Right ventricular volume and its relationship to functional tricuspid regurgitation

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ABSTRACT

Background: Significant right ventricular (RV) dilatation has long been considered integral to the pathogenesis of functional tricuspid regurgitation (FTR).

Objectives: To explore the relationship of RV dilatation and FTR in patients with 'pure' RV volume overload.

Methods: Patients (>17yrs) with RV dilatation due to pre-tricuspid shunts (atrial septal defect; ASD and/or partial anomalous pulmonary venous drainage; PAPVD) referred to our service (2000–2019) were retrospectively identified. Those with pulmonary hypertension, primum ASD or left-heart disease were excluded. Using standard cardiac MRI protocols, RV, right atrial and TV parameters were measured and compared.

Results: Of 52 consecutively eligible patients (42 ± 15yrs, 25 males), 25 had ASDs, 13 had PAPVD and 14 had both conditions. All were in sinus rhythm and none had pulmonary regurgitation. Left and right ventricular ejection fractions were normal (LVEF 63 ± 8%, RVEF 56 ± 8%). Indexed RV end-diastolic volumes (RVEDVi) were moderately increased (males 148 ± 33 mL/m^2 and females 141 ± 42 mL/m^2, range 95–267 mL/m^2). Despite substantial RV volume overload, no patients had severe tricuspid regurgitation (TR). Only two had > mild TR. There was a weak correlation between tricuspid annular diameter and both degree of RV dilatation (r = 0.37; p = 0.01) and degree of TR (r = 0.38; p = 0.006). There was a similarly poor correlation between right atrial dimensions and the degree of TR (r = 0.34; p = 0.02).

Conclusion: When RV dilatation is simply due to volume overload, we find that significant TR is extremely rare. This gives an important and novel insight; that RV dilatation *per se* does not result in FTR.

1. Introduction

Despite our improved understanding of the incremental morbidity and mortality attributable to significant tricuspid regurgitation (TR), its pathophysiology remains incompletely understood. TR may be caused by intrinsic abnormalities of the tricuspid valvular apparatus ('primary TR'), although much more commonly it occurs in conjunction with volume or pressure overload of the right ventricle and structurally normal tricuspid valve (TV) leaflets, so-called 'functional TR' (FTR) [1]. Left-sided valvular or ventricular dysfunction and resultant or primary pulmonary hypertension have been described as the predominant driving forces behind the haemodynamic and structural disturbance resulting in FTR, as a consequence of RV dilatation [2].

Significant right ventricular (RV) dilatation has therefore long been considered integral to the pathogenesis of FTR, analogous to the relationship between left ventricular (LV) dilatation and functional mitral regurgitation (FMR). In the left heart, large and uniform papillary muscles play a major role in supporting the mitral apparatus and LV dilatation pulls these apart, in turn stretching the mitral annulus (via traction on the chordae) [3] and producing FMR. By contrast to the situation in the left heart, the papillary muscles in the RV are smaller, not uniformly disposed and do not support the tricuspid annulus well. The aim of our study was therefore to explore the relationship of RV dilatation and FTR in patients with "pure" RV volume overload, from isolated pre-tricuspid shunts; either atrial septal defect (ASD) and/or partial anomalous pulmonary venous drainage (PAPVD). We hypothesised that FTR would be much less likely to occur, from simply RV dilatation alone.

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2. Methods

We conducted a comprehensive search of our Adult Congenital Heart Disease (ACHD) database, at a quaternary level specialist centre, in order to identify all patients with PAPVD and/or ASD who had cardiac MRI (CMRI) imaging performed at our centre. This was a cross-sectional study. We included those individuals aged ≥ 17yrs who had been seen at least once since January 2000. Those with primum ASD, organic TV disease, significant pulmonary hypertension and left ventricular or valvular disease were excluded. Significant pulmonary hypertension was defined as an estimated systolic pulmonary artery pressure (SPAP) > 50 mmHg on transthoracic echocardiography or invasively measured mean pulmonary artery pressure (mPAP) > 25 mmHg on a haemodynamic study. We defined 'RV volume overload' as a condition where the Qp:Qs ratio exceeded 1.0. This study was approved by our locally appointed ethics committee (Sydney Local Health District; Sydney Local Health District Ethics Review Committee, RPAH Zone, ID 2020/ETH00740) and complies with the Declaration of Helsinki. Informed consent was obtained from all subjects (or their guardians). Neither patients, nor the public, were involved in the design and conduct of this study. Deidentified participant data are available upon reasonable request from the corresponding author.

