Implications of Early Aortic Stiffening in Patients With Transposition of the Great Arteries After Arterial Switch Operation

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Background—The elastic function of the aorta in patients with transposition of the great arteries after arterial switch operation (ASO) is suspected to be important for long-term prognosis.

Methods and Results—Fifty-one patients and 34 controls were studied at 3.0 Tesla with MRI. Forty-three patients (12.8±6.9 years) underwent 1-stage ASO, 8 patients (23.8±6.9 years) had prior pulmonary artery banding (2-stage ASO). Aortic dimensions, distensibility, pulse wave velocity, aortic arch angle, left ventricular (LV) mass, LV systolic function and left atrial (LA) volumes, and LA passive emptying function as marker of LV diastolic function were assessed. Compared with controls, patients had increased aortic root areas (602.6±240.5 versus 356.8±113.4 mm²/m²; P<0.01) and reduced distensibility of the thoracic aorta most pronounced at the aortic root (3.2±2.0 versus 9.1±4.7×10⁻³ mm Hg⁻¹; P<0.01). Aortic distensibility correlated negatively with the aortic areas (P<0.01). Pulse wave velocity was higher in adults after ASO (5.0±1.0 versus 3.8±1.3 m/s; P<0.01). In contrast to controls pulse wave velocity and distensibility correlated with aortic root and ascending aortic distensibility and positively with pulse wave velocity (P<0.05). In patients, LA passive emptying function was lower (27.3±8.9 versus 41.1±6.0; P<0.01) and correlated with aortic root distensibility (P=0.004).

Conclusions—Reduced aortic bioelasticity and aortic root dilatation are present in transposition of the great arteries patients post ASO and are likely to contribute to LV diastolic dysfunction. Impaired aortic bioelasticity was strongly associated with age, suggesting the usefulness of follow-up studies for early onset of degenerative cardiovascular disease. (Circ Cardiovasc Imaging. 2013;6:245-253.)

Key Words: arterial stiffness ■ left atrial volume ■ MRI ■ transposition of the great arteries

Since its introduction in the late 1970s, the arterial switch operation (ASO) has become the gold standard for surgical repair of transposition of the great arteries (TGA) in neonates and infants. However, several studies have shown evidence that even after successful anatomic repair, patients may be prone to long-term problems. The fate of the aorta and aortic valve has been assessed in previous studies. Most of the patients show nonprogressive dilatation of the aortic root, but few cases experience aortic insufficiency. In addition, reduced proximal aortic elasticity, structural abnormalities of the arterial walls, and increased carotid artery stiffness have been reported in TGA patients. In contrast to controls pulse wave velocity and distensibility correlated with aortic areas (P<0.01). Pulse wave velocity was higher in adults after ASO (5.0±1.0 versus 3.8±1.3 m/s; P<0.01). In contrast to controls pulse wave velocity and distensibility correlated with aortic root and ascending aortic distensibility and positively with pulse wave velocity (P<0.05). In patients, LA passive emptying function was lower (27.3±8.9 versus 41.1±6.0; P<0.01) and correlated with aortic root distensibility (P=0.004).

Conclusions—Reduced aortic bioelasticity and aortic root dilatation are present in transposition of the great arteries patients post ASO and are likely to contribute to LV diastolic dysfunction. Impaired aortic bioelasticity was strongly associated with age, suggesting the usefulness of follow-up studies for early onset of degenerative cardiovascular disease.

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Therefore, the purpose of this study was to evaluate the bioelastic properties of the thoracic aorta in TGA patients after ASO with respect to age, aortic dimensions, LV systolic function and left atrial (LA) volumes, and LA passive emptying function (LAEF_passive), as markers of LV diastolic function, using cardiovascular MRI (CMR).

Methods

Subjects

The study population consisted of 51 TGA patients and 34 controls with normal cardiac anatomy, and both groups were comparable in age, sex, size, and blood pressure (Table 1).
Table 1. Clinical Characteristics of Transposition of the Great Arteries Patients and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=51)</th>
<th>Controls (n=34)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>14.5±7.9</td>
<td>14.1±8.0</td>
<td>0.62</td>
</tr>
<tr>
<td>Women, %</td>
<td>43.1</td>
<td>64.7</td>
<td>0.08*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>50.2±24.5</td>
<td>43.4±22.0</td>
<td>0.16</td>
</tr>
<tr>
<td>Height, cm</td>
<td>151.7±34.5</td>
<td>146.7±26.9</td>
<td>0.17</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.4±0.5</td>
<td>1.3±0.5</td>
<td>0.21</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>104.4±15.4</td>
<td>101.6±10.5</td>
<td>0.37</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>54.1±11.9</td>
<td>59.3±12.5</td>
<td>0.07</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>50.0±10.8</td>
<td>46.8±6.8</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. BSA indicates body surface area; DBP, diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure. P values are from the Mann–Whitney U test or from the *Fishers exact test.

