Echocardiographic assessment of diastolic biventricular properties in patients operated for severe pulmonary regurgitation and association with exercise capacity

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Aims
We aimed to assess the impact of surgical pulmonary valve replacement (PVR) for severe pulmonary regurgitation (PR) on biventricular function and its effect on exercise capacity.

Methods and results
Seventy-three patients (mean age 23.6 ± 11.5 years, 47 females) underwent surgical PVR for PR. Echocardiogram and magnetic resonance imaging to assess ventricular size and function, and a cardiopulmonary exercise test were performed before, and 1-year post-surgery. Median New York Heart Association class improved from 2 to 1 but peak oxygen uptake (VO2) did not change. Left ventricular (LV) cardiac output increased from 3.2 ± 0.9 to 3.5 ± 0.7 L/min (P = 0.003). However, this was not associated with increased trans-mitral velocities (△E = −0.13, P = 0.004; △A = 0.03, P = 0.395), or increased heart rate (−0.002%, P = 0.993). Trans-tricuspid rapid right ventricular (RV) filling increased significantly, whereas early diastolic myocardial velocity in RV wall decreased (E velocity: 0.57 ± 0.14–0.65 ± 0.21, P = 0.034; and E/e′ from 6.7 ± 1.9 to 14.8 ± 7.0, P < 0.0001). RV and LV late diastolic velocities and their ratio to early velocities (A, a′, E/A, and e′/a′) correlated with pre- and/or post-PVR peak VO2. No correlations were found between indexes of systolic function and peak VO2, either before or after surgery. Doppler evidence of restrictive RV physiology resolved after elimination of PR.

Conclusion
Surgical PVR for PR improves RV filling and increases left ventricular stroke volume, however, this could not be demonstrated by conventional Doppler echocardiography. Diastolic ventricular function was associated with exercise capacity. Because of its load dependency, E/e′ ratio failed in assessing diastolic function. Pre-systolic flow in pulmonary trunk in presence of severe PR does not determine intrinsic myocardial stiffness.

Keywords
Congenital heart surgery • Pulmonary regurgitation • Exercise capacity • Doppler echocardiography

Background
The haemodynamic benefits of surgical pulmonary valve replacement (PVR) on cardiac performance have been recently confirmed by numerous studies.1–8 Besides the clinical criteria (presence of symptoms, reduced exercise capacity, and arrhythmias), ventricular volumes play a major role in the decision making process. Several authors have proposed thresholds for right ventricular (RV) end-diastolic (EDV) and end-systolic volumes (ESVs) beyond which, normalization of RV volumes following surgery is unlikely to happen.1,3,5 However, there is no clear evidence that the presence or the preservation of normal RV volumes correspond to a better long-term prognosis. Furthermore, in a recent study from our group we showed that patients operated on at a

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younger age had a greater improvement in the exercise capacity and LV systolic function.6 These younger patients had similar RV volumes and systolic function before surgery compared with older patients, but a higher pulmonary regurgitant fraction (PRF) which we have interpreted as being the result of a less fibrosed and, therefore, more compliant RV; this, in turn, could be the result of a shorter exposure to pulmonary regurgitation (PR).

No attention has been given so far to the diastolic properties of the ventricles, particularly of the RV; this is mainly the result of the difficult interpretation of the conventionally used parameters that are notoriously load dependent, and therefore, even less attractive in the context of volume overload and right bundle branch block.7 We assessed the hypothesis that diastolic function can explain the different levels of exercise capacity in patients who have similar pre-surgical volumes and systolic function on magnetic resonance imaging (MRI).

Methods

Between February 2004 and March 2007, 89 consecutive patients underwent PVR for severe PR. Mean age at the time of PVR was 23.6 ± 11.5 years and 47 patients were females. Body surface area (BSA) was 1.6 ± 0.3.

The original diagnosis was that of tetralogy of Fallot (TOF) in 62 patients (1 had additional atroventricular septal defect), pulmonary atresia (PA) in 13 (4 with intact ventricular septum), pulmonary stenosis (PS) in 10, double outlet right ventricle (DORV) in 2, and truncus arteriosus type 1 in 2. Patients underwent complete repair at a mean age of 3.9 ± 5.2 years (range 0–33.5 years); 36% of patients were initially palliated. At the time of complete repair, 57 patients had a trans-annular patch (TAP), 5 patients had a RV–PA conduit, and in 5 a monocusp valve was used. Mean number of previous surgical procedures was 1.5 ± 0.6.

