Transposition of Great Arteries Is Associated With Increased Carotid Artery Stiffness

Beatrix Mersich, Peter Studinger, Zsuzsanna Lenard, Krisztina Kadar, Mark Kollai

Abstract—Transposition of great arteries is the consequence of abnormal aorticopulmonary septation. Animal embryonic data indicate that septation and elastogenesis are related events, but human and clinical data are not available. We tested the hypothesis that large artery elastic function was impaired in patients with transposition of great arteries. We studied 34 patients aged 9 to 19 years, 12±3 years after atrial switch operation; 14 patients aged 7 to 9 years, 8±1 years after arterial switch operation; and 108 healthy control subjects matched for age. Carotid artery diastolic diameter and pulsatile distension were determined by echo wall-tracking; carotid blood pressure was measured by tonometry. Systolic pressure was higher and diastolic pressure was lower in patients than in controls. Patients with atrial and arterial switch repair were compared with their respective controls by 2-factor ANOVA. For patients with atrial switch repair versus control, stiffness index β was 4.9±1.5 versus 3.1±1.0 (P<0.001); for patients with arterial switch versus control, stiffness index β was 3.8±1.1 versus 2.1±0.6 (P<0.001). Similar differences were observed for carotid compliance, distensibility, and incremental elastic modulus as well. The interaction term was not significant for any of the elastic variables, indicating that carotid stiffening was a characteristic of the condition and not the consequence of different hemodynamics. Carotid artery is markedly stiffer in patients, suggesting that impaired elastogenesis may constitute part of the congenital abnormality. Since carotid artery stiffness has been established as an independent cardiovascular risk factor, this condition may have consequences in the clinical management of these patients. (Hypertension. 2006;47:1197-1202.)

Key Words: carotid arteries ■ arteries ■ elasticity

Transposition of great arteries (TGA) is a severe congenital heart defect in which the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. TGA is the consequence of abnormal aorticopulmonary septal development. In animal models it has been demonstrated that great vessel elastogenesis was related to aorticopulmonary septation. Neural crest cells in the avian embryo, which form the septum, also synthesize the elastogenic matrix of the large vessel wall. We hypothesized that elastogenesis and aorticopulmonary septation were related events in human subjects as well; therefore, we compared the elastic parameters of the common carotid artery, a representative of large elastic arteries, in TGA patients and in age-matched control subjects to investigate whether impairment of large artery elastic function constituted part of congenital abnormality.

Materials and Methods

Subjects
Forty-eight TGA patients (34 male, aged 7 to 19 years) were recruited from the Gottsegan Cardiology Institute, Budapest, Hungary. Thirty-four of them (24 male, aged 9 to 19 years) had an atrial switch (AT-S) operation (Senning procedure), which was performed between the ages 6 months to 3 years; average time after repair was 12±3 years. The AT-S operation creates a tunnel between the atria, redirecting oxygen-rich blood to the right ventricle and aorta and the oxygen-poor blood to the left ventricle and pulmonary artery. Fourteen TGA patients (13 male, aged 7 to 9 years) had arterial switch (AR-S) operation, which was performed in the first life-month of these patients; average time after repair was 8±1 years. In the AR-S operation the aorta and pulmonary artery are switched back to their normal positions. The AT-S and AR-S are hemodynamically very different operations, with the first putting a severe load on the right ventricle, which can undergo muscle failure, and the other essentially correcting the anomaly. Consequently, the prognosis for AR-S patients is more favorable as compared with that for AT-S patients. Surgical data were obtained from operative notes. All patients were in clinical status Class I as defined according to the New York Heart Association functional classifications. None of the children was taking any medications. Exclusion criteria included permanent pacing, atrial fibrillation or >2 ectopic beats per minute during data acquisition, clinical instability within the preceding 2 months, hypertension, and diabetes mellitus. One hundred-eight age- and gender-matched healthy control subjects were also studied. All subjects gave written informed consent to participate in the study, which was approved by the Ethical Committee of the Semmelweis University, Budapest, Hungary.