All patients underwent a CMR study between May 2008 and October 2010 at the Department of Congenital Heart Disease and Pediatric Cardiology at the University Hospital of Schleswig-Holstein. No formal power calculations were done. Simple TGA was present in 40 patients; 11 of these had additional ventricular septal defects. Forty-three patients were treated by ASO in their first days of life (1-stage ASO). Eight patients underwent a 2-stage operation with pulmonary artery banding (PAB) as the first step in the neonatal period, and ASO between 3 and 28 months of life. These 8 patients were young adults at the time of the CMR study. None of them had additional ventricular septal defect. From the whole patients group (n=51), 3 patients underwent ASO without Lecompte maneuver. In a subanalysis, we compared only the adult patients (>18 years) after 1-stage ASO with patients after 2-stage ASO.

In small children, sedation with propofol and midazolam was used for the CMR study. During examination heart rate, respiratory motion, oxygen saturation, and noninvasive blood pressure were monitored.

Control subjects were recruited among outpatients, medical students, healthy children of hospital staff, or from the department of pediatric neurology. In 5 controls, who were small children, sedation was performed. Three of them were referred for a clinical CMR for suspected cardiovascular disease, and sedation with propofol and midazolam was used in the same manner as in the patient group.

Two small children underwent diagnostic MRI of the central nervous system because of psychomotor retardation and epilepsy, they received phenobarbital or chloral hydrate for central nervous system MRI. Immediately after central nervous system MRI, noncontrast-enhanced CMR was performed with no further sedation.

All subjects or their parents or guardians (in case of minors) gave written informed consent to participate in the study, which was approved by the local ethics committee.

CMR Technique

CMR studies were performed with a 3.0-Tesla CMR scanner (Achieva 3.0T, Philips Medical Systems, Netherlands), using a phased-array coil for cardiac imaging, or in small children with a phased-array coil for extremities (SENSE Cardiac coil, SENSE Flex-L coil, Philips Medical Systems, The Netherlands).

Gradient echo cine CMR with retrospective ECG gating was performed to evaluate aortic cross-sectional areas and distensibility, LV volumes, mass, and systolic function as well as LA volumes and LAAEFpassive indicating LV diastolic function.12,13 Furthermore, the an-gulation of the aortic arch angle was measured. The scan parameters for the cine sequences were as follows: field of view, 280x224 mm; voxel size, 1.88x1.94x6 mm; repetition time/time to echo=4.4/2.5 ms; 25 cardiac phases; nonbreath-hold; number of repetitions, 2; total scan duration, 3 to 6 minutes.

Figure 1. Three-dimensional volume rendered gadolinium-enhanced MR angiography in a patient with transposition of the great arteries showing the bifurcation of the pulmonary arteries in front of the aorta after arterial switch operation with Lecompte procedure. Note the steep course of the aortic arch.

A phase-contrast cine pulse sequence, with through-plane velocity encoding, was applied for assessment of aortic pulse wave velocity (PWV) between the ascending aorta at the level of the sinotubular level, and the proximal descending aorta, with a slice plane intersecting the aorta at both locations at an approximately right angle. Phase-contrast flow velocity measurements in the proximal ascending aorta were also used for assessment of aortic valve competence. The phase-contrast sequence parameters were as follows: field of view, 270x270 mm; voxel size, 1.64x21.4x27 mm; repetition time/time to echo=4.4/2.7 ms; max. velocity encoding, 200 cm/s.

In addition, high-resolution gadolinium-enhanced MR angiography was performed in all patients for detailed 3-dimensional (3D) visualization of the aorta (Figure 1), using a keyhole technique, with the following imaging parameters: field of view, 380x380 mm; 70 slices; keyhole percentage, 20%; 20 dynamics; keyhole scan time, 1.7 s; repetition time/time to echo=2.4/0.93 ms; scan duration, 0:40 minutes. Gadolinium (Magnevist, Bayer Schering Pharma AG, Germany) was injected intravenously at a dose of 0.1 mmol/kg, with an injection rate of 2 mL/s, followed by a normal saline flush at the same rate. Healthy controls did not receive any contrast injections because of concerns by the ethics committee.