Indications for PVR were the presence of severe PR (regurgitant fraction >35% on MRI), with evidence of qualitative echocardiographic progressive RV dilatation and dysfunction (RV/LV EDV > 1.5 in presence of symptoms, ≥2 if asymptomatic), reduced exercise capacity (peak VO2 < 65% of predicted), and/or arrhythmias.6 The surgical technique has recently been fully described.6 At the time of PVR, a pulmonary homograft (PH) was used in 80 patients, a Hancock conduit in 4, a St Jude Epic bio-prosthesis in 2, a Carpentier–Edwards in 2, and an aortic homograft in 1. In one patient, the PH has been replaced with a Hancock conduit on Day 1 for twisting with consequent severe stenosis. Mean size of the RV–PA conduit was 21.9 ± 2.1.

All patients underwent clinical examination, echocardiographic study comprehensive of tissue Doppler analysis, cardiac MRI, and cardiopulmonary exercise test (CPET). Assessment was performed before and 1-year after surgery. All investigations were performed on the same day, both pre- and post-surgery.

In order to study changes in clinical and functional parameters following correction of volume overload, we excluded from our analysis 15 patients who had either a PRF >20% on MRI, or more than mild tricuspid valve regurgitation (TR) on echocardiography or both at 1-year from surgery, in order to avoid interferences of residual volume overload on the measured parameters. From the initial cohort of 89 patients, a total of 73 have been considered for subsequent analysis.

The local research ethics committees approved the study, and all subjects (and/or a parent/guardian) gave informed consent. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Echocardiography

Echocardiography was performed using a Vivid 7 machine (GE Medical Systems, Milwaukee, WI, USA) with a 3.5 MHz transducer.

From the trans-tricuspid and trans-mitral flow Doppler profiles, peak early (E) and late (A) diastolic velocities were measured. Trans-tricuspid velocities were measured at the end of expiration during breath-hold. Right ventricular systolic pressure was calculated from the continuous-wave Doppler profile of the tricuspid regurgitant jet and peak right ventricular outflow tract (RVOT) gradient was calculated in the same fashion from the signal across the RVOT.7 Severity of tricuspid and mitral valve regurgitation was semi-qualitatively assessed using colour Doppler and classified as absent, trivial, mild, moderate, and severe.

Right and left atrium area were measured from a four chamber view and results were z-scored against normal values.10 Similarly, the z-score values were obtained for the tricuspid valve annulus diameter measurements.

The percentage of collapse of the inferior vena cava was obtained during forced inspiration from the subcostal view.

For the tissue Doppler analysis, the RV-free wall and left ventricular lateral wall were imaged from the apical position during quiet breathing. Colour-coded myocardial velocities of the tricuspid and mitral annuluses were acquired with a mean frame rate of 177 ± 26 s⁻¹. In order to assess regional systolic function, peak myocardial velocity during systole (e'), which has been demonstrated to correlate with ejection fraction (EF),11,12 was measured at the lateral tricuspid and mitral annuluses. Myocardial velocities during early diastole (e’) and late diastole (d’) were also measured. Images were digitally stored for offline analysis with EchopAC software (GE Vingmed, Horten, Norway). All measurements were averaged from three consecutive cardiac cycles.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed, on the same day as echocardiography and MRI on an electronically braked bicycle ergometer with respiratory gas exchange analysis, just before and 1-year post-PVR. We used a ramp protocol consisting of a 3-min initial period of load-less cycling followed by a 10–25 W/min of load increase with the aim of reaching exhaustion in 10–12 min of exercise. A period of active recovery (slow cycling with 10-W load) followed maximal exertion. Heart rate, blood pressure, and oxygen saturation were monitored in all subjects for the duration of the test and peak oxygen uptake (peak VO2) was measured as the average of the last 30 s of exercise.

Magnetic resonance imaging

MRI was performed using a 1.5 T MR scanner (Avanto, Siemens Medical Systems). Techniques and results have previously been described.6 Ventricular volumes were obtained by manual segmentation of endocardial borders from end-diastolic and end-systolic frames; these were obtained from a stack of short-axis images (9–12 slices) using retrospective state-state free precession cine MRI images obtained during single breath-hold.13 Stroke volume (SV), EF, and CO were then calculated. Pulmonary artery and aortic flow data were acquired using a flow-sensitive gradient-echo sequence during free breathing. PRF was calculated as percent backward flow over
forward flow. All volume and flow measurements were indexed for BSA.