Carotid Ultrasonography
Diameter of the left common carotid artery, its pulsatile distension, and the intima-media thickness (IMT) of the posterior wall were measured with ultrasonography. The scanner was positioned 1.5-cm proximal to the bifurcation. The ultrasound device consisted of a...
vessel wall echo-tracking system (Wall Track System, Pte Medical, Maastricht, The Netherlands) combined with a conventional ultrasound scanner (Scanner 200 Pte Medical, Maastricht, The Netherlands) and has been described in detail before. Carotid artery diameter was recorded in 5 to 7 epochs, each containing 5 to 8 distension pulses.

**Carotid Artery Pulse Pressure**

Carotid artery pressure was measured by applanation tonometry (SPT-301, Millar Instruments, Houston, Tex), and the carotid pulse wave recording was calibrated by using diastolic and mean brachial pressure values measured by sphygmomanometry on the right brachial artery. Diastolic brachial pressure was assigned to the minimum value of the carotid pressure pulse wave and the mean pressure to its electrically averaged value. This calibration of the tonometric signal was based on the assumption that mean pressure did not change in large conduit arteries and that diastolic pressure was not substantially different between the brachial and carotid arteries. The carotid tonometric pressure was used to calculate carotid artery elastic parameters. The cut-off frequencies of the recording devices were above 25 kHz, therefore, no distortion was induced into the frequency content of pulsatile signals.

**Carotid Artery Elastic Variables**

Carotid compliance was calculated as \( \Delta D/\Delta P \), where \( \Delta D \) is the change in diameter from end diastole to peak systole, and \( \Delta P \) is carotid pulse pressure. The distensibility coefficient (DC) was calculated as \( 2 \times \Delta D/ (D \times \Delta P) \), where \( D \) is end-diastolic diameter. Stiffness index \( \beta \) was expressed as \( \ln(SB/P) \times (\Delta D/\Delta P) \), where \( SB \) and \( P \) are systolic and diastolic carotid pressure, respectively. Carotid artery lumen cross-sectional area (LCSA) and intima-media cross-sectional area (IMCSA) were calculated as LCSA = \( \pi (D/2)^2 \), and IMCSA = \( \pi (D/2 + IMT)^2 - \pi (D/2)^2 \). Incremental elastic modulus was determined as \( E_u = [3(1 + LCSA/IMCSA)]/DC \).

**ECG and Respiration**

ECG was recorded continuously from the limb lead with the largest R wave. Respiration was recorded with an inductive system (Respirate System, Ambulatory Monitoring Inc).

**Ventricular Volumes and Ejection Fraction**

Ventricular volumes and ejection fraction of AT-S patients were determined by cardiac MRI (CMRI), which involved a standardized protocol that results in a series of short-axis cine loops covering the left ventricle (LV) and right ventricle (RV) from the atrioventricular valve plane to the apex. All studies were performed on a General Electric 1.5T Infinity MR instrument, equipped with EchoSpeed ACGD gradients running Signa LX 9.1. An ECG-triggered gradient echo steady-state free precession cine sequence (FIESTA, time of repetition 3.0 to 3.5 ms, echotime 1.0 to 1.2 ms, flip angle 45 to 60 degrees) was used to acquire images in the short axis plane in contiguous 8-mm locations from the valve plane to the apex of the heart. The resulting data were distributed along s cardiac cycle to reconstruct 20 cardiac phases at each location. The images were transferred to an independent computer workstation (Sun Ultra 60, 512Mb RAM, dual UltraSparc, Solaris, Advantage Workstation 4.0) for data analysis. By use of visual inspection of the cine loops, the endocardial borders of the LV and RV were outlined at each phase of the cardiac cycle at all levels from base to apex. All borders were marked by the same observer. LV volumes and ejection fractions of AR-S patients were determined by transthoracic 2-dimensional echocardiography, using conventional techniques.