Phase-contrast cine imaging for assessment of PWV and aortic regurgitation (AR) was applied in 44 patients and 30 controls. PWV assessment was not possible in 11 patients, and AR could not be measured in 7 patients because of susceptibility artifacts from surgical implants or sedation problems. In all other patients, image quality was considered good or excellent.

Image Analysis and Calculations

All CMR images were analyzed on a workstation with dedicated software (ViewForum release 6.3, Philips Medical Systems, The Netherlands), except for the measurements of the aortic arch angle. The latter was performed with DICOM image viewer software with tools for measuring angles (eFilm Workstation version 2.1.0, Merge Healthcare, Milwaukee, WI).

The maximal and minimal areas of the aorta (Amax and Amin) were determined at 4 locations (Figure 2): (1) aortic root at the level of the sinus of valsalva, (2) ascending aorta, (3) descending aorta at the level of the isthmus, and (4) descending aorta above the diaphragm. The
Aortic flow measurements were analyzed from phase-contrast cine sequences to calculate AR. AR was considered to be mild if the regurgitant fraction was 5% to 15%, moderate if the regurgitant fraction was 16% to 30%, moderate to severe if the regurgitant fraction was 31% to 50%, and severe if the regurgitant fraction was >50% of the systolic forward flow volume.\textsuperscript{13}

LV end-diastolic volume and LV end-systolic volume were determined by planimetry of all short-axis images. Stroke volume was calculated by defining the LV volume at end diastole, and then subtracting the LV volume at end systole. LV ejection fraction was calculated by dividing the stroke volume by the LV end-diastolic volume. LA volumes were assessed from axial cine images by manual tracing of the endocardial contours at different times in the cardiac cycle\textsuperscript{16}: (1) maximal LA volume before mitral valve opening (LAVol\textsubscript{max}), (2) minimal LA volume at mitral valve closure (LAVol\textsubscript{min}), (3) before LA contraction (LAVol\textsubscript{i}). The LV and LA volumes were indexed to body height. LA volumes were used to calculate LAEFPassive according to the following formula: LAVol\textsubscript{max}−LAVol\textsubscript{min} × 100%/LAVol\textsubscript{i}.\textsuperscript{15}

In 37 patients the aortic arch angle was measured from oblique sagittal gradient echo cine images between the intersection of 2 lines (A, B). The lines started at the midpoint of the ascending (line A) or descending aorta (line B) at the level of the pulmonary artery bifurcation and were connected with the highest point of the aortic arch as shown in Figure 4.\textsuperscript{11} In 14 patients metal artifacts or deficient sagittal angulation did not allow reliable angle measurements.

### Statistical Analysis

Data were analyzed using MedCalc (version 11.5.1.0, Mariakerke, Belgium) and the R program\textsuperscript{17} especially the irr package for reliability analysis.\textsuperscript{18} All continuous variables are displayed as mean±SD. The Mann–Whitney U test for independent samples was used to compare patients and controls. Categorical data were compared using Fisher exact test. The strength of association was measured by Spearman rank correlation coefficients. A locally weighted polynomial regression method was used to describe relations between 2 measured variables with minimal prior assumptions. All comparison tests were 2 tailed and P values <0.05 were considered statistically significant. For results in Table 2 significant differences between groups did not lose or gain statistical significance (except for aortic distensibility at the isthmus, LV mass, and PWV) when adjusted by sex, and diastolic or pulse pressures with a linear regression model. No adjustments were made for multiple comparisons because of the exploratory nature of the study.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the article as written.
Results

The patient characteristics are listed in Table 1. There were no differences in age, weight, height, body surface area, and blood pressure between patients and healthy subjects. Arterial hypertension was present in 1 adult male patient.

Aortic Dimensions, Aortic Arch Angle, Aortic Insufficiency, and LV Function

The data on aortic dimensions and LV function are presented in Table 2.

The maximal aortic root area was significantly increased in TGA patients compared with the control subjects. Maximal areas of the ascending aorta and the descending aorta at the isthmus were negatively correlated with distensibility at the same level (Table 3).

The aortic arch angle was significantly steeper in patients compared with controls.

Twenty-nine patients had competent aortic valves, but 15 had AR, which was mild in 10, moderate in 4, and moderate to severe in 1 patient. The degree of AR was similar in patients after 1-stage and 2-stage ASO (6.6±10.2% versus 7.8±6.9%; P=0.35). None of the controls had an AR fraction that exceeded 4%. TGA patients showed positive correlation between the AR fraction and the cross-sectional area of the aortic root (r=0.36; P=0.03) and the ascending aorta (r=0.5; P<0.01).

