegible]w, geometric alterations and ventricular remodeling, [illegible]e are impor[illegible] pathophysiological mechanisms in CTEPH. W[illegible]highli[illegible]he poten[illegible]relevance of the RV:LV volume ratio on MR[illegible] clinically [illegible]ant[illegible]relate of baseline functional status, baseli[illegible]VR and[illegible]ange in[illegible]ional status, after successful PEA surgery in[illegible]PH pa[illegible]ts.

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