**Protocol**

Subjects were studied in the early morning under standardized conditions, in a quiet room at a comfortable temperature. All fasted at least 2 hours before testing and were asked to refrain from strenuous exercise or drinking alcohol or caffeine-containing beverages for 24 hours before the study. On arrival at the investigation unit, the subjects were equipped with measurement devices, and then rested in supine position for \( \approx 15 \) minutes until the absence of evident heart rate and mean blood pressure trends demonstrated that satisfactory baseline conditions had been achieved. Carotid artery tonometric pressure on one side and diameter and wall thickness on the other side were recorded simultaneously, and these recordings were used to determine carotid elastic parameters. When recording sites were reversed, corresponding data from the opposite sides were not significantly different. Using the Bland–Altman analysis for paired data obtained from 34 TGA patients, the mean paired difference and the limit of agreement for stiffness index \( \beta \) was \( -0.02 \) and \( -0.52 \) to \( +0.46 \), respectively. CMRI and echocardiography was performed on the same week in the morning hours.

**Data Analysis**

Data are expressed as mean\( \pm SD \). Differences in variables between patients (AT-S and AR-S) and respective controls were analyzed by 2-factor ANOVA and the Tukey post hoc test. We selected control subjects, matched for age and sex, for each patient. Age ranges for AT-S and AR-S patients did not overlap, as AT-S subjects were older than AR-S subjects. We used a 2-factor ANOVA design, where one factor was condition (control versus TGA) and the other was type of operation (AT-S versus AR-S), which coincided with the age factor (older versus younger than aged 9 years). Relations between variables were investigated by univariate correlation analyses. Independent predictors of carotid artery elastic parameters were determined by multiple stepwise regression analyses. Significance was accepted at \( P<0.05 \). Statistical analysis was performed by the SigmaStat for Windows Version 2.03 (SPSS Inc) program package.

**Results**

Patients with different types of operation (AR-S versus AT-S) were evaluated separately. Clinical characteristics of patients and controls are given in Table 1. Patients had lower body mass index. Systolic pressure was higher (although not

**TABLE 1. Clinical Characteristics of TGA Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>AT-S (&lt;9 years)</th>
<th>AR-S (&lt;9 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>n, male</td>
<td>34 (24)</td>
<td>34 (24)</td>
</tr>
<tr>
<td>Age, y</td>
<td>13.2±2.9</td>
<td>13.3±3.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td>154±17</td>
<td>160±14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>45±15†</td>
<td>53±12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.1±3.0*</td>
<td>20.3±1.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>115±9†</td>
<td>109±19</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>62±7*</td>
<td>70±8</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>80±7</td>
<td>82±8</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>81±11</td>
<td>79±14</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic brachial pressure; DBP, diastolic brachial pressure; MBP, mean brachial pressure; HR, heart rate. Patients and controls were compared for differences by 2-factor (patients vs controls and AR-S vs AT-S) ANOVA. The interaction term was not significant for any of the variables; further comparisons were made within AR-S and AT-S groups using Tukey post-hoc tests. Data are given as mean\( \pm SD \).