LAEF_{Passive} was significantly lower in the TGA group compared with the age-matched controls. LV volumes, LV ejection fraction, and LA volumes were not significantly different between patients and controls, but LV mass was significantly increased in patients.

Aortic Distensibility

Wall distensibility of the aortic root and the ascending aorta and the descending aorta at the level of the aortic isthmus were significantly lower with TGA compared with healthy controls (Table 2). Among all aortic segments, the aortic root had the lowest distensibility (P=0.04 to <0.01).

The relationship of distensibility with clinical, anatomic, and functional parameters in TGA patients was assessed by Spearman rank correlation (Table 3). Distensibility of the entire thoracic aorta worsened significantly with increasing age, with a strong correlation at the aortic root (Figure 5), the ascending aorta, and the aortic isthmus. In contrast to the patient group, we found no significant correlation of aortic distensibility with age in healthy controls (Figure 5). Aortic root distensibility in patients correlated negatively with LAVol_{max}, LAVol_{min}, and LAVol_{max} and positively with LAEF_{Passive}. The latter correlation could also be found for the combined group of patients and controls (Figure 6). Aortic distensibility in TGA after ASO was not related to the aortic arch angle, AR, LV ejection fraction, LV end-diastolic volume, LV end-systolic volume, and LV mass.

Aortic PWV and the Effects of Aortic Arch Angle

PWV did not differ significantly between young patients (<18 years) after ASO and age-matched controls (3.8±1.3 versus 3.2±0.5 m/s). In adult patients, PWV was significantly higher compared with children after ASO (5.0±1.0 versus 3.8±1.3 m/s; P<0.01). PWV correlated with age in TGA patients, but not in volunteers (Figure 7). In TGA patients, the Spearman
rank correlation coefficient for PWV versus age did not change substantially, when the 8 patients after 2-stage ASO were excluded ($r=0.46; P<0.01$). Furthermore, PWV correlated negatively with the distensibility at the aortic root and the descending aorta (Table 3) and was also associated with LA volumes (LAVol$_{max}$: $r=0.54, P<0.01$; LAVol$_{min}$: $r=0.50, P<0.05$; LAVol: $r=0.47, P<0.05$; total LA emptying volume: $r=0.47, P<0.05$) in patients. Furthermore, we found a relation between LAEFPassive and PWV for the combined group of patients and controls (Figure 6). There was no relationship between PWV and the steepness of the aortic arch angle in patients after ASO.

### Table 3. Relationship of Distensibility and PWV With Clinical, Anatomical, and Functional Parameters in Transposition of the Great Arteries Patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Distensibility of the Aortic Root (Spearman Correlation)</th>
<th>Distensibility of the Ascending Aorta (Spearman Correlation)</th>
<th>Distensibility of the Descending Aorta at the Isthmus (Spearman Correlation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>−0.40*</td>
<td>−0.38*</td>
<td>−0.45*</td>
</tr>
<tr>
<td>Maximal aortic area, mm$^2$/m</td>
<td>−0.28</td>
<td>−0.42†</td>
<td>−0.53†</td>
</tr>
<tr>
<td>Aortic root</td>
<td>−0.05</td>
<td>−0.10</td>
<td>−0.20</td>
</tr>
<tr>
<td>Aorta ascendens</td>
<td>0.13</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>Aorta descendens at the isthmus</td>
<td>−0.49*</td>
<td>−0.30</td>
<td>−0.41*</td>
</tr>
<tr>
<td>AR fraction, %</td>
<td>−0.01</td>
<td>0.12</td>
<td>0.23</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>−0.49*</td>
<td>−0.30</td>
<td>−0.41*</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.13</td>
<td>0.22</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEDV, mL/m</td>
<td>−0.29</td>
<td>−0.27</td>
<td>0.08</td>
</tr>
<tr>
<td>LVESV, mL/m</td>
<td>−0.22</td>
<td>−0.23</td>
<td>0.11</td>
</tr>
<tr>
<td>LV mass, g/m</td>
<td>−0.11</td>
<td>−0.12</td>
<td>0.24</td>
</tr>
<tr>
<td>LAVol$_{max}$, mL/m</td>
<td>−0.40*</td>
<td>−0.29</td>
<td>−0.34</td>
</tr>
<tr>
<td>LAVol$_{max}$, mL/m</td>
<td>−0.48†</td>
<td>−0.35*</td>
<td>−0.15</td>
</tr>
<tr>
<td>LAVol$_{min}$, mL/m</td>
<td>−0.48†</td>
<td>−0.31</td>
<td>−0.26</td>
</tr>
<tr>
<td>LAEFPassive, %</td>
<td>0.5†</td>
<td>0.21</td>
<td>−0.13</td>
</tr>
</tbody>
</table>

AR indicates aortic regurgitation; LVEF, left ventricular ejection fraction; LVESV, left ventricular stroke volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAVol$_{max}$, maximal left atrial volume; LAVol$_{max}$, minimal left atrial volume; LAVol$_{max}$, left atrial volume just before atrial contraction; LAEFPassive, left atrial passive emptying fraction; and PWV, pulse wave velocity.

