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CLINICAL RESEARCH
Valvular and congenital heart disease

Refining the assessment of pulmonary regurgitation in adults after tetralogy of Fallot repair: should we be measuring regurgitant fraction or regurgitant volume?

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Aims Pulmonary regurgitation (PR) is an important determinant of outcome after tetralogy of Fallot (TOF) repair. The physiologic impact of PR on the right ventricle remains incompletely understood. We hypothesized that a volumetric expression of PR would be a better measure of ventricular preload and a more accurate reflection of degree of insufficiency.

Methods and results Patients ($n = 64$) with magnetic resonance imaging after TOF repair were identified. PR was quantified using: (i) phase contrast (PC) analysis of main pulmonary artery flow and (ii) differential right and left ventricular stroke volumes. PR was expressed as a volume (PR_{volume}) and percentage of total forward flow ($PR_{fraction}$). The median $PC_{PR\ volume}$ was 19 mL/m^2 (range 0–63 mL/m^2) and $PC_{PR\ fraction}$ was 29% (range 0–58%). $PR_{fraction}$ was found to be highly variable in terms of absolute PR_{volume}. In those with significant PR, PR_{volume} was better than $PR_{fraction}$ for the identification of severe RV dilation (receiver-operator curve area: 0.83 vs. 0.71, $P = 0.003$). PR_{volume} using PC analysis was better at differentiating moderate from severe RV dilation ($P = 0.005$) as compared with $PR_{fraction}$ ($P = 0.064$).

Conclusion PR_{volume} and $PR_{fraction}$ are not interchangeable. PR_{volume} may be a more accurate reflection of RV preload and may better represent physiologically significant PR as compared with $PR_{fraction}$.

Keywords MRI • Tetralogy of Fallot • Pulmonary regurgitation

Introduction

Pulmonary regurgitation (PR) is now recognized as an important determinant of late outcome after tetralogy of Fallot (TOF) repair.[1] A common finding after right ventricular (RV) outflow tract surgery, pulmonary insufficiency may result in a cascade of haemodynamic sequelae that can include RV dilation, RV dysfunction, and ultimate deterioration in clinical status.[2] Impaired exercise tolerance, ventricular arrhythmia, and sudden death have all been associated with the secondary effects of chronic PR.[1,3–5] With the growing population of adult patients with TOF who have residual PR, determining the optimal method of PR assessment is of increasing importance.

Owing to the accuracy and reproducibility of its measurements, cardiac magnetic resonance (CMR) imaging is accepted as the imaging modality of choice for the quantification of PR and assessment of RV size and systolic function.[6–8] For these reasons, CMR evaluation is recommended during the routine follow-up of patients after TOF repair.[8,9]

However, despite the importance of PR in this population, PR measurement and the assessment of its physiological impact remain incompletely understood. The expression of the

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regurgitant burden as a fraction of forward pulmonary flow is commonplace and is beginning to form the basis of recommendations for treatment. Because PR fraction ($PR_{fraction}$) may be highly variable in terms of absolute volumes (PR_{volume}), we speculated that a volumetric measurement of PR may be a better measure of ventricular preload and therefore the more accurate measure of the degree of insufficiency. We therefore sought to evaluate the optimal method of PR quantification in patients after repair of TOF.

Methods

Subjects

Consecutive patients with repaired TOF and CMR examinations at the Toronto Congenital Cardiac Centre for Adults, University Health Network from 2004 to 2006 were identified from an existing cardiology database. Patients were included if there was echocardiographic evidence of PR and if there was a complete CMR study consisting of acquisition of biventricular volumes and flow data for quantification of PR. Candidates were excluded if: (i) CMR data was insufficient for PR analysis, (ii) a prosthetic pulmonary valve had been implanted, (iii) residual shunt lesions were seen, and/or (iv) valvular incompetence at a valve other than the pulmonary valve was more than mild on echocardiography. The local Institutional Research Ethics Board approved the study.