Significantly different from respective control at *\( P<0.001 \); †\( P<0.01 \); ‡\( P<0.05 \).
Carotid artery were related inversely, stiffness index in health. In control subjects, compliance and DC of the which is an important variable determining arterial elasticity as 1 group. Analysis of the elastic variables, AT-S and AR-S patients were not significant; indicating the difference in carotid controls, determined by 2-factor ANOVA. The interaction term, ejection fractions were slightly lower as compared with reference values. In AR-S patients, LV volumes and ejection fractions, determined by echocardiography, were within normal limits. Representative carotid artery distension and pressure pulse waveforms are illustrated in Figure 1; carotid artery dimensions and elastic parameters are summarized in Table 2. In the AT-S group, carotid artery end-diastolic diameter was smaller and pulsatile distension was less despite the higher pulse pressure. In the AR-S group, end-diastolic diameter was not different from control, and pulsatile distension was reduced relative to the much higher pulse pressure in AR-S than in controls. IMT was significantly larger in patients than in controls; however, this significance was lost when AT-S and AR-S patients were examined separately. Within both the AT-S and AR-S groups, all elastic parameters indicated significant stiffening of the carotid artery in comparison with their respective controls, determined by 2-factor ANOVA. The interaction term, however, was not significant; indicating the difference in carotid stiffness between TGA patients and their respective controls was not dependent on the type of operation. Consequently, in further analysis of the elastic variables, AT-S and AR-S patients were treated as 1 group.

From all control data, nomograms were constructed to age, which is an important variable determining arterial elasticity in health. In control subjects, compliance and DC of the carotid artery were related inversely, stiffness index β and Einc, were related directly to age (Figure 2). When patients’ data were inserted into the nomograms, 15 of 48 patients had compliance and DC values below the lower 95% confidence limits of control data, and 21 and 14 patients had stiffness index β and Einc values, respectively, higher than the upper 95% confidence limits of control data. In univariate analysis performed separately in patients and in controls, carotid artery elasticity parameters were associated with age, systolic and diastolic pressures, and heart rate, but were not related to time after repair, right or left ventricular dimensions, and

<table>
<thead>
<tr>
<th>Carotid Variables</th>
<th>AT-S (&gt;9 years)</th>
<th>AR-S (&lt;9 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid Variables</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>ΔP, mm Hg</td>
<td>47 ± 11*</td>
<td>36 ± 9</td>
</tr>
<tr>
<td>D, μm</td>
<td>5670 ± 425†</td>
<td>5986 ± 544</td>
</tr>
<tr>
<td>ΔD, μm</td>
<td>679 ± 144*</td>
<td>851 ± 159</td>
</tr>
<tr>
<td>IMT, μm</td>
<td>546 ± 66</td>
<td>486 ± 55</td>
</tr>
<tr>
<td>Compliance, μm/mm Hg</td>
<td>15.3 ± 4.9*</td>
<td>25.5 ± 8.1</td>
</tr>
<tr>
<td>DC, 10⁻⁷/mm Hg</td>
<td>5.5 ± 2.0*</td>
<td>8.6 ± 2.8</td>
</tr>
<tr>
<td>Stiffness index β</td>
<td>4.9 ± 1.5*</td>
<td>3.1 ± 1.0</td>
</tr>
<tr>
<td>Einc, mm Hg</td>
<td>2.1 ± 0.8*</td>
<td>1.5 ± 0.5</td>
</tr>
</tbody>
</table>

D indicates end-diastolic diameter; IMT, intima-media wall thickness; Einc, incremental elastic modulus. Patients and controls were compared for differences by 2-factor (patients vs controls and AR-S vs AT-S) ANOVA. The interaction term was not significant for any of the variables; further comparisons were made within AR-S and AT-S groups using Tukey post-hoc tests. Data are given as mean ± SD.

Significantly different from respective control at *P < 0.001; †P < 0.01.

Figure 1. Representative waveforms of carotid artery distension and pressure pulses in a control subject and in a TGA patient with AT-S operation.

