Left ventricular contractile reserve after arterial switch operation for complete transposition of the great arteries: an exercise echocardiographic study

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Aims
This study tested the hypothesis that left ventricular (LV) contractile reserve is altered in patients after arterial switch operation (ASO) for complete transposition of the great arteries (TGA) by non-invasive determination of LV force–frequency relationship (FFR).

Methods and results
Thirty-two patients aged 16.2 ± 2.1 years and 22 healthy controls were studied. M-mode parameters, transmitral early (E) and late (A) diastolic velocities, and tissue Doppler-derived systolic ($s_m$), early ($e_m$), and late ($a_m$) diastolic mitral annular velocities were determined at baseline and during submaximal exercise testing. The LV myocardial isotropic acceleration (IVA) was measured at different heart rates during exercise for derivation of LV FFR and the average slope of IVA increment with heart rate. At baseline, patients had significantly greater E velocity, E/A and E/em ratios, shorter E deceleration time, and reduced mitral annular $s_m$, $e_m$, and $a_m$ velocities (all $P < 0.05$), but similar IVA ($P = 0.29$) compared with controls. During exercise, $s_m$ and $e_m$ remained significantly reduced ($P < 0.001$), and LV IVA became lower ($P < 0.001$) in patients. The average FFR slope was significantly lower in patients ($0.039 ± 0.019$ vs. $0.070 ± 0.024$ m/s² bpm, $P < 0.001$). The weighted average FFR curve of patients was flatter compared with the reported positive FFR reference curve based on a healthy paediatric cohort ($P < 0.0001$).

Patients with variant compared with those with usual coronary arterial anatomy had significant flattening of FFR ($P < 0.001$) and a reduced FFR slope ($P = 0.007$).

Conclusion
In adolescents and young adults after ASO, exercise stress revealed reduced LV contractile reserve, which is worse in those having variant coronary arterial anatomy.

Keywords
Transposition of the great arteries • Arterial switch operation • Left ventricle • Contractile reserve • Exercise echocardiography

Introduction
Anatomic correction of complete transposition of the great arteries (TGA) by arterial switch operation (ASO) is the standard of management in the present era. Intermediate- and long-term outcomes in terms of operative and late mortality and the need for re-intervention of residual structural sequelae have been encouraging. Nonetheless, impaired exercise capacity has been shown in a significant proportion, up to 49–82%, of adolescents and young adults late after ASO. While the cause of exercise incapacity in these patients remains uncertain, contractile reserve of the left ventricle during exercise has been shown to be an important determinant of exercise capacity in patients with systemic hypertension, aortic stenosis post-aortic valve replacement, and mitral regurgitation after mitral valve replacement. Similarly, contractile reserve as assessed by dobutamine stress echocardiography in idiopathic-dilated cardiomyopathy has been shown to be an important determinant of exercise capacity. Assessment of left
ventricular (LV) systolic function in patients after ASO has, however, primarily been focused on measurement of resting fractional shortening (FS), ejection fraction, end-systolic wall stress, and rate corrected mean velocity of fibre shortening and which has largely been found to lie within limits of normal. In these patients, contractile reserve of the left ventricle during stress has hitherto not been explored.

Cardiac contractile reserve can be assessed by the determination of the force–frequency relationship (FFR), which represents an intrinsic regulatory mechanism of cardiac contractility. In most mammalian ventricular myocardium, the FFR is positive and the increase in contractile force in association with elevation of cardiac stimulation frequency reflects contractile reserve. Assessment of FFR in human subjects has previously been limited to in vitro measurements of isometric twitch tension of LV myocardial strip or the use of invasive cardiac catheterization with atrial pacing. Non-invasive assessment of FFR has been attempted by determining the variability of the peak-systolic pressure to end-systolic LV volume ratio with increasing heart rate during exercise stress. Cuff brachial peak systolic blood pressure was used as a surrogate for end-systolic pressure, while calculation of LV systolic volume by modified Simpson’s method required acquisition of both apical four- and two-chamber views at various stages of exercise. Recently, myocardial acceleration during isovolumic contraction (IVA) has been demonstrated to be a relatively load-independent and reproducible assessment of ventricular contractility. Utilizing the characteristic positive variability of IVA with heart rate, FFR has been constructed with the use of inotropic infusion or atrial pacing to increase heart rate. Subsequently, a more non-invasive technique to generate FFR by tracking the changes in IVA during exercise stress has been described.