Patient data

Clinical data were retrospectively abstracted from hospital medical records including date of birth, gender, anatomic diagnoses, age and type of each surgical procedure, and age at CMR evaluation. Transthoracic echocardiographic data within 1 year of the CMR study were reviewed, particularly for assessment of valvular regurgitation and identification of residual shunt lesions, and the results were recorded.

Cardiac magnetic resonance

The CMR protocols and technical aquisition parameters utilized at our institution for the evaluation of global ventricular systolic function, ventricular volumes, and PR have been previously published in detail.[10–12] Briefly, studies were performed using a commercially available 1.5 T scanner (Signa Horizon, GE Medical Systems, Waukesha, WI, USA). Steady-state free-precession cine imaging of the ventricles in two- and four-chamber planes was performed followed by prescription of contiguous short-axis slabs (8–10 mm thick) oriented perpendicular to the long-axis of the left ventricle (LV) extending from the base to the apex. Phase contrast (PC) analysis of flow (antegrade and retrograde) in the main pulmonary artery was achieved using an ECG-triggered fast gradient echo cine pulse sequence at end-expiration at a location just below the pulmonary artery bifurcation derived from double oblique plane prescriptions across the main pulmonary artery.

End-diastolic (maximal) and end-systolic (minimal) volumes, stroke volumes (SV), and ejection fractions (EF) for the RV and LV were obtained using a commercially available software package (MASS, Medis, Leiden, The Netherlands).[13] Analysis of flow in the main pulmonary artery was derived using previously published methodology[12] and commercially available software (FLOW, Medis, The Netherlands). All volumes were adjusted to body surface area and corresponding *z*-scores were calculated using published normative data.[14]

CMR was used to quantify PR using two distinct methods. With PC analysis of flow through the main pulmonary artery, retrograde flow or indexed $PC_{PR\ volume}$ and $PC_{PR\ fraction}$ (retrograde flow/antegrade flow volume × 100%) were determined. With ventricular SV differential measurements derived from steady-state free-precession cine imaging, indexed regurgitation volume or $SV_{PR\ volume}$ (RVSV − LVSV) and $SV_{PR\ fraction}$ (RVSV − LVSV/RVSV × 100%) were calculated.

A single investigator (R.M.W.) performed all CMR measurements used in the primary analysis. To examine intra-observer reliability, additional measurements from 10 randomly chosen studies (for a total of 20 studies) were performed by the same observer. To determine inter-observer reliability, 10 studies were randomly selected and measurements were compared between two observers (R.M.W. and A.P.). Repeat measures were made within a 3-month time interval.

Statistical analysis

Data analyses were performed using SPSS statistical software (Version 11.5, 2002). Descriptive data were expressed as medians with interquartile ranges (IQRs), unless otherwise specified. Mann–Whitney and χ^2 tests were used to compare groups, as appropriate. Comparisons of PR_{volume} or $PR_{fraction}$ between patients with mild, moderate, and severe RV dilation were performed using the Kruskal–Wallis test. Correlations were examined using the Spearman correlation co-efficient. Statistical significance was set at a *P*-value <0.05 (two-sided). In the subset of patients with significant PR (at least moderate insufficiency defined as regurgitation fraction $\geq$20%), receiver-operator curves (ROC) were constructed to examine the ability of the differing expressions of PR (PR_{volume} and $PR_{fraction}$) as well as differing techniques for PR quantification (PC vs. SV differentials) to detect significant RV dilation, defined as indexed RV end-diastolic volume (RVEDVi) $\geq$170 mL/m^2. This cut-point was used because prior studies from our centre and others have suggested that RVEDVi > 160–170 mL/m^2 may be an appropriate threshold whereby pulmonary valve replacement should be considered in the presence of significant PR in the asymptomatic patient with repaired TOF.[11,15,16] Agreement between methods for PR quantification (PC vs. SV differentials) and intra- and inter-observer variabilities were evaluated using intra-class correlation co-efficients.