Spearman correlation coefficients $r$ were calculated for the entire patient cohort (1- and 2-stage arterial switch operation); $*P<0.05$ and †$P<0.01$.

### Comparison of Adult TGA Patients After 1- and 2-Stage ASO

The findings for the subgroups of adult patients after 1- and 2-stage ASO are compared in Table 4.

In the 2-stage ASO group, maximal cross-sectional areas of the aortic root and the ascending aorta were larger than in patients after 1-stage ASO.

No difference of PWV was found between 1- and 2-stage ASO patients (Table 4). But compared with age-matched controls, all adult TGA patients from both groups had a significantly higher PWV (all adult TGA patients: 4.9±1.1 versus 3.5±0.6 m/s, $P<0.01$; 1-stage ASO: 4.6±1.1 versus 3.4±0.5 m/s).

Figure 5. Relationship between age and distensibility of the aortic root in transposition of the great artery (TGA) patients (left) and controls (right). The solid line shows a locally weighted polynomial regression fit, with dashed lines representing the 95% confidence limits for the predicted values ($±2×$ the SE for the predicted values). Both graphs use the same vertical scale limits to highlight differences between patients and volunteers.
that impairment of the bioelastic properties affects the thoracic aorta, including locations remote from the dilated aortic root and sections of the aorta directly affected by surgical manipulation. The strong correlation of both aortic distensibility and PWV with age suggests that the surgical intervention is followed by a decline of the bioelastic properties of the aorta, akin to premature aortic stiffening. The impaired aortic bioelasticity seems to have negative sequelae on cardiac function, as revealed by the correlation of aortic distensibility with LA volumes and LAEFPassive, which can be considered as surrogate markers of diastolic dysfunction.12,13

Aortic Dimensions and Aortic Insufficiency
Significant enlargement of the aortic root was found in our TGA patients, whereas cross-sectional areas of the ascending and descending aorta were not significantly different from the control group. Aortic root enlargement after ASO has previously been reported from our group4 and by other echocardiographic studies.19,20 A CMR study by Grotenhuis et al8 in 15 TGA patients also revealed significantly increased aortic root diameters. Furthermore, they showed that patients with AR had even larger aortic root diameters. This is in agreement with our findings in that TGA patients with a higher degree of AR had a larger cross-sectional area of the aortic root. However, only a small number of patients (n=5) had more than mild AR, and higher degree AR was infrequent (n=1).

Ventricular septal defects and previous PAB have been reported as risk factors for aortic root dilatation and AR after ASO.3,21,22 In a subanalysis of adult patients with simple TGA after 1-stage versus 2-stage ASO, we found significantly increased cross-sectional areas of the aortic root and the ascending aorta in the latter group, whereas the severity of AR was not different. Although we observed an overall relationship between the proximal aortic cross-sectional area and AR, the absence of significant differences of AR between 1- and

Figure 6. The pulse wave velocity (left), and distensibility in the ascending aorta at the level of the sinus of valsalva (right) and in the ascending aorta (P<0.001; not shown) correlated significantly with the left atrial (LA) passive emptying ejection fraction (EF), a marker of diastolic function, using Spearman’s rank-based correlation. The correlation between distensibility at the sinus of valsalva and LA passive emptying function remained significant (P=0.004), if only the data for transposition of the great artery (TGA) patients were included (filled circles). The solid lines show a locally weighted polynomial regression fit, with dashed lines representing the 95% confidence limits for the predicted values (±2× the SE for the predicted values). The passive emptying volume EF for the LA was significantly different between TGA patients and volunteers (P<0.0001 for both t test, and nonparametric Mann–Whitney U test).

