Implications of Early Aortic Stiffening in Patients with Transposition of the Great Arteries after Arterial Switch Operation

Voges et al: Aortic Elasticity after Arterial Switch Operation

Inga Voges, MD1; Michael Jerosch-Herold, PhD4; Jürgen Hedderich3;
Christopher Hart, MD1; Colin Petko, MD1; Jens Scheewe, MD2;
Ana Cristina Andrade, MD1; Minh Pham, MD1; Dominik Gabbert, PhD1;
Hans-Heiner Kramer, MD1; Carsten Rickers, MD1

1Department of Congenital Heart Disease and Pediatric Cardiology,
2Department of Cardiac and Vascular Surgery,
3Department for Medical Informatics and Statistics, University Hospital of Schleswig-Holstein, Arnold-Heller-Straße 3, 24105 Kiel, Germany
4Department of Radiology, Brigham & Women's Hospital, Harvard University, 75 Francis Street, Boston, MA 02115

Correspondence to:
Carsten Rickers, MD
Department of Congenital Heart Disease and Pediatric Cardiology
University Hospital of Schleswig-Holstein, Campus Kiel
Arnold-Heller-Str. 3
24105 Kiel, Germany
Telephone: 0049-431-597-1728
Fax: 0049-431-597-1828
Email: rickers@pedcard.uni-kiel.de

DOI: 10.1161/CIRCIMAGING.112.000131

Journal Subject Code: Imaging [150]
Abstract

Background—The elastic function of the aorta in patients with transposition of the great arteries (TGA) 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 magnetic resonance imaging. Forty-three patients (12.8±6.9 years) underwent one-stage ASO, 8 patients (23.8±6.9 years) had prior pulmonary artery banding (two-stage ASO). Aortic dimensions, distensibility, pulse wave velocity (PWV), aortic arch angle, left ventricular (LV) mass, LV systolic function and left atrial (LA) volumes, and LA passive emptying function (LAEPassive) as marker of LV diastolic function were assessed. Compared to controls, patients had increased aortic root areas (602.6±240.5 vs. 356.8±113.4 mm²/m, p<0.01) and reduced distensibility of the thoracic aorta most pronounced at the aortic root (3.2±2.0 vs. 9.1±4.7 10⁻³ mmHg⁻¹, p<0.01). Aortic distensibility correlated negatively with the aortic areas (p<0.01). PWV was higher in adults after ASO (5.0±1.0 vs. 3.8±1.3 m/s, p<0.01). In contrast to controls PWV and distensibility correlated with age in patients (p=0.04-<0.01). LV mass was higher in patients (p=0.02). LA volumes correlated negatively with aortic root and ascending aortic distensibility and positively with PWV (p<0.05). In patients LAEPassive was lower (27.3±8.9 vs. 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 TGA 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.

Key Words: transposition of the great arteries, arterial stiffness, left atrial volume, magnetic resonance imaging
Since its introduction in the late 1970’s, the arterial switch operation (ASO) has become the gold standard for surgical repair of transposition of the great arteries (TGA) in neonates and infants.\textsuperscript{1,2} However, several studies have shown evidence, that even after successful anatomical repair, patients may be prone to long term problems. The fate of the aorta and aortic valve has been assessed in previous studies.\textsuperscript{3,4,5} The majority of patients show non-progressive dilatation of the aortic root, but only few cases suffer from aortic insufficiency.\textsuperscript{6} In addition, reduced proximal aortic elasticity, structural abnormalities of the arterial walls, and increased carotid artery stiffness have been reported in TGA patients.\textsuperscript{7-10} Additionally, a correlation between the typically steep angle of the aortic arch after the Lecompte maneuver and a higher augmentation index of the ascending aorta, an indirect marker of reduced elasticity, was found in a recent study using aortography and applanation tonometry.\textsuperscript{11} However, data are lacking about the functional status of the entire length of the thoracic aorta as well as its potential change with age after surgical repair, and the impact on left ventricular (LV) function.

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 passive emptying function (\textit{LAEF\textsubscript{Passive}}), as markers of LV diastolic function,\textsuperscript{12,13} by using cardiovascular magnetic resonance imaging (CMR).