Results

Patient population

A total of 131 patients with TOF and CMR data from 2004 until 2006 were identified: however, 67 patients were excluded as they did not meet the inclusion criteria, as detailed above [specifically, there was absence of PR and/or presence of a prosthetic pulmonary valve ($n = 29$), more than mild valvular insufficiency at a valve other than the pulmonary valve ($n = 28$), residual intracardiac shunt lesions ($n = 9$), and an incomplete CMR data set ($n = 1$)]. CMR data was of sufficient quality for study analysis in all patients who met inclusion criteria ($n = 64$). The clinical and CMR characteristics of the study population are summarized in *Table 1*. Detailed surgical reports were available for 47 (73%) patients.

Those with transannular patches had larger RV volumes as compared with those without patching across the pulmonary valve annulus [RVEDVi 185 mL/m^2 (IQR 129–202) vs. 137 mL/m^2 (IQR 120–160), $P = 0.01$; indexed RV end-systolic volume 97 mL/m^2 (IQR 64–113) vs. 77 mL/m^2 (IQR 59–89), $P = 0.03$] as well as more PR [$PC_{PR\ volume}$ 38 mL/m^2 (IQR 21–39) vs. 17 mL/m^2 (IQR 2–28), $P < 0.001$; $SV_{PR\ volume}$ 34 mL/m^2 (IQR 12–42) vs. 16 mL/m^2 (IQR 4–29), $P = 0.04$; $PC_{PR\ fraction}$ 43%

Table 1 Characteristics of the study population[a]

Baseline characteristics	
Total population	$n = 64$
Male gender	$n = 38$ (59%)
Age at TOF repair (years)	5 (IQR 4–8)
Age at CMR study (years)	32 (IQR 24–40)
Time from TOF repair to CMR (years)	23 (IQR 19–32)
Type of TOF repair	
Transannular patch	25 (39%)
Non-transannular patch	22 (34%)
Conduit	0 (0%)
Details unknown	17 (27%)
CMR characteristics	
PR volume by phase contrast (mL/m^2)	20 (IQR 10–35)
PR volume by stroke volume Δ[b] (mL/m^2)	19 (IQR 6–32)
PR fraction by phase contrast[c] (%)	29 (IQR 13–42)
PR fraction by stroke volume Δ[d] (%)	30 (IQR 10–41)
RVEDVi (mL/m^2)	148 (IQR 121–176)
RVEDVi *z*-score	5 (IQR 3–7)
RVESVi (mL/m^2)	83 (IQR 61–101)
RVSV (mL/beat)	120 (IQR 97–136)
RVEF (%)	44 (IQR 40–50)
LVSV (mL/beat)	81 (IQR 69–96)
LVEF (%)	59 (IQR 54–63)

EF, ejection fraction, IQR, inter-quartile range; LV, left ventricle; LVSV, left ventricular stroke volume; PR, pulmonary regurgitation; RV, right ventricle; RVSV, right ventricular stroke volume; RVESVi, indexed right ventricular end-systolic volume; RVEDV, right ventricular end-diastolic volume; RVEDVi, indexed right ventricular end-diastolic volume; TOF, tetralogy of Fallot; CMR, cardiac magnetic resonance.

[a] Continuous variables reported as medians.

[b] PR volume (stroke volume Δ) = (RVSV − LVSV).

[c] PR fraction (phase contrast) = (retrograde flow)/(antegrade flow).

[d] PR fraction (stroke volume Δ) = (RVSV − LVSV)/RVSV.