In the present study, we aimed (i) to test the hypothesis that LV contractile reserve is altered in patients after ASO for complete TGA by non-invasive determination of LV FFR, and (ii) to identify factors associated with flattening of FFR in these patients.

Methods

Subjects

Thirty-two (24 males) patients who have undergone ASO for complete TGA and who were 12 years and above were recruited from the paediatric cardiac clinic. The following clinical data were collected: age at study, sex gender, follow-up duration since ASO, coronary arterial anatomy, associated cardiac lesions, age at and type of operation, residual cardiac lesions after ASO, and the need for cardiac intervention after ASO. Twenty-two healthy subjects (15 males) were recruited as controls. The body weight and height of all subjects were measured and body surface area was calculated accordingly. All of the subjects underwent baseline echocardiographic evaluation at rest and at different heart rates during supine bicycle exercise as described below. The Institutional Review Board approved the study and patients and parents of minors gave informed written consent.

Exercise testing

Submaximal exercise testing was performed using a bicycle ergometer (Ergosana Schiller Semi-couch Safety Ergometer ERG 911 S/L, Swabian Alb, Germany). The subjects were asked to avoid caffeine-containing food or drinks and exercise other than walking on the day of study. Baseline assessment was performed after at least 5 min of rest. The bicycle ergometer was adjusted to a semi-recumbent and left lateral decubitus position to facilitate echocardiographic acquisitions. The initial workload was 25 W, with a stepwise increase of 25 W of workload at 2-min intervals until a maximum of 150 W or when further increment of workload was not tolerated. The exercise test was terminated when 70% of age-predicted maximum heart rate (220 per min minus age) was reached or at a lower rate when the subject felt exhausted.

Echocardiographic assessment

Transthoracic echocardiography was performed using the Vivid 7 ultrasound system (General Electric, Vingmed, Horten, Norway). Echocardiographic cineloops were stored on digital versatile discs for offline analysis using the Echopac software (General Electric). The average values of echocardiographic parameters from three cardiac cycles were obtained at baseline for statistical analysis.

M-mode echocardiography was performed from the parasternal short axis view and the following measurements were made: LV end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), and FS.

Transmitral Doppler echocardiography was performed to obtain the early (E) and late (A) diastolic inflow velocities and E deceleration time. Pulsed tissue Doppler imaging was performed from the apical four-chamber view with the sample volume positioned at the mitral annular–LV free wall junction. The following tissue Doppler indices were determined: peak systolic myocardial tissue velocity (vsm), peak early (vₑₑ) and late (vₐₐ) diastolic myocardial tissue velocities, and vₑₑ/vₐₐ ratio. The E/Eₑₑ ratio was calculated as an estimate of LV filling pressure.

Myocardial acceleration during isovolumic contraction at the mitral annular–LV free wall junction was measured as previously described. Briefly, colour-coded tissue Doppler cineloops were obtained from the standard apical four-chamber view with frame rates >100 Hz. The IVA was calculated as the difference between peak and zero-crossing isovolumic contraction velocity divided by the acceleration time.

During bicycle ergometry, colour-coded tissue Doppler cineloops were captured at increments of 10–15 bpm heart rate. At least, 10 cardiac cycles were recorded at each increment. The sampling area was continuously adjusted during exercise to provide the best alignment, most commonly with movement downward along the LV free wall towards the apex from its initial position. At each heart rate, five IVA measurements were made to obtain the average. Individual FFR curve was constructed by plotting IVA against the simultaneous heart rate at different stages of exercise. To estimate the average increase in IVA with heart rate, we further calculated an average FFR slope accordingly to the formula: (changes in IVA from baseline to submaximal exercise)/(changes in heart rate from baseline to submaximal exercise). When the target heart rate was reached, the sₑₑ and vₑₑ velocities were also measured.