\textbf{Methods}

\textbf{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 (see Table 1). 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 (one-stage ASO). Eight patients underwent a two-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 one-stage ASO with patients after two-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 non-invasive 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 five 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 magnetic resonance imaging (MRI) of the central nervous system (CNS) because of psychomotor retardation and epilepsy, they received phenobarbital or chloralhydrate for CNS MRI. Immediately after CNS MRI non-contrast 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. The
scans of controls, including the addition of CMR sequences in studies of sedated patients, were part of the protocol 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, 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 LA E' indicating LV diastolic function. Furthermore, the angulation of the aortic arch angle was measured. The scan parameters for the cine sequences were as follows: FOV 280x224 mm, voxel size 1.88x1.94x6 mm, TR/TE=4.4/2.5 ms, 25 cardiac phases, non-breath-hold, number of repetitions: 2, total scan duration: 3-6 min.

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: FOV 270x270 mm, voxel size 1.64x1.4x7 mm, TR/TE=4.4/2.7 ms, max. velocity encoding: 200 cm/s.

Additionally, high resolution gadolinium-enhanced MR-angiography was performed in all patients for detailed 3D visualization of the aorta (Figure 1), using a keyhole technique, with the following imaging parameters: FOV 380x380 mm, 70 slices, keyhole percentage
20%, 20 dynamics, keyhole scan time 1.7 s, TR/TE=2.4/0.93 ms, scan duration 0:40 min.

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 due to 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 artefacts 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, 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, Wisconsin).

The maximal and minimal areas of the aorta (Amax and Amin) were determined at four 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 measurements were made at the time of the maximal distension of the aorta and were used for comparison of aortic dimensions between patients and controls. Area measurements were also used for further calculations, specifically the aortic distensibility calculation.
Aortic distensibility was assessed from two-dimensional axial cine images at the aortic root, and the ascending aorta as well as in the descending aorta at the level of the aortic isthmus and above the diaphragm in patients and controls. The systolic and diastolic blood pressures ($P_{\text{max}}$ and $P_{\text{min}}$) were obtained non-invasively using a CMR-compatible monitor with sphygmomanometer (Invivo Precess$^\text{TM}$ 3160, Invivo, Orlando, USA), with the cuff placed around the right arm.

Distensibility was calculated according to the following formula:\textsuperscript{14}

$$\text{Distensibility} = \frac{(A_{\text{max}} - A_{\text{min}})}{[A_{\text{min}} \times (P_{\text{max}} - P_{\text{min}})]}$$

PWV was determined from aortic flow versus time curves, as the ratio of the aortic segment length, ($\Delta x$, meters; Figure 3A) divided by the time delay of the distal flow curve, relative to the proximal flow curve ($\Delta t$, seconds; Figure 3B):

$$\text{PWV} = \frac{\Delta x}{\Delta t}.$$  

Aortic flow measurements were analyzed from phase-contrast cine sequences to calculate aortic regurgitation (AR). AR was considered to be mild if the regurgitant fraction was 5%-15%, moderate if the regurgitant fraction was 16%-30%, moderate to severe if the regurgitant fraction was 31-50%, and severe if the regurgitant fraction was >50% of the systolic forward flow volume.\textsuperscript{15}

LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) 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 (LVEF) was calculated by dividing the stroke volume by the LVEDV. 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$_{\text{max}}$), 2) minimal LA volume at mitral valve closure (LAVol$_{\text{min}}$), 3) before LA contraction
(LAVol_{ac}). The LV and LA volumes were indexed to body height. LA Volumes were used to calculate LAEF_{Passive} according to the following formula: \((\text{LAVol}_{\text{max}} - \text{LAVol}_{\text{ac}}) \times 100\% / \text{LAVol}_{\text{max}}\).^{13}

In 37 patients the aortic arch angle was measured from oblique sagittal gradient echo cine images between the intersection of two 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 artefacts or deficient sagittal angulation did not allow reliable angle measurements.

Statistical analysis
Statistical analysis was performed using MedCalc\textsuperscript{49} (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 values \pm standard deviation. The Mann-Whitney-U test for independent samples was used to compare patients and controls. Categorical data were compared using Fisher’s exact test. The strength of association was measured by Spearman rank correlation coefficients. A locally weighted polynomial regression method (LOESS) was used to describe relations between two measured variables with minimal prior assumptions. All comparison tests were two tailed and p-values of less than 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 gender, and diastolic or pulse pressures with a linear regression model. No adjustments were made for multiple comparisons due to 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 manuscript 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 one 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 to 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 to controls.