Table 2 Correlations between pulmonary regurgitation and ventricular size, stroke volume, and ventricular function

Variable	*R*-value	*P*-value
RVEDVi		
PC$_{\text{PR volume}}$	0.83	<0.001
PC$_{\text{PR fraction}}$	0.75	<0.001
SV$_{\text{PR volume}}$	0.77	<0.001
SV$_{\text{PR fraction}}$	0.69	<0.001
RVESVi		
PC$_{\text{PR volume}}$	0.73	<0.001
PC$_{\text{PR fraction}}$	0.68	<0.001
SV$_{\text{PR volume}}$	0.58	<0.001
SV$_{\text{PR fraction}}$	0.53	<0.001
RVSV		
PC$_{\text{PR volume}}$	0.62	<0.001
PC$_{\text{PR fraction}}$	0.54	<0.001
SV$_{\text{PR volume}}$	0.72	<0.001
SV$_{\text{PR fraction}}$	0.63	<0.001
LVSV		
PC$_{\text{PR volume}}$	−0.34	0.007
PC$_{\text{PR fraction}}$	−0.41	0.001
SV$_{\text{PR volume}}$	−0.38	0.002
SV$_{\text{PR fraction}}$	−0.49	<0.001
RVEF		
PC$_{\text{PR volume}}$	−0.27	0.03
PC$_{\text{PR fraction}}$	−0.31	0.02
SV$_{\text{PR volume}}$	−0.02	0.90
SV$_{\text{PR fraction}}$	−0.03	0.85
LVEF		
PC$_{\text{PR volume}}$	−0.15	0.24
PC$_{\text{PR fraction}}$	−0.19	0.14
SV$_{\text{PR volume}}$	−0.04	0.75
SV$_{\text{PR fraction}}$	−0.10	0.43

(IQR 29–47) vs. 24% (IQR 4–35), $P < 0.001$; SV$_{\text{PR fraction}}$ 47% (IQR 21–50) vs. 28% (IQR 9–41), $P = 0.008$].

Methods for quantification of pulmonary regurgitation

Analysis of flow through the main pulmonary artery by PC imaging was possible in all but two patients and SV differential calculations were achieved in all patients. The median indexed PR$_{\text{volume}}$ and PR$_{\text{fraction}}$ derived by PC analysis and SV differentials were similar: PC$_{\text{PR volume}}$ 20 mL/m^2 (IQR 10–35) vs. SV$_{\text{PR volume}}$ 19 mL/m^2 (IQR 6–32); PC$_{\text{PR fraction}}$ 29% (IQR 13–42) vs. SV$_{\text{PR fraction}}$ 30% (IQR 10–41). The intra-class correlation co-efficient for PC and SV differential measurements of PR$_{\text{volume}}$ was 0.89 (95% CI 0.82–0.93, $P < 0.001$) and was 0.88 (95% CI 0.81–0.93, $P < 0.001$) for PC and SV differential measurements of PR$_{\text{fraction}}$.

All quantitative measures of PR were well-correlated with RV size and biventricular SVs, as shown in *Table 2*. However, for a given method of PR quantification (i.e. PC imaging or SV differential), measures of RV volumes were more closely correlated with indexed PR$_{\text{volume}}$ when compared with PR$_{\text{fraction}}$. RVSV was positively correlated with, and LVSV was negatively correlated with, measures of PR. Neither RVEF nor LVEF had a strong correlation with PR.

Quantification of pulmonary regurgitation: use of absolute volume vs. fraction

The relationship between PR volume and PR fraction is demonstrated in *Figure 1*. Despite reasonable correlations between these expressions of PR, significant variability existed between the measures in individual patients and thus were not interchangeable. For instance, a PR$_{\text{fraction}}$ of 52% can represent a PR$_{\text{volume}}$ between 31 and 65 mL/beat/m^2 and a PR$_{\text{volume}}$ of 34 mL/beat/m^2 can represent a PR$_{\text{fraction}}$ between 35 and 58% This dispersion from the regression line was most apparent with more signficant degrees of PR.