Statistical analysis

Data are expressed as mean ± SD unless otherwise stated. Demographic and echocardiographic variables of patients and controls were compared by unpaired Student’s t-test or Fisher’s exact test where appropriate. The intra- and interobserver variability for IVA measurements was assessed in 10 subjects (5 patients and 5 controls) and reported as the coefficients of variation, calculated by dividing the SD of the differences between measurements by the mean and
expressed as a percentage. Smooth curve fitting was applied to individual FFRs to estimate the weighted average FFRs in patients and controls and differences between the two groups were compared using regression analysis. Additionally, curves from our patients and controls were plotted against the 95% confidence interval of IVA variation with heart rate determined from a larger Caucasian cohort. Statistical analyses were performed using SPSS version 16 (SPSS, Inc., Chicago, IL, USA) and SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Subjects

Of the 32 patients, 25 (78%) patients had an intact ventricular septum, while 7 (21.9%) had an associated ventricular septal defect (VSD). Eleven patients had variant coronary arterial anatomy (Table 1). The median age of patients at ASO was 14 days (range, 7–387 days). Seven patients, six of whom had a VSD, underwent ASO beyond the neonatal period. The remaining patient had borderline small LV cavity and palliated initially with pulmonary arterial banding. This patient eventually underwent successful ASO at 387 days of life.

The patients were studied at 16.2 ± 2.1 years of age. At the time of study, six patients had moderate to severe aortic regurgitation, two of whom required enalapril therapy. Twenty-two age-matched healthy adolescents aged 15.6 ± 2.3 years (P = 0.31) were recruited as controls. There were no significant differences in body weight (P = 0.89), height (P = 0.58), and body surface area (P = 0.75) between the two groups (Table 2).

Baseline echocardiographic parameters

Table 2 summarizes the baseline echocardiographic parameters in patients and controls. The coefficients of variation for intra- and interobserver measurements of IVA at baseline were 5.8 and 6.9%, respectively. At rest, the LVESD, LVEDD, FS, and IVA were similar between the two groups (all P > 0.05). However, patients had significantly lower s_m than controls (P = 0.002).

For transmural diastolic flow velocities, patients had significantly greater E velocity (P < 0.001), lower A velocity (P = 0.049), higher E/A ratio (P < 0.001), and a shorter E deceleration time (P < 0.001). Tissue Doppler imaging revealed significantly lower e_m (P = 0.003) and a_m (P = 0.001) velocities, while the E/e_m ratio (P < 0.001) was significantly greater in patients than controls.

Exercise tissue Doppler parameters

Table 3 summarizes the echocardiographic parameters in patients and controls at submaximal exercise. The s_m (P < 0.001) and e_m (P < 0.001) remained significantly lower in patients than controls during submaximal exercise. While the LV IVA was similar between the two groups at rest (P = 0.13), it became significantly lower in patients than controls at submaximal exercise (P < 0.001) (Figure 1). At submaximal exercise, the intra- and interobserver variability as assessed by the coefficient of variation was 9.4 and 11.6%, respectively.

Force–frequency relationship

The maximal heart rate attained by patients and controls were similar at submaximal bicycle exercise (144 ± 16 vs. 144 ± 8 bpm, P = 0.94). Figure 2A and B shows, respectively, individual

Table 1 Coronary arterial anatomy in patients

<table>
<thead>
<tr>
<th>Coronary arterial anatomy</th>
<th>Number of patients</th>
</tr>
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<tbody>
<tr>
<td>Usual 1LCx, 2R</td>
<td>21</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
</tr>
<tr>
<td>1L, 2CxR</td>
<td>6</td>
</tr>
<tr>
<td>1LCxR</td>
<td>3</td>
</tr>
<tr>
<td>2CxR</td>
<td>2</td>
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</tbody>
</table>

Cx, circumflex; L, left; R, right.