**Statistical analysis**

Data distribution was tested using Kolmogorov–Smirnov test. The paired Student’s t-test was performed to compare parameters before and after PVR. For ordinal data within patients, pre- and post-procedure, the Wilcoxon’s signed-rank test was used to calculate a statistical significance. For categorical data between groups, we used Chi-squared test. Spearman’s rank correlation coefficient has been used as non-parametric measure of correlation between two variables. A P-value < 0.05 has been considered statistically significant. Statistical analysis has been performed using SPSS version 16.0 for Windows (SPSS, Chicago, IL, USA).

**Results**

Following surgery, patients had a subjective improvement in symptoms so that median New York Heart Association (NYHA) class improved from 2 to 1. Nine patients had more than mild residual PR (PRF > 20% on MR); out of these 80 patients, 7 had more than mild tricuspid valve regurgitation on echocardiography and these patients were excluded from further analysis. Demographic and MRI data are summarized in Table 1.

**Echocardiographic results**

Pre- and post-surgery conventional echo and tissue Doppler imaging parameters are summarized in Tables 2 and 3. Before surgery, there was a slight increase in RV systolic pressure as assessed through the tricuspid regurgitant jet velocity. IVC collapse was also reduced compared with normal subjects (31%), thus reflecting an increased right atrial pressure and ultimately an increased RV end-diastolic pressure. The right atrium was dilated (mean z-score = 5.3 ± 4.6), whereas the left atrium was not (mean z-score = 0.1 ± 3.3). Peak velocity across the RV outflow tract was also slightly increased. Following PVR, there was a reduction in TR jet velocity, peak RVOT velocity, and an increase in IVC collapse (from 69 ± 30 to 89 ± 19%, P = 0.004). No significant change in tricuspid anulus diameter and RA area was noted; LA dimensions also did not change significantly after PVR, thus mirroring the E/e’ relationship.

Pre-surgical myocardial right and left ventricular systolic velocities were reduced compared with normal subjects, as also were the RV early diastolic velocities (e’); in the LV, early myocardial diastolic velocities (e’) were within normal range.

Following PVR, there was a significantly increased RV early filling velocity (E wave increased from 0.57 ± 0.14 to 0.65 ± 0.21, P =

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TR vel, tricuspid regurgitant jet velocity; RVOT, right ventricular outflow tract; IVC, inferior vena cava; TV index, tricuspid valve index; RA index, right atrium index; LA index, left atrium index; TV E, LV myocardial early diastolic velocities; LV A, LV myocardial late diastolic velocities; MV E, LV myocardial early diastolic velocities; MV A, LV myocardial late diastolic velocities; MV E/A, trans-tricuspid diastolic velocities.

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<th>Table 3: TDI echo parameters pre- and post-PVR</th>
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LV s’, myocardial systolic velocity at the lateral mitral valve annulus; RV s’, myocardial systolic velocity at the lateral tricuspid valve annulus; LV e’ and LV a’, myocardial early and late diastolic velocities, respectively, at the lateral mitral valve annulus; RV e’ and RV a’, myocardial early and late diastolic velocities, respectively, at the lateral tricuspid valve annulus.
PR had a persistent antegrade flow in the main pulmonary artery echocardiography, only this last patient with residual significant absent in 2 (TOF), mild in 1 (PS) and still severe in 1 (PA). On ment in RV and LV systolic function on MR imaging and PR was velocity ($e'$) also decreased after surgery.

Evidence of restrictive physiology
From the whole cohort of patients, including those with residual PR and/or tricuspid valve regurgitation, four patients had restrictive physiology pre PVR, echocardiographically defined by an antegrade flow on continuous-wave Doppler into the main pulmonary artery following atrial contraction. We did not confirm this finding with simultaneous invasive pressures measurements. Two of these patients had TOF as original anatomical diagnosis, 1 had PA and 1 PS; they all received a TAP at the time of complete repair. Age at PVR ranged from 10.3 to 64.7 years. NYHA class ranged from I to IV. The two older patients (40 and 64.7 years) had a much lower peak VO$_2$ at exercise. After surgery, they all had an improvement in RV and LV systolic function on MR imaging and PR was absent in 2 (TOF), mild in 1 (PS) and still severe in 1 (PA). On echocardiography, only this last patient with residual significant PR had a persistent antegrade flow in the main pulmonary artery during atrial systole.

CPET results
All patients completed a maximal exercise test. Overall, exercise capacity did not improve following surgery. An anaerobic threshold was detected in all patients. Detailed results are summarized in Table 1.

MRI results
There was a significant reduction in RV volumes and an increase in LV EDV thus indicating a higher LV filling. We also observed an improvement in biventricular systolic function, as also previously described. A summary of these results is given in Table 1.