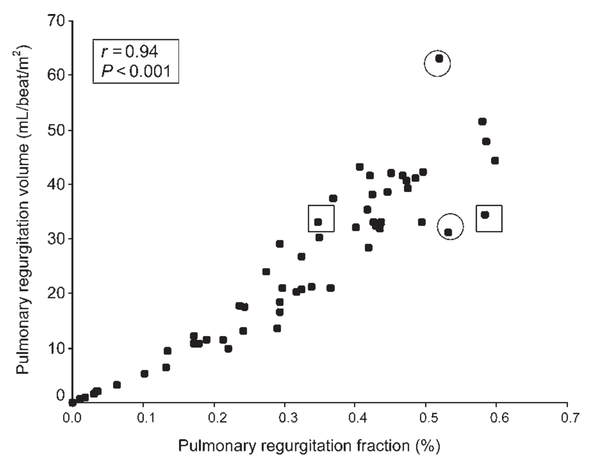

Figure 1 Comparison between quantification of pulmonary regurgitation volume and fraction by phase contrast imaging. Scatter plot demonstrating that, for a pulmonary regurgitation fraction of 52% in two patients (designated by circles), regurgitant volume in one patient may be twice that of the other (i.e. 65 vs. 31 mL/beat/m^2). Similarly, for a pulmonary regurgitation volume of 34 mL/beat/m^2 in two patients, regurgitant fractions may range between 35 and 58%.

In those patients with significant PR, PR_{volume} was better than $PR_{fraction}$ for identification of severe RV dilation using either PC analysis (ROC area for volume vs. fraction: 0.83 vs. 0.71, $P = 0.003$) or SV differential methods (ROC area for volume vs. fraction: 0.74 vs. 0.64, $P = 0.004$). When RVEDVi was classified as mild dilation (110–140 mL/m^2), moderate dilation (141–170 mL/m^2), or severe dilation (>170 mL/m^2), indexed $PC_{PR\ volumes}$ were better able to discriminate between moderate and severe RV dilation ($P = 0.005$) compared with $PC_{PR\ fraction}$ ($P = 0.06$), as illustrated in *Figure 2*. When comparing PC and SV techniques for quantification of PR, there was a trend for PC measures of PR_{volume} to better identify signficant RV dilation when compared with SV differential methods (ROC area: 0.83 vs. 0.74, $P = 0.07$).

Intraobserver and interobserver variability in the assessment of pulmonary regurgitation

Intra-observer intra-class correlation co-efficients for $PC_{PR\ fraction}$ and $PC_{PR\ volume}$ were 0.99 (95% CI 0.98–1.0) and 0.99 (95% CI 0.99–1.0), respectively. Inter-observer intra-class correlation coefficients for $PC_{PR\ fraction}$ and $PC_{PR\ volume}$ were 0.99 (95% CI 0.95–1.0) and 0.99 (95% CI 0.99–1.0), respectively. *P*-values for all intra-class correlation co-efficients were significant at $P < 0.001$.

Discussion

Over the past decade, the functional and prognostic importance of PR and related haemodynamic sequelae have been firmly established in patients with repaired TOF. Furthermore, the use of CMR in the assessment of RV volumes and quantification of PR has become established as the 'gold standard' for longitudinal assessment.