Figure 7. Relationship between age and pulse wave velocity in transposition of the great artery patients (left) and controls (right). The solid line shows a locally weighted polynomial regression fit, with dashed lines representing the 95% confidence limits for the predicted values (±2× the SE for the predicted values).
Aortic Distensibility

In agreement with data from echocardiographic and CMR studies, we found reduced distensibility of the aortic root in TGA patients after ASO.\textsuperscript{8,10} This finding was explained among other factors by the increased aortic wall stress of the dilated aortic root.\textsuperscript{8,10} However, our results did not show any significant relation between the normalized aortic cross-sectional area and its distensibility. Probably, other factors contribute to reduced distensibility. Niwa et al\textsuperscript{7} observed abnormalities of elastic fibers, smooth muscle, collagen, and ground substance of the medial layer already in the native aortic wall of neonates with TGA, which may affect distensibility. Alternatively in surgical patients, fibrous tissue around the transposed arteries after ASO or the pulmonary artery branches embracing the aorta after Lecompte maneuver may impede aortic root distensibility. Stefanadis et al\textsuperscript{23,24} detected severe structural changes of the aortic wall and a decrease of distensibility in animals after experimental aortic dissection and argued that this may be caused by damaging of the vasa vasorum.

Especially, for the decreased aortic root distensibility, which was measured approximately at the suture line after ASO, a combination of fibrosis resulting directly from surgery, and intrinsic aortic wall abnormalities may explain why aortic distensibility was most impaired near the aortic root and sinus of vasa saliva, compared with other more distal locations. Nevertheless, the direct impact from surgical manipulation is unlikely to be only culprit cause of impaired bioelasticity, as PWV measured between the ascending aorta at the level of the right pulmonary artery, and a corresponding level in the descending thoracic aorta was also significantly different between TGA patients and healthy controls.

The impairment of arterial distensibility is a known risk factor for cardiovascular morbidity and mortality because of the development of systolic arterial hypertension, premature atherosclerosis, and aneurysm formation.\textsuperscript{25–28} It may also adversely affect ventriculo-arterial coupling because of the increased ventricular afterload, with the consequence of LV hypertrophy and dysfunction in the long-term.\textsuperscript{26,29,30} In patients with other aortic pathologies, as bicuspid aortic valve and Marfan syndrome, or after Ross procedure it has been shown that a reduced aortic distensibility seems to be associated with LV systolic dysfunction and hypertrophy, and that in those patients, the descending aorta can also be affected.\textsuperscript{31–33} We demonstrated that the decreased aortic distensibility is accompanied by increased LA volumes. Furthermore, we

Table 4. Comparison of Cardiovascular MRI Measurements in Adult Transposition of the Great Arteries Patients After 1- and 2-Stage ASO

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults With 1-Stage ASO (n=10)</th>
<th>Adults With 2-Stage ASO (n=8)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>20.9±2.1</td>
<td>23.8±6.9</td>
<td>0.05</td>
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<tr>
<td>Maximal aortic area, mm(^2)/m</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root</td>
<td>529.3±70.7</td>
<td>870.4±311.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>336.1±58.3</td>
<td>459.5±134.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Descending aorta at the isthmus</td>
<td>194.4±30.6</td>
<td>223.1±61.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Descending aorta at the level of the diaphragm</td>
<td>179.4±43.4</td>
<td>179.2±50.2</td>
<td>0.83</td>
</tr>
<tr>
<td>Aortic arch angle, °</td>
<td>55.7±7.5</td>
<td>60.4±12.2</td>
<td>0.31</td>
</tr>
<tr>
<td>AR percentage, %</td>
<td>3.9±2.1</td>
<td>7.8±6.9</td>
<td>0.52</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>56.0±9.4</td>
<td>54.8±8.3</td>
<td>0.31</td>
</tr>
<tr>
<td>LVSV, mL/m</td>
<td>50.8±7.0</td>
<td>43.4±9.0</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEDV, mL/m</td>
<td>91.5±18.3</td>
<td>82.3±21.1</td>
<td>0.37</td>
</tr>
<tr>
<td>LVESV, mL/m</td>
<td>40.7±18.0</td>
<td>38.8±14.1</td>
<td>0.82</td>
</tr>
<tr>
<td>LV mass, g/m</td>
<td>61.4±11.6</td>
<td>56.0±17.5</td>
<td>0.16</td>
</tr>
<tr>
<td>LAVol(_{max}), mL/m</td>
<td>42.5±15.0</td>
<td>38.4±9.9</td>
<td>0.64</td>
</tr>
<tr>
<td>LAVol(_{min}), mL/m</td>
<td>21.7±7.7</td>
<td>22.8±7.2</td>
<td>0.82</td>
</tr>
<tr>
<td>LAVol(_{ac}), mL/m</td>
<td>32.5±11.5</td>
<td>29.2±8.9</td>
<td>0.49</td>
</tr>
<tr>
<td>LAEF(_{pass}), %</td>
<td>22.7±5.9</td>
<td>24.3±7.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Distensibility (10(^{-3}) mm(^{-1}) Hg(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root</td>
<td>2.4±0.9</td>
<td>1.9±1.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>3.8±2.3</td>
<td>2.5±0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Descending aorta at the isthmus</td>
<td>6.9±2.2</td>
<td>5.7±1.1</td>
<td>0.63</td>
</tr>
<tr>
<td>Descending aorta at the level of the diaphragm</td>
<td>7.5±3.2</td>
<td>8.2±1.5</td>
<td>0.25</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>4.6±1.1</td>
<td>5.3±1.0</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. AR indicates aortic regurgitation; ASO, arterial switch operation; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAVol\(_{max}\), maximal left atrial volume; LAVol\(_{min}\), minimal left atrial volume; LAVol\(_{ac}\), left atrial volume just before atrial contraction; LAEF\(_{pass}\), left atrial passive emptying fraction; and PWV, pulse wave velocity.