29 patients had competent aortic valves, but 15 had AR, which was mild in 10, moderate in 4 and moderate to severe in one patient. The degree of AR was similar in patients after one-stage and two-stage ASO (6.6%±10.2 vs. 7.8%±6.9, p=0.35). None of the controls had an AR fraction which 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 to the age-matched controls. LV volumes, LVEF 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’s compared to healthy controls (Table 2). Among all aortic segments, the aortic root had the lowest distensibility (p= 0.04 – <0.01).

The relationship of distensibility with clinical, anatomical and functional parameters in TGA patients was assessed by Spearman’s 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\textsubscript{max}, LAVol\textsubscript{min} and LAVol\textsubscript{ac} and positively with LAEF\textsubscript{reserv}. 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, LVEF, LVEDV, LVESV and LV mass.

Aortic pulse wave velocity and the effects of aortic arch angle

PWV did not differ significantly between young patients (<18 yrs) after ASO and age-matched controls (3.8±1.3 vs. 3.2±0.5 m/s). In adult patients PWV was significantly higher compared to children after ASO (5.0±1.0 vs. 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’s rank correlation coefficient for PWV vs. age did not change substantially, when the 8 patients after two-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\textsubscript{max}: r=0.54, p<0.01; LAVol\textsubscript{min}: r=0.50, p<0.05; LAVol\textsubscript{ac}:
r=0.47, p<0.05; total LA emptying volume: r= 0.47, p<0.05) in patients. Furthermore, we found a relation between LAEF\textsubscript{passive} 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.

Comparison of adult TGA patients after one- and two-stage ASO

The findings for the sub-groups of adult patients after one-stage and two-stage ASO are compared in Table 4.

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

No difference of PWV was found between one- and two-stage ASO patients (Table 4). But compared to age-matched controls all adult TGA patients from both groups had a significantly higher PWV (all adult TGA patients: 4.9±1.1 vs. 3.5±0.6 m/s; p<0.01; one-stage ASO: 4.6±1.1 vs. 3.4±0.5 m/s; p<0.01; two-stage ASO: 5.3±1.0 vs. 3.5±0.6 m/s; p<0.01). Between both groups, there were no differences of the aortic arch angle, AR, aortic distensibility and LV dimensions, mass and systolic and diastolic function.

Discussion

While aortic root dilation has been previously described in young adults with TGA after ASO, this study demonstrates 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 appears to have negative sequelae on cardiac function, as revealed by the
correlation of aortic distensibility with LA volumes and \( \text{LAEF}_{\text{Passive}} \), which can be considered
as surrogate markers of diastolic dysfunction.\textsuperscript{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
group,\textsuperscript{4} and by other echocardiographic studies.\textsuperscript{19,20} A CMR study by Grotenhuis et al. in 15
TGA patients also revealed significantly increased aortic root diameters.\textsuperscript{8} 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.\textsuperscript{3,21,22} In a sub-analysis of adult patients with simple
TGA after one-stage vs. two-stage ASO, we found significantly increased cross-sectional
areas of the aortic root and the ascending aorta in the latter group, while 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 one- and
two-stage TGA patients may be due to the limited number of patients with two-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.\(^{8,10}\) This finding was explained among other factors by the increased aortic wall stress of the dilated aortic root.\(^{8,10}\) 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. observed abnormalities of elastic fibres, smooth muscle, collagen, and ground substance of the medial layer already in the native aortic wall of neonates with TGA,\(^{7}\) 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. detected in animals after experimental aortic dissection severe structural changes of the aortic wall and a decrease of distensibility and argued that this may be caused by damaging of the vasa vasorum.\(^{23,24}\)