Figure 2. Nomogram to age of carotid artery elastic parameters for control data (△), with patients data (○) inserted. Solid lines indicate the actual regression line for control data; dashed lines designate the 95% confidence limits. In control subjects compliance and distensibility coefficient (DC) were inversely (r = −0.45 and −0.50, respectively, and P < 0.001) related to age; whereas stiffness index β and incremental elastic modulus (Einc) were directly (r = 0.55 and 0.56, respectively, and P < 0.001) related to age.
TABLE 3. Univariate Analysis: Correlation Coefficients For Relations Between Carotid Artery Elastic Parameters and Potential Predictors in Control Subjects and In All TGA Patients

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Compliance</th>
<th>DC</th>
<th>Stiffness Index β</th>
<th>E_{inc}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>–0.24†</td>
<td>–0.40*</td>
<td>0.37*</td>
<td>0.53*</td>
</tr>
<tr>
<td>SBP</td>
<td>–0.81*</td>
<td>–0.73*</td>
<td>0.55*</td>
<td>0.57*</td>
</tr>
<tr>
<td>DBP</td>
<td>0.74*</td>
<td>0.63*</td>
<td>–0.82*</td>
<td>–0.47*</td>
</tr>
<tr>
<td>HR</td>
<td>–0.27*</td>
<td>–0.21†</td>
<td>0.23†</td>
<td>0.19‡</td>
</tr>
<tr>
<td>TGA patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>–0.30‡</td>
<td>–0.32‡</td>
<td>0.37†</td>
<td>0.33‡</td>
</tr>
<tr>
<td>SBP</td>
<td>–0.37†</td>
<td>–0.41†</td>
<td></td>
<td>0.36‡</td>
</tr>
</tbody>
</table>

DC indicates distensibility coefficient; E_{inc}, incremental elastic modulus; SBP, systolic brachial pressure; DBP, diastolic brachial pressure; HR, heart rate.

‘*P<0.05; †P<0.01; ‡P<0.001.”

TABLE 4. Independent Predictors of Carotid Artery Elastic Parameters

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Compliance</th>
<th>DC</th>
<th>Stiffness Index β</th>
<th>E_{inc}</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>3.30†</td>
<td>1.16†</td>
<td>–0.85*</td>
<td>–0.27†</td>
</tr>
<tr>
<td>Age</td>
<td>–0.49*</td>
<td>–0.15*</td>
<td>0.12*</td>
<td>0.08*</td>
</tr>
<tr>
<td>SBP</td>
<td>–0.43*</td>
<td>–0.58*</td>
<td>0.05*</td>
<td>0.03*</td>
</tr>
<tr>
<td>DBP</td>
<td>0.45*</td>
<td>0.15*</td>
<td>–0.07*</td>
<td>–0.20*</td>
</tr>
<tr>
<td>HR</td>
<td>–0.12*</td>
<td>–0.03‡</td>
<td>0.02†</td>
<td>0.01*</td>
</tr>
<tr>
<td>R²</td>
<td>0.67</td>
<td>0.69</td>
<td>0.62</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Coefficient values for multiple forward stepwise regression analysis of the relations between carotid artery compliance, distensibility coefficient (DC), stiffness index β, and incremental elastic modulus (E_{inc}) on one hand and TGA status, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) on the other. R² indicates cumulative explained variance.

‘*P<0.001; †P<0.01; ‡P<0.05.”

Discussion

We compared carotid artery elasticity parameters in TGA patients and in age-matched healthy control subjects and found that all elastic variables indicated significant stiffening of the carotid artery in the patient group.

To our best knowledge, this is the first study in which arterial stiffness was studied in patients with congenital heart disease. We studied patients with transposition of great arteries and hypothesized that, in addition to disturbed development of the aorticopulmonary septum, arterial elastic function was also abnormal. This assumption was based on embryonic data. The neural crest also contributes to the media of the aorta, pulmonary artery, and other aortic arch derivatives (ie, to all vascular regions that are destined to become elastic-walled vessels). The elastic matrix of great vessels was also found to be disordered when the neural crest was ablated. Our present data demonstrate that in TGA patients, abnormal aorticopulmonary septation is associated with impaired carotid artery elasticity, indicating that septation and elastogenesis are related events in human subjects as well.