P values are from the Mann–Whitney U test.

2-stage TGA patients may be because of the limited number of patients with 2-stage ASO (n=8).

Aortic Distensibility

In agreement with data from echocardiographic and CMR studies, we found reduced distensibility of the aortic root in TGA patients after ASO.\textsuperscript{8,10} This finding was explained among other factors by the increased aortic wall stress of the dilated aortic root.\textsuperscript{8,10} However, our results did not show any significant relation between the normalized aortic cross-sectional area and its distensibility. Probably, other factors contribute to reduced distensibility. Niwa et al\textsuperscript{7} observed abnormalities of elastic fibers, smooth muscle, collagen, and ground substance of the medial layer already in the native aortic wall of neonates with TGA, which may affect distensibility. Alternatively in surgical patients, fibrous tissue around the transposed arteries after ASO or the pulmonary artery branches embracing the aorta after Lecompte maneuver may impede aortic root distensibility. Stefanadis et al\textsuperscript{23,24} detected severe structural changes of the aortic wall and a decrease of distensibility in animals after experimental aortic dissection and argued that this may be caused by damaging of the vasa vasorum.

Especially, for the decreased aortic root distensibility, which was measured approximately at the suture line after ASO, a combination of fibrosis resulting directly from surgery, and intrinsic aortic wall abnormalities may explain why aortic distensibility was most impaired near the aortic root and sinus of vasa saliva, compared with other more distal locations. Nevertheless, the direct impact from surgical manipulation is unlikely to be only culprit cause of impaired bioelasticity, as PWV measured between the ascending aorta at the level of the right pulmonary artery, and a corresponding level in the descending thoracic aorta was also significantly different between TGA patients and healthy controls.

The impairment of arterial distensibility is a known risk factor for cardiovascular morbidity and mortality because of the development of systolic arterial hypertension, premature atherosclerosis, and aneurysm formation.\textsuperscript{25–28} It may also adversely affect ventriculo-arterial coupling because of the increased ventricular afterload, with the consequence of LV hypertrophy and dysfunction in the long-term.\textsuperscript{26,29,30} In patients with other aortic pathologies, as bicuspid aortic valve and Marfan syndrome, or after Ross procedure it has been shown that a reduced aortic distensibility seems to be associated with LV systolic dysfunction and hypertrophy, and that in those patients, the descending aorta can also be affected.\textsuperscript{31–33} We demonstrated that the decreased aortic distensibility is accompanied by increased LA volumes. Furthermore, we
found lower LAEF_{Passive} in TGA patients, and a positive correlation of LAEF_{Passive} with aortic root distensibility (Figure 6). Both LA volumes and LAEF_{Passive} have been used as markers of LV diastolic dysfunction.\textsuperscript{11,13} Therefore, our data suggest that impaired aortic distensibility is likely to contribute to LV diastolic dysfunction in TGA patients.

In contrast to healthy volunteers, who showed no change of aortic distensibility until the young adult age, the aortic root after ASO displayed a negative correlation between patient age and aortic distensibility (Figure 5). This indicates that there is an earlier loss of bioelasticity of the aorta in TGA patients. As a possible consequence, in our relatively young patient cohort, LV mass was significantly increased. It will be important to monitor the change of aortic elasticity and the impact on LV function during follow-up in patients after ASO.

An early angiographic study from our institution investigated the impact of PAB on the distensibility of the neo-aortic root in a small group of 7 patients along 2-stage ASO.\textsuperscript{34} Although distensibility before PAB was normal, it significantly decreased after the operation. At the time of ASO, histological examination showed fragmentation and shortening of elastic fibers of the neo-aortic wall. In our study, aortic distensibility was similarly reduced in adults who underwent 2-stage and 1-stage ASO (Table 4). PAB obviously does not enhance the loss of aortic bioelasticity, which occurs much earlier in all patients after ASO in comparison with healthy young adults because of factors discussed above.