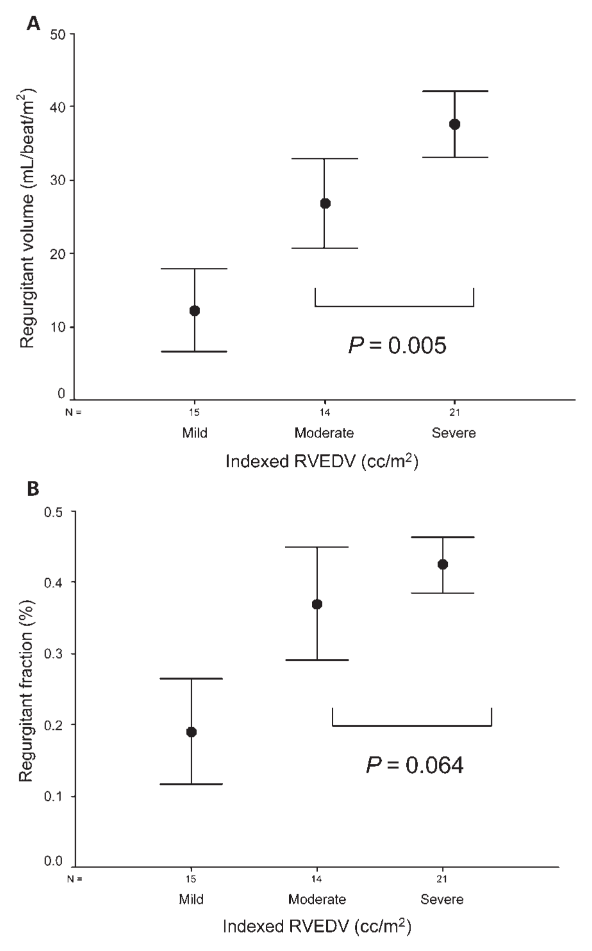

Figure 2 Regurgitation volume (*A*) and fraction (*B*) compared with right ventricular end-diastolic volume (indexed). Indexed pulmonary regurgitation volume differentiates moderate from severe right ventricular dilation, whereas regurgitation fraction does not (right ventricular end-diastolic volume categories: mild = 110–140 mL/m^2, moderate = 141–170 mL/m^2, severe >170 mL/m^2).

Nonetheless, while the quantification of valvular regurgitation using CMR has been extensively studied and validated for the aortic and mitral valves,[17–20] considerably less has been published regarding the use of CMR for the assessment of PR and its relevance to functional outcomes.[7,21–23] Indeed, our understanding of the optimal method for quantifying PR, and its relationship to secondary effects on the RV, remains incomplete. This study aimed to assess the current methods for describing PR using current and widely available CMR technology, in order to explore their ability to describe important secondary effects in individual patients and in an unselected population after repair of TOF. Our data suggest that the use of PR expressed volumetrically, rather than as a percentage of antegrade MPA flow, is a more appropriate method for quantification in both group data and in the assessment of individual patients.

In 1993, Rebergen *et al.*[7] demonstrated the feasibility and accuracy of PC analysis for PR quantification in 18 patients with repaired TOF. This landmark paper established CMR as the modality of choice for the assessment of PR, but used techniques that have been changed considerably in the interim or have been completely abandoned. For instance, the conventional gradient echo sequences with prospective gating for ventricular imaging as used by Rebergen *et al*. have been replaced with steady-state free-precession cine imaging with retrospective gating, with consequent improvements in accuracy of volumetric measurements.[24] In addition, velocity encoding mapping could not be performed in almost 20% of the patients reported by Rebergen due to signal void, a limitation that is far less frequent with current CMR platforms.[25,26] Additionally, over half of the patients reported in this original series were children, making it difficult to extrapolate the potential relationships between quantified PR and its secondary effects in a purely adult population, in which the chronic effects of PR, and its consequences, are clearly more relevant. Later work from the same group validated PR measurements by CMR in an exclusively pediatric population.[27] Although the clinical effects of PR, assessed using a variety of CMR techniques, have been addressed in several subsequent studies, to the best of our knowledge the current study is the first specifically focused on the CMR quantification of PR in an adult population and its secondary effects using contemporary CMR techniques.

Although our data demonstrate reasonable agreement between PR quantified by PC analysis and the SV differential technique using current CMR techniques, it should be noted that PC and SV derived measures may not be interchangeable. Application of the SV differential technique relies on the assumption that additional sources of volume loading (from shunts or other valvular lesions) have been excluded. On the other hand, data derived from PC velocity mapping may be significantly affected by technical concerns related to the susceptibility of this technique to phase errors imposed by various extrinsic factors associated with magnetic field inhomogeneities such as eddy currents and uncorrected concomitant gradients.[24,28] Differences between volumes derived from PC analysis when compared with SV differential data have been well established in the context of assessment of aortic regurgitation.[29,30] The optimal method for PR quantification will likely vary based on the characteristics of the individual patient as well as the strengths of a particular CMR laboratory.