Interestingly, there was an inverse association between LV $E/e'$ and LV EDV ($r = -0.264, P = 0.039$) after surgery. An inverse correlation was also seen between the late diastolic RV velocity ($A$) and RV end-diastolic volume ($r = -0.313, P = 0.010$). These findings support the hypothesis that the higher the degree of PR and RV dilation, the more RV filling relies on right atrial kick for diastolic filling; the LV is squashed by the dilated RV and as a consequence of ventricular–ventricular interaction it requires increased filling pressure (higher $E/e'$) for an appropriate filling.

Correlation between echocardiographic parameters and exercise capacity
Correlation between both systolic and diastolic echo parameters, and conventional exercise data were tested. Significant correlations with exercise variables were found only for diastolic velocities. For the RV, trans-tricuspid $E/A$ ratio, myocardial $a'$ velocity, and $e'/a'$ ratio significantly correlated with pre- and post-operative peak VO$_2$. For the LV, trans-tricuspid and myocardial late diastolic velocities ($A$, $a'$), and their ratio to early diastolic velocities ($E/A$, $e'/a'$), correlated with pre- and post-operative peak VO$_2$. Results are summarized in Table 4.

Discussion
In this study, we showed that surgical PVR for severe PR improves RV forward filling and increases left ventricular SV. However, as suggested by trans-atrioventricular valves flow studies and myocardial systolic and diastolic velocities interrogation, we could not demonstrate any improvement in conventional measures of biventricular function.

Following PVR, there was a significant increase in $E/e'$ parameter, thus suggesting diastolic impairment; this was the result of a increased trans-tricuspid rapid filling on pulsed Doppler ($E$) and a significantly reduced RV myocardial early diastolic velocity ($e'$). This, however, reflects the change in RV loading rather than change in intrinsic myocardial function. We strongly believe that in volume overloaded ventricle, $E/e'$ parameter should not be used in clinical practice for assessing RV diastolic function similar to the myocardial performance index—also known as Tei index.

Although we demonstrated some significant pre- and post-PVR changes in LV diastolic filling patterns on pulsed and tissue Doppler, we failed to demonstrate better LV diastolic filling.
either by increased E velocity or E/A ratio, or by E/e′. Although increased E velocity across tricuspid valve after PVR demonstrated improved RV filling during passive relaxation, active atrial contraction did not change as A velocity remained same. This can possibly be explained by ongoing right atrial myocardial stiffness particularly if right atrium remained significantly enlarged one year after PVR.

Previous studies have described that the presence of an antegrade flow in main pulmonary artery during atrial systole (pre-systolic) throughout the respiratory cycle is an echocardiographic sign of restrictive physiology. This would be the result of a reduced RV diastolic compliance, or increased RV stiffness, which in turn is causing the RV to act as passive conduit between the right atrium and the pulmonary artery. Patients operated on for TOF who present with restrictive physiology are known to have a slower recovery in the immediate post-operative period but may present with a superior exercise tolerance 15–35 years later. This last is thought to be the consequence of the effect of increased RV stiffness on limiting PR, which would protect the RV from its deleterious effects. In our study, four patients presented with restrictive physiology. PVR was performed at a young age (<17.5 years) in two (PS and PA) and at an older age in two (40 and 64 years). The younger patients had a better exercise capacity as measured by peak VO2. Following PVR, only one patient maintained this late diastolic antegrade flow; this patient (PA) had significant PR at follow-up (RF = 38%), whereas in three patients in whom diastolic forward flow in the pulmonary artery disappeared, PR was completely abolished in two and was mild in one. This finding would suggest that, in the presence of severe PR, pre-systolic antegrade flow in main pulmonary artery does not determine intrinsic myocardial restriction. We believe that antegrade flow generated by atrial contraction is related to high EDV in significantly volume overloaded ventricle and pericardial constrain or perhaps rather to adhesions as pericardium is usually widely resected. Furthermore, in the presence of severe PR, diastolic pulmonary artery pressure is lower and, therefore, it is easier for the right atrium to produce forward flow during atrial systole. Caution is, therefore, requested in this data interpretation.