Table 2 Comparison of demographic and resting echocardiographic indices between patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 32)</th>
<th>Controls (n = 22)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>16.2 ± 2.1</td>
<td>15.6 ± 2.3</td>
<td>0.31</td>
</tr>
<tr>
<td>No. of males (%)</td>
<td>24 (75%)</td>
<td>15 (68%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.1 ± 10.6</td>
<td>163.5 ± 10.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.0 ± 2.1</td>
<td>54.4 ± 11.5</td>
<td>0.89</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.59 ± 0.20</td>
<td>1.58 ± 0.20</td>
<td>0.75</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78.2 ± 14.5</td>
<td>76.1 ± 13.9</td>
<td>0.61</td>
</tr>
<tr>
<td>M-mode echocardiography</td>
<td></td>
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</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.63 ± 0.59</td>
<td>4.46 ± 0.47</td>
<td>0.24</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>2.98 ± 0.47</td>
<td>2.74 ± 0.40</td>
<td>0.053</td>
</tr>
<tr>
<td>FS (%)</td>
<td>35.78 ± 3.90</td>
<td>37.89 ± 3.83</td>
<td>0.07</td>
</tr>
<tr>
<td>Mitral Doppler inflow indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (cm/s)</td>
<td>103.9 ± 20.3</td>
<td>83.9 ± 14.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>50.1 ± 9.3</td>
<td>55.7 ± 11.3</td>
<td>0.049*</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.10 ± 0.38</td>
<td>1.52 ± 0.18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>E deceleration (ms)</td>
<td>146.2 ± 36.1</td>
<td>184.2 ± 25.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mitral annular tissue velocity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e_m (cm/s)</td>
<td>14.2 ± 3.3</td>
<td>17.0 ± 2.9</td>
<td>0.003*</td>
</tr>
<tr>
<td>a_m (cm/s)</td>
<td>5.9 ± 1.4</td>
<td>7.2 ± 1.3</td>
<td>0.001*</td>
</tr>
<tr>
<td>s_m (cm/s)</td>
<td>8.2 ± 2.7</td>
<td>10.5 ± 2.5</td>
<td>0.002*</td>
</tr>
<tr>
<td>e_m/a_m ratio</td>
<td>2.47 ± 0.48</td>
<td>2.38 ± 0.31</td>
<td>0.43</td>
</tr>
<tr>
<td>E/e_m ratio</td>
<td>7.74 ± 2.72</td>
<td>5.12 ± 1.47</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>IVA (m/s²)</td>
<td>0.94 ± 0.41</td>
<td>1.11 ± 0.37</td>
<td>0.13</td>
</tr>
</tbody>
</table>

A, peak mitral inflow velocity at late diastole; a_m, peak late diastolic myocardial tissue velocity; bpm, beats per minute; BSA, body surface area; E, peak mitral inflow velocity at early diastole; e_m, peak early diastolic myocardial tissue velocity; FS fractional shortening; IVA, isovolumic acceleration; LVEDD, left ventricular end-diastolic dimension; LVEDD, left ventricular end-systolic dimension; s_m, peak systolic myocardial tissue velocity.

*Statistically significant.
FFR curves of patients and controls plotted against the 95% confidence interval of IVA changes with heart rate reported previously in a larger cohort of 50 healthy children. Whereas individual FFR curves of our healthy control subjects fell within the 95% CI limits, FFR curves of patients showed significantly flattening ($P < 0.0001$, Figure 2A and C). The weighted average curve derived from our control subjects showed no significant difference compared with that reported (Figure 2D). On the other hand, the weighted average curve of our patient cohort showed significant flattening compared with our controls ($P < 0.0001$, Figure 2E).

Within the patient group, significant flattening of the FFR curve was observed in patients with variant coronary anatomy compared with those with usual coronary artery anatomy ($P < 0.0002$) (Figure 3). By contrast, no significant differences in weighted average of FFRs were found between patients of different genders, with or without VSD, having moderate to severe aortic regurgitation or not, or receiving early (operated before day 55) vs. late ASO (all $P > 0.05$).

The average slope of FFR was also significantly reduced in patients compared with controls ($0.039 \pm 0.019$ vs. $0.070 \pm 0.024 \text{ m/s}^2 \text{ bpm}$, $P < 0.001$). Patients with variant coronary anatomy were similarly found to have significantly reduced FFR slope compared with those having the usual anatomy ($0.029 \pm 0.011$ vs. $0.043 \pm 0.023 \text{ m/s}^2 \text{ bpm}$, $P = 0.018$). The FFR slope did not correlate with age at study, age at ASO, follow-up duration since ASO, and intraoperative parameters including duration of bypass, aortic occlusion, and circulatory arrest (all $P > 0.05$).

**Discussion**

Understanding of the increase in myocardial contractile force with escalating heart rate, an intrinsic characteristic of normal myocardium so-called FFR provides insight not only into cardiac physiology but also ventricular contractile reserve. Derivation of FFR has relied on invasive methodologies until recently with the report of non-invasive tracking of LV IVA changes during exercise stress. Using this technique, disruption of LV FFRs has been demonstrated in childhood cancer survivors after anthracyline therapy and patients after repair of tetralogy of Fallot. To our knowledge, this is the first study to assess dynamic changes in LV contractility as assessed by IVA variability with increased heart rate during exercise stress in patients after ASO, in whom we found evidence of impaired LV contractile reserve. Importantly, LV contractile reserve was worse in patients with variant than those with usual coronary anatomy. Additionally, our data suggested LV diastolic dysfunction both as rest and during exercise after ASO.