Standard 1.5 T MR (GE system) imaging included cines of the left-ventricular long axis, 4-Chamber (4Ch) and short-axial (SAX) views. RV volumes were calculated by manual segmentation of sequential SAX cine slices with endocardial outlines and compared to reference standards for age and sex, according to standard recommendations [4,5]. Through-plane phase contrast imaging for atrioventricular valve (AV) inflow and transaortic (AO) outflow was performed. Tricuspid regurgitant volume (=RV stroke volume – pulmonary forward flow) and TR regurgitant fraction (TR volume/RV stroke volume × 100%) were calculated. We quantified TR fraction according to recommendations from current guidelines as mild ≤ 15%, moderate 16–25%, moderately severe 26–48% and severe > 48% [6,7]. No patients had pulmonary regurgitation. All images obtained were imported into the viewing software (Osirix®) for further analysis. Tricuspid annular diameter was measured at end-diastole in a 4-Ch view. In order to indirectly measure RV geometry we measured the RV end-systolic eccentricity index (RVEI) using the SAX stack in a mid-ventricular slice, as well as the Sphericity Index ((RV mid-diameter × RV length)/(RV basal diameter)) in a 4Ch view in systole, as previously described [8,9]. Right atrial (RA) area was measured in a 4-Ch view with endocardial outline. RA volume was estimated using 4-Ch and 2-Ch (RVLA) RA area measurements (RA volume (RAV) = 3.08*(2C area) + 3.36*(4C area) −44.4) [10] and the results compared to current reference standards for age and gender [11]. Four patients had incomplete data to allow measurement of annular dimensions and right atrial area/volume, and a further 2 patients had insufficient RVLA images to calculate RAV. In 15 randomly selected patients, a second observer measured the variables of tricuspid valve morphology and RA area to assess interobserver variability.

2.1. Statistical analysis

Statistical analysis was performed using SPSS version 26 (IBM, Armonk, New York). All data are presented as n (%) for categorical variables and mean ± standard deviation for normally distributed continuous variables. Comparative analysis of continuous variables and inter-observer variability was performed using the Pearsons Correlation method, with a two-tailed significance inferred at $p < 0.05$.

3. Results

3.1. Patient characteristics

We identified 52 eligible patients (≥17yrs) for inclusion in the study. Mean age was 42 ± 15yrs and 48% (n = 25) were male. 25 (48%) had

ASDs, 13 (25%) had PAPVD and 14 (27%) had both conditions. No individuals had any history of hypertension or coronary artery disease, and none were on any regular cardiovascular medications. CMRI imaging had been performed in all patients between 2009 and 2019 using identical imaging protocols (as described above). All patients were in sinus rhythm. Left and right ventricular ejection fractions (EF) were normal (LVEF 63 ± 8%, RVEF 56 ± 8%) and mean shunt fraction (Qp: Qs) was 1.9 ± 0.6.

3.2. Right atrial and ventricular indices

Indexed RV end-diastolic volumes (RVEDVi) for both genders were moderately increased (M 148 ± 33 mL/m^2 and F 141 ± 42 mL/m^2) and the range of RVEDVi for the whole cohort was 95–267 mL/m^2. Right atrial area and volume measurements were also increased; mean RA area 27.4 ± 6.3 cm^2, RAV 132 ± 41.4 mL and RAV indexed for BSA (RAVi) was 73.1 ± 23.6 mL/m^2 (range of 39.1 – 151.3 mL/m^2) (Fig. 3A).

3.3. Tricuspid valve structure and function

All subjects had trileaflet tricuspid valves with no calcification in any patient. Mean TV annular diameter was 38 ± 4.8 mm (range 29–48) (Fig. 3C) and there was no significant tricuspid valve tethering with mean tenting height of 5.2 mm and tenting area 0.9 cm^2. The mean TR fraction was only 5.6 ± 6.7% and TR volume 9 ± 11 mL. With regard to right ventricular dimensions and geometry, we found that basal right ventricular width was increased relative to the mid-segment and longitudinal dimensions, as reflected in an RV sphericity index of 5.2, RV basal-mid-cavity ratio 1.2 and RV width-length ratio of 0.6.