Especially, for the decreased aortic root distensibility, which was measured approximately at the suture line following 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 valsalva, compared to other more distal locations. Nevertheless the direct impact from surgical manipulation is unlikely to be only culprit cause of impaired bioelasticity, as pulse wave velocity 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.\(^{25-28}\) It may also adversely affect
ventricle-arterial coupling due to the increased ventricular afterload, with the consequence of LV hypertrophy and dysfunction in the long-term.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 also the descending aorta can be affected.³¹-³³ We demonstrated that the decreased aortic distensibility is accompanied by increased LA volumes. Furthermore, we found lower passive emptying function (LAEF<sub>Passive</sub>) in TGA patients, and a positive correlation of LAEF<sub>Passive</sub> with aortic root distensibility (Figure 6). Both, LA volumes and LAEF<sub>Passive</sub> have been used as markers of LV diastolic dysfunction.¹²,¹³ 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 two-stage ASO.³⁴ While distensibility before PAB was normal, it significantly decreased after the operation. At the time of ASO, histological examination showed fragmentation and shortening of elastic fibres of the neo-aortic wall. In our study aortic distensibility was similarly reduced in adults who underwent two-stage and one-stage ASO, respectively (Table 4). PAB obviously does
not enhance the loss of aortic bioelasticity, which occurs much earlier in all patients after ASO in comparison to healthy young adults due to factors discussed above.

**Aortic pulse wave velocity**

Another surrogate marker for an impaired aortic elasticity is the increase of PWV. PWV was not increased in children after one-stage ASO, but the adult patients after one- or two-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. Previous studies which analyzed aortic PWV after ASO revealed conflicting results. While Grotenhuis et al. observed an increased aortic PWV investigating a small cohort of 15 patients by CMR with an age range from 12-21 years, Agnoletti et al. found normal data by using applanation tonometry in children aged 5-7 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).

While our study demonstrated no consequences of the steep aortic arch on PWV, Agnoletti et al. found an increased systolic pulse wave reflection with a sharper angulation of the aortic arch by 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 LA passive emptying function, providing compelling evidence for the relationship between aortic disease and an impairment of diastolic function.
Study Limitations

Our findings concerning patients after two-stage ASO are based on a rather small number. However, as the technique of two-stage ASO was rapidly abandoned when one-stage ASO in neonates become available, patients with two-stage ASO have become increasingly rare, worldwide. The results from this cross-sectional observational study do not allow to establish 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 artefacts 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 since 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. Since 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 left ventricular diastolic function.

Acknowledgements

We thank Mrs. Traudel Hansen, (CMR technologist) for her assistance in patient management.
Sources of Funding

This study was supported by the Fördergemeinschaft Deutsche Kinderherzzentren e. V., Friedrich-Wilhelm-Str. 45, 53113 Bonn, Germany.

Disclosures

None.

References

11. Agnoletti G, Ou P, Celermajer DS, Boudjemline Y, Marini D, Bonnet D, Aggoun Y. Acute angulation of the aortic arch predisposes a patient to ascending aortic dilatation and


### Table 1. Clinical Characteristics of TGA 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 (years)</td>
<td>14.5 ± 7.9</td>
<td>14.1 ± 8.0</td>
<td>0.62</td>
</tr>
<tr>
<td>Female (%)</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. P-Values are from the Mann-Whitney-U test or from the Fisher’s exact test.

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BSA, body surface area.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=51)</td>
<td>(N=34)</td>
<td></td>
</tr>
<tr>
<td>Maximal aortic area (mm²/m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root</td>
<td>602.6 ± 240.5</td>
<td>356.8 ± 113.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>340.8 ± 144.1</td>
<td>315.4 ± 89.3</td>
<td>0.70</td>
</tr>
<tr>
<td>Descending aorta at the isthmus</td>
<td>169.1 ± 51.9</td>
<td>153.9 ± 36.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Descending aorta at the level of the diaphragm</td>
<td>144.6 ± 51.3</td>
<td>129.0 ± 32.1</td>
<td>0.14</td>
</tr>
<tr>
<td>Aortic arch angle (°)</td>
<td>57.2 ± 8.0</td>
<td>70.7 ± 17.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AR percentage (%), range</td>
<td>6.8 (0.3 – 44.5)</td>
<td>0.6 (0 – 3.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.5 ± 9.3</td>
<td>60.1 ± 5.6</td>
<td>0.18</td>
</tr>
<tr>
<td>LVSV (ml/m)</td>
<td>42.8 ± 12.8</td>
<td>40.6 ± 11.2</td>
<td>0.39</td>
</tr>
<tr>
<td>LVEDV (ml/m)</td>
<td>77.4 ± 26.6</td>
<td>68.4 ± 20.8</td>
<td>0.16</td>
</tr>
<tr>
<td>LVESV (ml/m)</td>
<td>34.2 ± 18.3</td>
<td>29.5 ± 11.6</td>
<td>0.29</td>
</tr>
<tr>
<td>LV mass (g/m)</td>
<td>50.9 ± 19.5</td>
<td>42.7 ± 14.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LAVolmax (ml/m)</td>
<td>34.6 ± 11.5</td>
<td>39.4 ± 13.8</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Data are presented as mean ± SD or median and range. P-Values are from the Mann-Whitney-U test.