More important is the way in which the information yielded by these techniques is interpreted. The expression of PR burden as a fraction of forward pulmonary flow or total SV (% pulmonary incompetence) is commonplace within published TOF literature and is beginning to form the basis of recommendations for assessment and treatment in individuals.[31,32] We would advise caution in this regard. From first principles, the expression of a percentage does not allow one to appreciate the magnitude of the numerator or denominator, and thus a similar fraction of PR may occur in a patient with a small volume of PR in the setting of normal RVSV and size and in a patient with a huge PR volume in the setting of raised SV and a grossly dilated RV. Clearly, the physiologic effects and the implications for treatment might be quite different, despite a similar PR fraction. This phenomenon is illustrated in selected patients highlighted in *Figure 1*; given the same $PR_{fraction}$ of $\sim$50%, the PR_{volume} differed by almost 100%.

This is not only of fundamental importance to the assessment of the individual, but also has implications for better understanding the mechanisms of the secondary effects of PR. While clearly, and as expected, there was close correlation between the methods of PR quantification and RV volumes, for example, there was closer agreement between PR_{volume} and RVEDVi when compared with $PR_{fraction}$. Furthermore, using ROC analysis in those with significant PR, PR expressed as an absolute volume was better able to predict important RV dilation compared with PR expressed as a fraction. This is not unexpected, given that ventricular preload is by definition expressed (at least in part) as a volume parameter, and (as already stated above) $PR_{fraction}$ may be highly variable in terms of absolute PR_{volume}.

Significant PR and severe RV dilation are not the only prerequisites for surgical referral for pulmonary valve replacement. There is a complex interplay of multiple factors, which include deteriorating clinical status (such as development of heart failure or arrhythmia), impaired exercise tolerance, and/or ventricular dysfunction. Nevertheless, the presence of important PR and consequent RV dilation are necessary factors in the overall equation that determines timing and suitability for pulmonary valve replacement.

Recommendations

A standard approach should be applied to data acquisition and analysis within an institution to ensure that CMR measurements are accurate and reproducible between patients and within patients between examinations. In order to have an internal 'cross-check' for the accuracy of PR quantification (both PC and SV differential methods are known to have inherent technical shortcomings, as discussed above), we propose that independent methods of PR quantification be applied, as feasible and appropriate, in each CMR study. Clinicians should be comfortable interpreting both PR_{volume} and $PR_{fraction}$, although indexed PR_{volume} may be the more sensitive and accurate expression of significant pulmonary incompetence when compared with expression of PR burden as a $PR_{fraction}$.

Limitations

The limitations in applicability inherent in a retrospective, single-centre study must be acknowledged. Although not available at present, follow-up data to determine predictive value of regurgitant volumes when compared with regurgitant fractions in determination of development of progressive RV dilation, RV dysfunction and deterioration of clinical status would be of great interest and will serve as the subject of future research endeavours at our centre.

Even though there may be obvious difficulties in establishing endocardial definition of the RV and delineation of the outflow tract in the absence of a pulmonary valve as suggested by others,[31] we believe that these shortcomings can be minimized in the presence of a consistent institutional protocol. We did exclude patients with additional valvular lesions or residual shunts in order to utilize the SV differential method for PR quantification, and in doing so, our study population may not be representative of a larger population of patients with repaired TOF. Finally, restrictive RV physiology[33,34] was not specifically assessed in this study and may be a confounder whereby a regurgitant volume is measured at the pulmonary valve but there is no increase in RV dimensions. In this setting, the SV differential method may not reflect the degree of insufficiency at the pulmonary valve.

Conclusions

PR_{volume} and $PR_{fraction}$ are not interchangeable measures of PR. Particularly, when assessing its implications in the individual patient, PR_{volume} may be a more accurate reflection of RV preload and may better represent the physiological significance of PR when compared with $PR_{fraction}$.

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