The mechanisms of reduced exercise capacity in patients with RVOT dysfunction following repair of congenital heart disease (CHD) are not entirely understood and most likely multifactorial. Several studies have addressed this issue, each of them highlighting different aspects of the complex association between cardiac haemodynamics and exercise capacity. Some authors suggested that the chronically volume-overloaded myocardium has a limited contractile reserve, because they were not able to measure an improvement in peak VO2 following percutaneous pulmonary valve implantation to treat RVOT dysfunction characterized by predominant PR. Cheung et al. found that LV circumferential strain rate (SR) was playing a pivotal role in determining peak VO2 in patients with repaired TOF. Furthermore, the authors found that LV circumferential SR was negatively influenced by RV ESV, thus revealing an important ventricular–ventricular systolic interaction. Roche et al. explored the hypothesis that intraventricular mechanical dysynchrony induced by exercise would impact on ventricular dynamic as well as on exercise capacity. Nevertheless, they were not able to demonstrate such a correlation, although their results may be confounded by the young age group of the tested population. In a recent study, we demonstrated that following PVR for severe PR, patients younger than 17.5 years of age are more likely to normalize their submaximal exercise capacity. Younger patients pre-operative RV volumes as well as RV systolic function when compared with the older patients; nevertheless, they had a higher PRF, which we believe reflects a more compliant (less fibrosed) RV. We hypothesized that diastolic properties of the RV influence the exercise responses. We could demonstrate that late trans-valvar (mitral) diastolic velocities (A) and their ratio (mitral and tricuspid) to early diastolic (E/A) as well as late RV and LV myocardial diastolic velocities (a) and their ratio to early diastolic (ea) correlated with exercise capacity, both before and after PVR. Patients with higher (mitral) A values and lower E/A as well as patients with higher myocardial a′ values and lower e′/e′ had a reduced exercise capacity. In other words, patients with more abnormal Doppler filling pattern have a more compromised exercise performance. Furthermore, the fact that only diastolic velocities correlated with CPET parameters, would suggest that, in the absence of overt RV systolic dysfunction, the main determinant of the exercise capacity is the diastolic function. This would also explain why, despite similar ventricular volumes and cardiac systolic function, different patients might have different exercise capacity.

Other authors have recently demonstrated the impact of LV diastolic dysfunction on peak VO2. The patients, subject of this study, were younger than ours (median age 14 years, range 9–25 years), and MR imaging data were not available; this precluded the possibility to assess the presence of possible correlations with exercise capacity and particularly the impact of PR and RV dilatation on their results. Different from these authors, we were able to demonstrate significant correlations between peak VO2 and RV, in addition to LV, diastolic echocardiographic parameters but no with E/e′.

This study highlights the necessity to focus more attention on diastolic properties when assessing patients for a surgical indication. This is also suggested by a recent study that shows an important influence of RV parameters (in particular RV end-diastolic volume) on LV diastolic function in repaired TOF. In their paper, RV end-diastolic volumes were significantly larger in those patients with an invasively measured LV end-diastolic pressure > 12 mmHg (135.2 ± 47.8 ml/m²) than in those with a pressure < 12 mmHg (98.6 ± 28 ml/m²).

Unfortunately, we were unable to confirm LV diastolic dysfunction in our population by means of standard criteria (the size of left atrium, E/A, E/e′) as there are intrinsic limitations related to the well-known load dependency of the echocardiographic parameters. Despite that, we could demonstrated a good association between diastolic function and exercise capacity (corrected for the PR and TR); caution is still warranted in the interpretation of this result.

Limitations

There are other limitations that need mentioning such as a short follow-up (1-year), which would highlight mainly early changes; longer follow-up would be warranted;
Furthermore, there are no invasive measurements in this patient's population, as these are not routinely performed at Great Ormond Street Hospital.

Another important limitation comes from the fact that diastolic properties change with age; we did not correct the data by age, as the older patients were still young adults (mean age 24 ± 12 years). Recently, Sarikouch et al.29 have demonstrated—in a large prospective study on a cohort of patients with repaired TOF—that age and gender have important influences on the measured MRI parameters (volumes and function), which behave differently from the normal population. Clinical implications are that the currently uniform selected thresholds for re-interventions may reflect a different state in the disease progression and, therefore, in the degree of diastolic dysfunction. Our patients’ population is too small to test the impact of gender on the echocardiographic parameters in the context of corrected CHD, and further studies are warranted to investigate this matter.

Finally, peak VO₂ exercise parameter has a multifactorial nature because pulmonary function, muscular mass, and level of fitness are also impacting on the results in addition to central factors such as cardiac function.

Conclusions

Surgical PVR for severe PR improves RV forward filling and increases left ventricular SV. E/e' ratio failed in assessing diastolic function. Pre-systolic flow detected in the pulmonary trunk in presence of severe PR does not determine restrictive physiology. Pre-surgical biventricular diastolic function is the main determinant of post- and post-surgery exercise capacity.

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Conflict of interest: none declared.

References