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

<table>
<thead>
<tr>
<th></th>
<th>Aortic root</th>
<th>Ascending aorta</th>
<th>Descending aorta at the isthmus</th>
<th>Descending aorta at the level of the diaphragm</th>
<th>PWV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAVol\textsubscript{min} (ml/m)</td>
<td>18.5 ± 6.8</td>
<td>17.8 ± 6.7</td>
<td>0.60</td>
<td></td>
<td>3.8 ± 1.3</td>
</tr>
<tr>
<td>LAVol\textsubscript{ac} (ml/m)</td>
<td>25.3 ± 9.7</td>
<td>23.4 ± 9.0</td>
<td>0.45</td>
<td></td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>LAEFPassive (%)</td>
<td>27.3 ± 8.9</td>
<td>41.1 ± 6.0</td>
<td>&lt;0.01</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Distensibility (10^{-3} mmHg\textsuperscript{-1})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic root</td>
<td>3.2 ± 2.0</td>
<td>9.1 ± 4.7</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>4.4 ± 3.0</td>
<td>10.8 ± 5.5</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending aorta at the isthmus</td>
<td>7.3 ± 3.1</td>
<td>9.1 ± 5.1</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending aorta at the level of the diaphragm</td>
<td>9.0 ± 4.5</td>
<td>9.9 ± 4.9</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Downloaded from http://circimaging.ahajournals.org/ by guest on October 19, 2017
Table 3. Relationship of Distensibility and PWV with Clinical, Anatomical and Functional Parameters in TGA 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 (years)</td>
<td>-0.40*</td>
<td>-0.38*</td>
<td>-0.45*</td>
</tr>
<tr>
<td>Maximal aortic area (mm²/m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aortic root</td>
<td>-0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aorta ascendens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Aorta descendens at the isthmus</td>
<td></td>
<td></td>
<td>-0.53†</td>
</tr>
<tr>
<td>AR fraction (%)</td>
<td>-0.05</td>
<td>-0.10</td>
<td>-0.20</td>
</tr>
<tr>
<td>Aortic arch angle (°)</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>-0.22</td>
</tr>
<tr>
<td>LVESV (ml/m)</td>
<td>-0.22</td>
<td>-0.23</td>
<td>-0.11</td>
</tr>
</tbody>
</table>
Spearman correlation coefficients $r$ were calculated for the entire patient cohort (one- and two-stage ASO); *$p<0.05$, †$p<0.01$

<table>
<thead>
<tr>
<th>Variable</th>
<th>$r$</th>
<th>$p$</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g/m)</td>
<td>-0.11</td>
<td>-0.12</td>
<td>-0.24</td>
</tr>
<tr>
<td>LAVol$_{\text{max}}$ (ml/m)</td>
<td>-0.40*</td>
<td>-0.29</td>
<td>-0.34</td>
</tr>
<tr>
<td>LAVol$_{\text{min}}$ (ml/m)</td>
<td>-0.48†</td>
<td>-0.35*</td>
<td>-0.15</td>
</tr>
<tr>
<td>LAVol$_{\text{ac}}$ (ml/m)</td>
<td>-0.48†</td>
<td>-0.31</td>
<td>-0.26</td>
</tr>
<tr>
<td>LAEF$_{\text{Passive}}$ (%)</td>
<td>0.5†</td>
<td>0.21</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAVol$_{\text{max}}$, maximal left atrial volume; LAVol$_{\text{min}}$, minimal left atrial volume; LAVol$_{\text{ac}}$, left atrial volume just before atrial contraction; LAEF$_{\text{Passive}}$, left atrial passive emptying fraction; PWV, pulse wave velocity.
Table 4. Comparison of CMR measurements in adult TGA patients after one- and two-stage ASO