3.4. Relationship of right ventricular volume to tricuspid regurgitant fraction

The relationship between RVEDVi and TR fraction is shown in Fig. 1A. Below an RVEDVi of 170 mL/m^2, the threshold for severe RV dilatation, only two patients had mild TR (TR fraction 15.7 and 17.8%). Of the 14 patients with RVEDVi > 170 mL/m^2, TR fraction was < 15% in 12, moderate (24%) in one and moderately severe (31%) in another (who had an RVEDVi 267 mL/m2). No patients with RVEDVi > 170 mL/m^2 had TR fraction > 31% or severe TR from RV volume overload (Fig. 1A).

The correlation between RVEDVi and TV annular diameter was relatively weak also (r = 0.37; p = 0.01) (Fig. 1B), however there was a modest correlation between RA area or volume and TV annulus diameter (r = 0.59 and r = 0.54 respectively, both p < 0.001). A weak but significant correlation was demonstrated between TV annular diameter and degree of TR (r = 0.38; p = 0.006) as well as right atrial parameters (RAVi r = 0.34, p = 0.02 and RA area r = 0.36, p < 0.01) and degree of TR (see Fig. 2). A modest negative correlation was found between RVEI and TR fraction (r = -0.39; p = 0.007) and no significant correlation was found between RVEF and TR fraction (r = -0.2; p = 0.08). There was good correlation between RVEDVi and right atrial dimensions (r = 0.74 and p < 0.001 for RAVi and for RA area).

3.5. Interobserver variability

For the 15 patients in whom the tricuspid valve morphology and RA area were measured by a second observer, interobserver variability was excellent. The correlations between the variables obtained by the 2 observers were as follows; r = 0.92, p < 0.001 for tricuspid annulus diameter, r = 0.85, p < 0.001 for tricuspid valve tenting height, r = 0.94, p < 0.001 for tricuspid valve tenting area and r = 0.97, p < 0.001 for right atrial area.
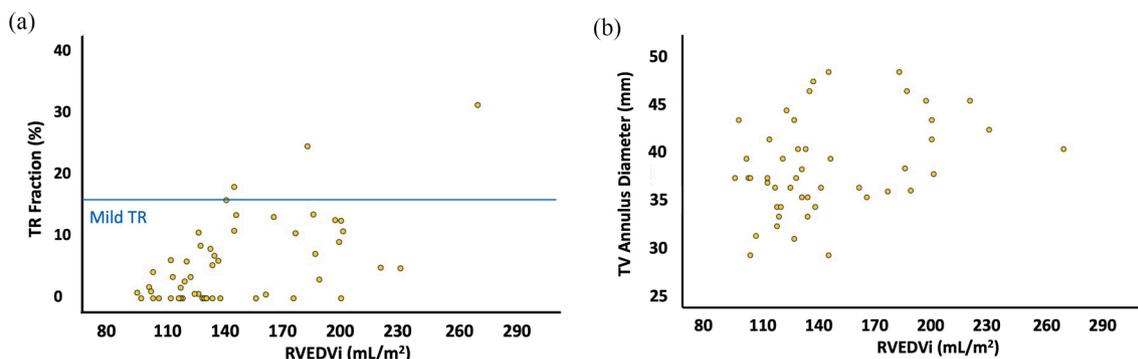
(a)

(b)

Fig. 1. Relationship of right ventricular (RV) dilatation with tricuspid regurgitation (TR fraction) and tricuspid annular dimensions. In patients with isolated RV volume overload, RV end-diastolic volume index (RVEDVi) correlated poorly with tricuspid regurgitation, r = 0.54; p < 0.01 (1A) and annular diameter, r = 0.37; p = 0.01 (1B).
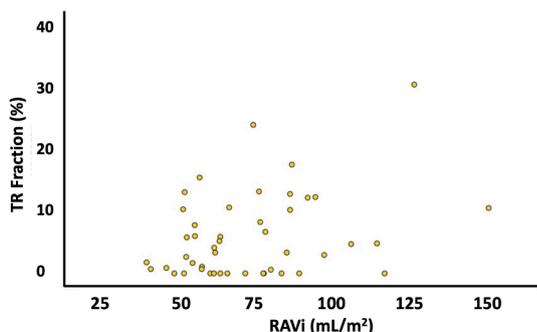

Fig. 2. Relationship of right atrial (RA) dilatation with tricuspid regurgitation (TR fraction), r = 0.36; p < 0.01.