**Aortic PWV**

Another surrogate marker for an impaired aortic elasticity is the increase of PWV. PWV was not increased in children after 1-stage ASO, but the adult patients after 1- or 2-stage ASO had a significantly higher PWV than controls. In contrast to healthy controls, TGA patients showed a strong correlation of PWV with age. The upslope of the polynomial regression curve in Figure 7 resembles the reported increase of PWV beyond the fourth decade in healthy individuals and indicates an earlier loss of aortic bioelasticity.\textsuperscript{35}

Previous studies that analyzed aortic PWV after ASO revealed conflicting results. Although Grotenhuis et al\textsuperscript{1} observed an increased aortic PWV investigating a small cohort of 15 patients by CMR with an age range from 12 to 21 years, Agnoletti et al\textsuperscript{1} found normal data using applanation tonometry in children aged 5 to 7 years. Considering that we evaluated both children and adults, our findings are consistent with both of these studies, as we found a normal PWV in small children and increased values in adolescents and young adults (Figure 7).

Although our study demonstrated no consequences of the steep aortic arch on PWV, Agnoletti et al\textsuperscript{1} found an increased systolic pulse wave reflection with a sharper angulation of the aortic arch using applanation tonometry. Except for the methodological differences between both studies, we see no other explanations for the different PWV results.

Both parameters of aortic elasticity, PWV and distensibility, were correlated to an increased size of the left atrium and LAEF_{Passive}, providing compelling evidence for the relationship between aortic disease and an impairment of diastolic function.

**Study Limitations**

Our findings concerning patients after 2-stage ASO are based on a rather small number. However, as the technique of 2-stage ASO was rapidly abandoned when 1-stage ASO in neonates became available, patients with 2-stage ASO have become increasingly rare worldwide. The results from this cross-sectional observational study do not allow the establishment of a cause and effect relationships, and this will require further longitudinal follow-up by CMR. In some patients PWV and AR assessment as well as aortic angle measurement were not possible because of metal artifacts from surgical implants.

Sedation was necessary in 13 small children (15\%) of the whole study population, including patients and controls. An influence of the sedation on blood pressure is likely and might have changed aortic distensibility because there is only a linear response of area change over a limited range of pulse pressures.

**Conclusions**

In patients after ASO, aortic root dilatation and impaired bioelastic properties of the thoracic aorta are present and are related to LV diastolic dysfunction. The correlations between aortic elasticity parameters and age in a young cohort of patients indicate early stiffening of the thoracic aorta. Because aortic stiffness is an important cardiovascular risk factor, our findings may have consequences in the clinical management after ASO to detect early onset of degenerative cardiovascular disease and its impact on LV diastolic function.

**Acknowledgments**

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**Disclosures**

None.

**References**

Aortic Elasticity After Arterial Switch Operation


**CLINICAL PERSPECTIVE**

In patients with transposition of the great arteries (TGA), the bioelastic function of the aorta is suspected to be important for long-term prognosis after the arterial switch operation. Nonprogressive aortic root dilatation and reduced proximal aortic elasticity have been reported previously. However, comprehensive data about the bioelastic properties of the entire thoracic aorta, their potential change with age, and their effect on left ventricular function have been lacking. The present study applied cardiac MRI to assess the bioelasticity of the thoracic aorta (distensibility and pulse wave velocity) and their association with age, aortic dimensions, left ventricular systolic and diastolic function in S1 transposition of the great artery patients after arterial switch operation. The results show that aortic root dilatation and impaired aortic bioelasticity were common in transposition of the great artery patients, and affected left ventricular diastolic function. In contrast to controls, aortic pulse wave velocity increased and aortic root stiffness decreased rapidly with age, suggesting premature aortic stiffening. Increased arterial stiffness and left ventricular dysfunction are known cardiovascular risk factors. Therefore, transposition of the great artery patients may need regular follow ups for cardiovascular evaluation and higher compliance with a healthy lifestyle to prevent an early onset of degenerative cardiovascular disease.
Implications of Early Aortic Stiffening in Patients With Transposition of the Great Arteries After Arterial Switch Operation

Inga Voges, Michael Jerosch-Herold, Jürgen Hedderich, Christopher Hart, Colin Petko, Jens Scheewe, Ana Cristina Andrade, Minh Pham, Dominik Gabbert, Hans-Heiner Kramer and Carsten Rickers

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