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


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 (PRvolume) and percentage of total forward flow (PRfraction). The median PCPR volume was 19 mL/m² (range 0–63 mL/m²) and PCPR fraction was 29% (range 0–58%). PRfraction was found to be highly variable in terms of absolute PRvolume. In those with significant PR, PRvolume was better than PRfraction for the identification of severe RV dilation (receiver-operator curve area: 0.83 vs. 0.71, P = 0.003). PRvolume using PC analysis was better at differentiating moderate from severe RV dilation (P = 0.005) as compared with PRfraction (P = 0.064).

Conclusion
PRvolume and PRfraction are not interchangeable. PRvolume may be a more accurate reflection of RV preload and may better represent physiologically significant PR as compared with PRfraction.

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. A common finding after right ventricular (RV) outflow tract surgery, pulmonary insufficiency may result in a cascade of hemodynamic sequelae that can include RV dilation, RV dysfunction, and ultimate deterioration in clinical status. Impaired exercise tolerance, ventricular arrhythmia, and sudden death have all been associated with the secondary effects of chronic PR. 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. For these reasons, CMR evaluation is recommended during the routine follow-up of patients after TOF repair. 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
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\text{fraction}) may be highly variable in terms of absolute volumes (PR\text{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 cardio-vascular 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 acquisition 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, indexed regurgitation volume or SVPR fraction (RVSV − LVSV) and SVPR 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 inter-quartile ranges (IQRs), unless otherwise specified. Mann–Whitney and chi\(^2\) tests were used to compare groups, as appropriate. Comparisons of PR\text{volume} or PR\text{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 ≥ 20%), receiver-operator curves (ROC) were constructed to examine the ability of the differing expressions of PR (PR\text{volume} and PR\text{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 (RVEDV) ≥ 170 mL/m\(^2\). This cut-point was used because prior studies from our centre and others have suggested that RVEDV > 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 (PR\text{volume} 38 mL/m\(^2\) (IQR 21–39) vs. 17 mL/m\(^2\) (IQR 2–28), P < 0.001; SVPR\text{volume} 34 mL/m\(^2\) (IQR 12–42) vs. 16 mL/m\(^2\) (IQR 4–29), P = 0.04; PCPR\text{fraction} 43%
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\(_{volume}\) and PR\(_{fraction}\) derived by PC analysis and SV differentials were similar: PC\(_{PR}\) volume, 20 mL/m\(^2\) (IQR 10–35) vs. SV\(_{PR}\) volume, 19 mL/m\(^2\) (IQR 6–32); PC\(_{PR}\) fraction, 29% (IQR 13–42) vs. SV\(_{PR}\) fraction, 30% (IQR 10–41). The intra-class correlation coefficient for PC\(_{PR}\) volume was 0.82–0.93, and PC\(_{PR}\) fraction 29% (IQR 13–42) vs. SV\(_{PR}\) fraction 30% (IQR 10–41). The median indexed PR\(_{volume}\) when compared with PR\(_{fraction}\). RV SV was positively correlated with, and LV SV 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\(_{fraction}\) of 52% can represent a PR\(_{volume}\) between 31 and 65 mL/beat/m\(^2\) and a PR\(_{volume}\) of 34 mL/beat/m\(^2\) can represent a PR\(_{fraction}\) between 35 and 58%. This dispersion from the regression line was most apparent with more significant degrees of PR.
In those patients with significant PR, PR$_{\text{volume}}$ was better than PR$_{\text{fraction}}$ 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 PCPR$_{\text{volume}}$ were better able to discriminate between moderate and severe RV dilation (P = 0.005) compared with PCPR$_{\text{fraction}}$ (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$_{\text{volume}}$ to better identify significant RV dilation when compared with SV differential methods (ROC area: 0.83 vs. 0.74, P = 0.07).

**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.
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. 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. 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. 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. 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. 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. 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 ~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 dilatation 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, 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 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
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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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References