4. Discussion

In this cohort of patients with moderate and severe RV dilatation, we observed that only a very small fraction (2 patients, 3.8%) had clinically significant TR. In addition, tricuspid annular dimensions correlated poorly with increasing RV size but modestly with increasing right atrial size or volume, and there was only a weak correlation between TV annular diameter or RA dimensions and TR fraction. Contrary to the common belief that significant RV dilatation and accompanying tricuspid annular enlargement are integral to the pathophysiology of FTR, the present study demonstrates that even severe RV volume overload in isolation is usually associated with only trivial or mild TR.

The pathophysiology of FTR is complex and is thought to consist of three dominant mechanisms including: 1) tricuspid annular dilatation 2) distortion of the spatial relationships of the tricuspid apparatus and 3) alterations in TA geometry and dynamics, all three reflective of initial insults to right ventricular or right atrial geometry [12]. The precise interplay or combination of these factors in FTR, however, remains poorly understood. The fact that the RV may drive the occurrence of FTR not only by way of chamber dilatation, but also by way of alterations in RV geometry, has been explored by Topilsky et al. who described alterations in RV geometry corresponding to the underlying aetiology of FTR [9]. Longitudinal RV deformation was observed in patients with FTR associated with pulmonary hypertension, compared to the more significant RV basal and TV annular dilatation (or conical dilatation) in patients with idiopathic FTR. The complex nature of the pathophysiology of FTR is further illustrated in a cohort of patients all with severe pulmonary hypertension, in whom only half had significant TR [13].
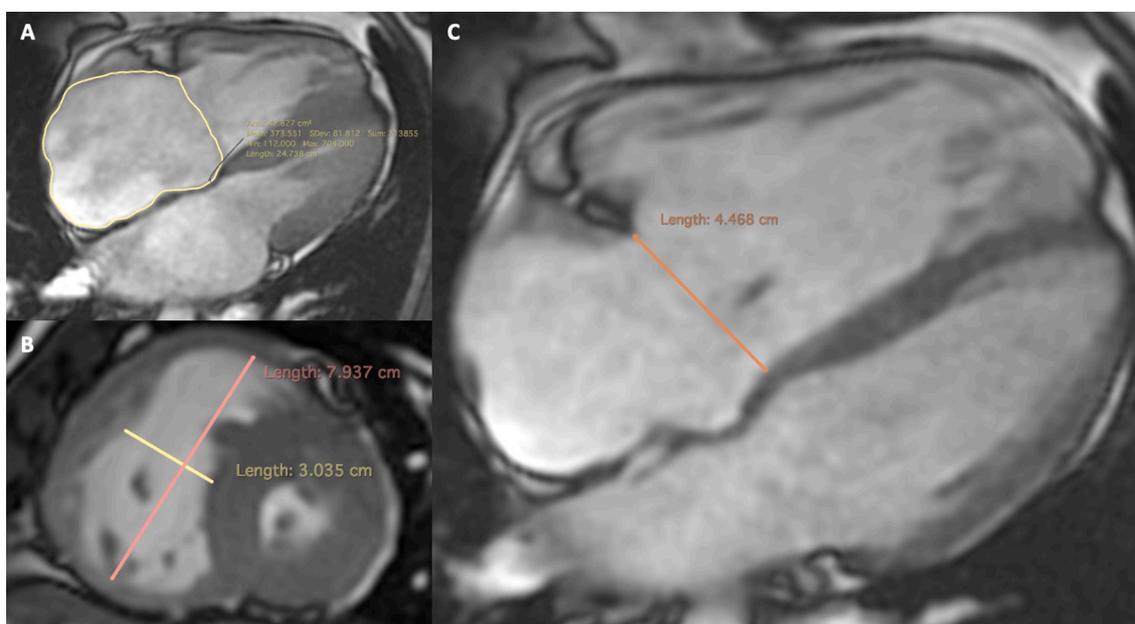

Fig. 3. Cardiac magnetic resonance imaging (CMR) assessment of (A) right atrial area, measured in 4-Ch view at end-ventricular systole (B) RV end-systolic eccentricity index (RVEI) using the SAX stack in a mid-ventricular slice and (C) tricuspid annular diameter, measured at end-diastole in a 4-Ch view.