Previous studies have largely reported on normal resting LV systolic function as assessed by M-mode echocardiography in patients after ASO. Using speckle tracking echocardiography, Petersen et al. showed slight reduction in global LV longitudinal strain and torsion, but not LV strain rate, in ASO patients under again resting condition. Data on stressed LV function after ASO for complete TGA are nonetheless limited. In the early postoperative setting, Cheung et al. have demonstrated marked reduction in the trajectory of IVA variability with pacing-induced increase in heart rate in neonates assessed within 24 h of ASO, which has been attributed to injury induced by ischaemia and reperfusion. In children studied at a mean of 9.4 years after ASO, our group has demonstrated using dobutamine stress

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**Table 3** Comparison of heart rate and echocardiographic indices at submaximal exercise between patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients $(n = 32)$</th>
<th>Controls $(n = 22)$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>$144 \pm 16$</td>
<td>$143 \pm 7$</td>
<td>0.67</td>
</tr>
<tr>
<td>$s_m$ (cm/s)</td>
<td>$11.0 \pm 3.2$</td>
<td>$14.8 \pm 2.6$</td>
<td>$&lt; 0.001^*$</td>
</tr>
<tr>
<td>$e_m$ (cm/s)</td>
<td>$13.5 \pm 2.8$</td>
<td>$17.5 \pm 2.8$</td>
<td>$&lt; 0.001^*$</td>
</tr>
<tr>
<td>IVA (m/s$^2$)</td>
<td>$3.46 \pm 1.40$</td>
<td>$5.81 \pm 1.57$</td>
<td>$&lt; 0.001^*$</td>
</tr>
<tr>
<td>Average FFR slope</td>
<td>$0.039 \pm 0.019$</td>
<td>$0.070 \pm 0.024$</td>
<td>$&lt; 0.001^*$</td>
</tr>
</tbody>
</table>

$e_m$, peak early diastolic myocardial tissue velocity; FFR, force–frequency relationship; IVA, isovolumic acceleration; $s_m$, peak systolic myocardial tissue velocity.

*Statistically significant.

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**Figure 1** Box plots showing LV isovolumic acceleration (IVA) at rest and at submaximal exercise in patients and controls.
echocardiography the existence of LV segmental wall motion abnormalities, which corresponded to regions of impaired myocardial perfusion. Whether intrinsic contractility of the left ventricle and its contractile reserve is affected in the long-term have, however, not been explored previously.

Our findings of significantly lower LV IVA during exercise stress, flattening of FFRs, and reduced average FFR slope in patients compared with healthy subjects support the notion that LV contractile reserve is impaired in adolescents and young adults late after ASO. While the mechanisms of impaired contractile reserve remain to be defined, substrates for its development potentially exist in these patients.

Reversible myocardial perfusion defects have been demonstrated even in the absence of coronary stenosis or obstruction after ASO. These perfusion defects do not correlate with specific coronary arterial territory. Proposed mechanisms include abnormal coronary arterial vasomotor response and reduced coronary flow reserve. In patients with dilated cardiomyopathy, coronary flow reserve has been associated with the corresponding contractile reserve in the vascular territory as assessed by

Figure 2  (A) Individual force frequency curves of the 32 patients and (B) those of 22 healthy control subjects plotted against published normal 95% confidence interval (blue lines). Comparisons of weighted average FFR curves between (C) present patient cohort and published healthy cohort, (D) present control cohort and published healthy cohort, and (E) patients and controls recruited in this study.
Cardiac sympathetic denervation with variable degree of reinnervation occurs after aortic surgery including ASO. Interestingly, cardiac autonomic neuropathy has been associated with reduced exercise ejection fraction and end-systolic pressure-volume ratio in patients with type 1 diabetes, and exercise LV $s_e$ in patients with type 2 diabetes. While chronotropic incompetence due to sympathetic denervation may play a role in limiting cardiac contractile reserve, endomyocardial biopsies taken from patients with dilated cardiomyopathy revealed an association between $^{123}$I-labelled meta-iodobenzylguanidine (MIBG) uptake, which reflect the status of cardiac innervation, and expression of messenger RNA for contractile regulatory protein. Hence, it is tempting to speculate that cardiac sympathetic denervation probably plays an important role in limiting LV contractile reserve after ASO. Our finding of worse LV contractile reserve in those having variant coronary arterial anatomy compared with those having coronary arterial variants.