We obtained data from TGA patients who had undergone either of 2 radically different forms of surgery to correct TGA. In the AT-S operation, a severe load is put on the right ventricle, whereas the AR-S operation essentially corrects the anomaly. The question arises whether the exposure of large vessels to right or left ventricular contraction might expose the carotid artery to different hemodynamic stresses, which might have different effects on the development of carotid artery stiffness. To clarify this issue we performed 2-factor ANOVA comparing AT-S and AR-S patients with their respective controls. Although the carotid artery was stiffer both in AT-S and AR-S, the interaction term between factors was not significant, indicating that the observed differences were not operation-dependent. This lack of differential effect further supports the notion that the increased stiffness observed is a fundamental characteristic of the condition.

We found that end-diastolic diameter of the carotid artery was smaller in patients than in controls. This finding suggests that in addition to disturbed elastogenesis other elements of the vessel wall may also be affected. This assumption is supported by findings obtained in the avian embryo, which indicated that the interstitial collagen type III in the wall of the great vessels was also disordered and the collagen type I in the intima appeared to be coarsened. Collagen composition and structure of the carotid artery might also be abnormal in TGA patients, although in the present study this has not been investigated.

The increased systolic blood pressure and decreased diastolic blood pressure seems to be a marker of early systemic arterial stiffness. This pattern is also observed with aging, when large elastic arteries are known to stiffen considerably. Alternately, increased arterial stiffness might be the consequence of increased pulsatile stress, since these patients were exposed for several years to an increased pulse pressure. This, however, seems unlikely, because carotid elastic parameters were less related to age in patients than in controls, and no relationship was found with years after repair. Generating pulsatile pressure requires extra energy expenditure from the ventricle, and the higher the pulse amplitude the larger the extra amount of energy needed. Pressure pulse amplitude, on the other hand, is importantly determined by large artery stiffness. With normal circulation, the pulsatile load on the left ventricle is much higher than that on the right ventricle. Since in TGA patients with AT-S repair the right ventricle is connected to the systemic circulation, the pulsatile load on the right ventricle is larger to start with, and our present data indicate that it is further increased by the additional power that is needed to distend the stiffer central arteries. RV ejection fractions in our patients was 50.1 ± 7.1%, which is lower than normal control values reported in the litera-
We found no correlation between AT-S patients' carotid artery stiffness and RV ejection fractions. This might be attributed to the relatively low number of patients and the low scatter of elastic data. It is also possible, however, that the impaired right ventricular function was also the result of abnormal myocardial development, which was not directly related to large artery stiffness. After neural crest ablation in the embryo, myocardial dysfunction developed and persisted throughout embryonic life. As for the mechanism underlying this myocardial dysfunction, depressed L-type calcium current, exhibition–contraction coupling, and calcium sensitivity of the contractile apparatus was found. No comparable data are available in human congenital heart disease.

**Limitations**

Since in AT-S patients the right ventricle may undergo muscle failure, it was of primary concern to determine right ventricular volumes and ejection fraction in this group of patients. For that purpose CMRI was used, because echocardiography is not considered as a reliable technique for quantitative determination of right ventricular function. On the other hand, CMRI is relatively expensive, and data evaluation is very time consuming. Therefore, in AR-S patients, where right ventricular function was of no particular concern, only left ventricular function was determined by conventional transthoracic echocardiography, as part of the routine diagnostic procedure. Because of the more regular and symmetric geometry of the LV, LV volumes and ejection fraction can be measured reliably by echocardiography. Although CMRI is thought to be a more precise method to determine ventricular volumes and ejection fractions, it is comparable to conventional 2-dimensional echocardiography. This difference in used methodology, however, is considered as a limitation.

Because of the cross-sectional design of the study, we could not examine the direct influence of surgical procedures on arterial stiffness. Also, we were not able to establish whether carotid artery stiffening was the result of gradual postoperative derangement in vessel wall distensibility. Another limitation is the relatively low number of patients, although it represents all of the patients who had been operated on in Hungary.

**Acknowledgments**

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**References**


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