The importance of the right atrium as a determinant of FTR has also recently been highlighted. In patients with atrial fibrillation (AF) who develop FTR (so-called AF-TR) [14], tricuspid annular dilatation is more closely correlated with right atrial, as opposed to right ventricular volumes, when compared to those with FTR from left-heart causes. Muraru et al. reported that RA volume appeared to be the major determinant of annular dilatation and FTR, irrespective of right ventricular loading conditions or the aetiology of RV dilatation [15].

Many previous mechanistic studies of FTR have been hindered by heterogeneity of the underlying aetiology of FTR as well as patient characteristics [8]. Our cohort with 'pure' RV volume overload from pre-tricuspid shunts, without atrial arrhythmia or pulmonary hypertension, therefore provides a rare opportunity to study the relationship of the tricuspid valve and right heart chambers. We found that despite markedly increased right ventricular volumes and volume loaded right atria, there was very little associated tricuspid regurgitation, in this unique cohort. In addition, tricuspid annular dimensions correlated poorly with both RV size and degree of TR. This is relevant as it suggests that additional factors are likely necessary for the development of FTR, over and above simply dilatation of the right heart chambers.

As we deliberately chose to study a patient group with "pure" right heart volume overload, without concomitant left heart disease or pulmonary hypertension, the patients in our study represented a much younger cohort (42 ± 15 years) than has characteristically been included in studies of FTR. Whilst RV geometric changes in our cohort were similar to those found by Topilsky et al. in subjects with idiopathic (or AF-TR), additional factors contributing to the development of FTR in older cohorts may include age-related abnormalities of the tricuspid annulus itself. Previous authors have suggested that a "weaker" fibrous skeleton of the TV annulus may be associated with advanced age and female gender, in patients with AF [16].

The overall prevalence of moderate and severe FTR has been found in between 14 and 54% of subjects with left heart disease, pulmonary hypertension, atrial fibrillation or RV dysfunction [13,17]. By contrast, we find that significant TR is extremely rare when RV dilatation is simply due to volume overload. This gives an important and novel insight; that RV dilatation *per se* does not result in FTR and emphasises the likelihood of a more complex and multifactorial pathogenesis for the development of FTR. Further research to differentiate FTR subtypes is important not only for future mechanistic insights, but in order to adequately prescribe therapeutic intervention at a time when multiple novel transcatheter devices for FTR are on the horizon.

4.1. Limitations

The primary limitations of this study include its relatively small sample size and cross-sectional nature. In addition, the indirect method for TR quantification using CMRI. The same methods for TR quantification, however, have been previously described and utilised in several other studies evaluating FTR [6,18]. Due to the limited temporal resolution of CMRI, timing of tricuspid annular measurements precisely with end-diastole can be challenging, however all measurements were recorded using the same frame to limit variability in this regard. In addition, the use of 2-dimensional annular measurements are known to be subject to significant limitations, given the complex 3D geometry of the tricuspid annulus.

5. Conclusions

Tricuspid regurgitation is associated with significant morbidity and mortality with few therapeutic options currently available, not least due to our incomplete understanding of this complex condition. Few studies have examined pathogenically homogenous cohorts to address the contribution of different underlying mechanisms in the pathophysiology of FTR. This study contributes to our growing understanding of the interplay between the right heart chambers and tricuspid apparatus and

demonstrates that when RV dilatation is simply due to volume overload, significant TR is extremely rare. This gives an important and novel insight; that RV dilatation *per se* does not result in FTR and highlights the importance of an improved understanding of FTR subtypes to better elucidate the mechanisms of FTR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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