Figure 3 Flattening of weighted average of the left ventricular isovolumic acceleration (LV IVA) variability with heart rate for patients with normal coronary arterial anatomy compared with those having coronary arterial variants.

dobutamine stress echocardiography. In patients with LV dysfunction due to coronary artery disease, the capacity of myocardial segments to exhibit contractile reserve depends in part on the level of myocardial blood flow at rest and during inotropic stimulation. Hence, although none of our patients has significant residual coronary arterial lesions, perfusion mismatch during exercise stress may possibly play a contributory role to a flattened FFR.

Cardiac sympathetic denervation with variable degree of reinnervation occurs after aortic surgery including ASO. Interestingly, cardiac autonomic neuropathy has been associated with reduced exercise ejection fraction and end-systolic pressure-volume ratio in patients with type 1 diabetes, and exercise LV $s_e$ in patients with type 2 diabetes. While chronotropic incompetence due to sympathetic denervation may play a role in limiting cardiac contractile reserve, endomyocardial biopsies taken from patients with dilated cardiomyopathy revealed an association between $^{123}$I-labelled meta-iodobenzylguanidine (MIBG) uptake, which reflect the status of cardiac innervation, and expression of messenger RNA for contractile regulatory protein. Hence, it is tempting to speculate that cardiac sympathetic denervation probably plays an important role in limiting LV contractile reserve after ASO. Our finding of worse LV contractile reserve in those having variant coronary arterial anatomy compared with those having coronary arterial variants.

The flattened FFR in our patients may have implications on their exercise capacity. Previous studies have shown LV contractile reserve to be an important determinant of exercise capacity in patients with systemic hypertension, valvular heart disease, and cardiomyopathy. Reduced exercise capacity as assessed by peak oxygen consumption has been shown in patients after ASO at intermediate- and long-term follow-up. While deconditioning and over-protection from physical activity have been regarded as factors contributing to subnormal exercise capacity, a recent study failed to demonstrate differences in activity level between patients after ASO and healthy subjects. Our speculation of possible contribution of impaired LV contractile reserve to reduced exercise capacity after ASO requires, however, further studies for its confirmation.

Another important finding of the present study is the demonstration of LV diastolic dysfunction, as reflected by reduced $e_m$ and $a_m$ velocities and increased $E/e_m$ ratio, even at rest in patients late after ASO. Earlier studies that reported on normal LV diastolic function were performed in young children and based primarily on the greater load-dependent conventional Doppler indices. Using tissue Doppler echocardiography, a recent study showed slight reduction of $e_m$ although not statistically significant. Several reasons for the abnormal LV diastolic function in our patients late after ASO can perhaps be hypothesized. Right ventricular hypertrophy and diastolic dysfunction, reported in patients studied at a mean of 16.5 years after ASO, may affect LV function through ventricular–ventricular interaction. Arterial stiffening found in ASO patients may increase LV afterload and has been associated with LV diastolic dysfunction. Further studies to explore the aetiology and clinical significance of LV diastolic dysfunction after ASO are undoubtedly warranted.

Several limitations to this study warrant comments. First, myocardial perfusion scan was not performed within the study period in our patients. It is our institutional practice to catheterize patients after ASO at 3–5 years of age and all of our patients studied had documented patency of the coronary arteries. There exists, inevitably, an interval between cardiac catheterization and the present exercise echocardiographic study. All of our patients are, however, free from symptoms suggestive of cardiac ischaemia. Secondly, it would have been ideal to explore the relationship between peak oxygen consumption during cardiopulmonary exercise testing and the slope of FFR to better understand the clinical implications of impaired cardiac contractile reserve in patients. Submaximal exercise testing was performed at 70% of age-predicted maximum heart rate in the present study given the reported sympathetic denervation and chronotropic incompetence after ASO. Finally, while hypothesized as a potential cause of impaired cardiac contractile reserve, the status of cardiac denervation in our patients has not been assessed by MIBG scan.

In conclusion, the present study provides the first evidence in adolescents and young adults late after ASO of reduced LV contractile reserve, which is worse in those having variant coronary arterial anatomy. This together with the additional finding of LV diastolic dysfunction suggest that despite anatomical repair of complete TGA by ASO, continued monitoring of late consequences secondary to ventricular dysfunction is warranted.

**Conflict of interest:** none declared.

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