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adults with one-stage ASO (N=10)</th>
<th>Adults with two-stage ASO (N=8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.9 ± 2.1</td>
<td>23.8 ± 6.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Maximal aortic area (mm²/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 ± 8.3</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>
</tbody>
</table>
LAVol\textsubscript{max} (ml/m) & 42.5 ± 15.0 & 38.4 ± 9.9 & 0.64 \\
LAVol\textsubscript{min} (ml/m) & 21.7 ± 7.7 & 22.8 ± 7.2 & 0.82 \\
LAVol\textsubscript{lac} (ml/m) & 32.5 ± 11.5 & 29.2 ± 8.9 & 0.49 \\
LAEFP\textsubscript{Passive} (%) & 22.7 ± 5.9 & 24.3 ± 7.3 & 1.0 \\

Distensibility (10\textsuperscript{-3} mmHg\textsuperscript{-1})

<table>
<thead>
<tr>
<th></th>
<th>Aortic root</th>
<th>Ascending aorta</th>
<th>Descending aorta at the isthmus</th>
<th>Descending aorta at the level of the diaphragm</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (m/s)</td>
<td>4.6 ± 1.1</td>
<td>5.3 ± 1.0</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. P-Values are from the Mann-Whitney-U test.

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAVol\textsubscript{max}, maximal left atrial volume; LAVol\textsubscript{min}, minimal left atrial volume; LAVol\textsubscript{lac}, left atrial volume just before atrial contraction; LAEFP\textsubscript{Passive}, left atrial passive emptying fraction; PWV, pulse wave velocity.
Figure Legends

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

Figure 2. Aortic area measurements. Aortic area was assessed from axial MR images acquired with a gradient echo cine sequence at three different locations of the thoracic aorta: aortic root (1), ascending aorta (2), descending aorta at the aortic isthmus (3), descending aorta above the diaphragm (4). Aortic area measurements were used for distensibility estimation.

Figure 3. Pulse wave velocity. A) This sagittal image of the aorta was generated with a gradient echo cine sequence and shows the sites where phase contrast cine images were acquired. First, the distance along a midline through the aortic arch (Δx) between the measurement locations in the ascending and descending aorta was measured. B) Next, the transit delays (Δt) of the systolic flow curves in the descending (a1) relative to the ascending (a2) aorta were determined.

Figure 4. Aortic arch angle. Oblique sagittal magnetic resonance image acquired with a gradient echo cine sequence shows the aortic arch. The aortic arch angle was measured between the intersection of two lines (A, B) which are connecting the midpoint of the ascending (line A) and descending aorta (line B) at the level of the pulmonary artery bifurcation with the highest point of the aortic arch.

Figure 5. Relationship between age and distensibility of the aortic root in TGA patients (left) and controls (right). The solid line shows a locally weighted polynomial regression fit
LOESS method), with dashed lines representing the 95% confidence limits for the predicted values (±2 x times the standard error for the predicted values). Both graphs use the same vertical scale limits to highlight differences between patients and volunteers.

**Figure 6.** The pulse wave velocity (left panel), and distensibility in the ascending aorta at the level of the sinus of valsalva (right panel) 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 LAEF\textsubscript{passive} remained significant (p=0.004), if only the data for TGA patients were included (filled circles). The solid lines show a locally weighted polynomial regression fit (LOESS method), with dashed lines representing the 95% confidence limits for the predicted values (±2 x times the standard error 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 non-parametric Mann-Whitney-U test).

**Figure 7.** Relationship between age and PWV in TGA patients (left) and controls (right). The solid line shows a locally weighted polynomial regression fit (LOESS method), with dashed lines representing the 95% confidence limits for the predicted values (±2 x times the standard error for the predicted values).
Pulse Wave Velocity [f/s]

r = 0.29, p=0.032

Ao Distensibility (Sinus of Valsalva) [10^{-3} mmHg^{-1}]

r = 0.66, p<0.001

LA Passive EF [%]
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

_Circ Cardiovasc Imaging_. published online January 30, 2013;
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/early/2013/01/30/CIRCIMAGING.112.000131

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Imaging_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Imaging_ is online at:
http://circimaging.ahajournals.org//subscriptions/