Impaired Elastic Properties of the Ascending Aorta in Newborns Before and Early After Successful Coarctation Repair
Proof of a Systemic Vascular Disease of the Prestenotic Arteries?

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Patients with coarctation of the aorta have a significantly increased cardiovascular morbidity and reduced life expectancy even after successful surgical correction at a young age.1,2 Arterial hypertension, coronary heart disease, and heart failure affect mid- and long-term outcomes of this disease. Since 1976, altered vascular reactivity in rest and under maximal exercise in the upper extremities of patients after successful repair of coarctation was recognized by means of 133Xe clearance,3 whereas lower extremities showed normal flow reaction. More collagen and fewer smooth muscle cells in the precoarctation aorta could be demonstrated histologically in fresh aortic tissue of resected coarctation walls of 20 patients compared with postcoarctation tissue, postulating a more rigid aortic wall in the precoarctation region.4

Noninvasive assessment of the elastic properties of peripheral conduit arteries is possible through measurement of flow-mediated dilatation and analysis of pulse-wave velocity.5–9 Recently, distensibility and wall stiffness of the aortic wall has also been measured by means of transthoracic,10–12 transesophageal,13 or intravascular echocardiography.14 Examinations in patients with coarctation of the aorta showed reduced elasticity of the vascular system in the prestenotic region even after successful surgical correction.5–14 Early surgical correction (<4 months) seems to be associated with better preserved elastic properties of conduit arteries in the upper part of the body.5

The fact that early surgery can prevent long-term alterations of arterial stiffness in conduit arteries might be explained by 2 theories: Either vascular stiffness in newborns with coarctation is not impaired primarily and changes happen later in life, or elastic properties in newborns are affected primarily but can improve and become normal if surgery is done early. Until now, no data have been available in the literature on elastic properties of newborns with coarctation before and early after surgery.

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To answer the question of whether aortic elastic properties in newborns are primarily affected or not, we examined 17 newborn patients with aortic coarctation (mean age, 20±26 days) before and early after surgery (mean, 10±6 days) and compared their aortic stiffness data with those obtained in 17 healthy newborns matched in age, weight, and gender.

### Methods

#### Study Population

Clinical characteristics of the study population are shown in Table 1. Seventeen neonates who presented with coarctation of the aorta at our institution between November 2001 and April 2004 were prospectively included in the study. Patients had a mean age of 20±26 days at the preoperative examination. The postoperative examination was performed 10±6 days after surgical correction, with a mean age of 33±26 days.

Seventeen healthy children matched for age, weight, and gender served as a control group. All children underwent clinical examination by a pediatric cardiologist and a complete echocardiographic examination. None had any abnormalities of the heart or great vessels. None of them had a patent ductus arteriosus. All had a tricuspid aortic valve.

Before the operation, 10 patients received continuous infusion of prostaglandin E2 to restore or to maintain patency of the arterial duct. One patient received sotalol for supraventricular tachycardia. Six patients took no medication.

After the operation, 7 patients took no medication, whereas 10 were on a diuretic therapy with furosemide and spironolactone. One patient received an additional antihypertensive therapy with propanolol because of systolic blood pressure values above the 97th percentile. In the patient with supraventricular tachycardia, treatment with sotalol was continued after the operation.

#### Study Protocol

All subjects underwent a complete transthoracic echocardiographic examination using a General Electric Vingmed System V echo machine with 5- and 7.5-MHz multifrequency probes. In patients, the first examination served to establish the diagnosis preoperatively; the second examination was performed postoperatively just before discharge. Healthy control subjects were examined on 1 occasion following the same protocol. Two-dimensional guided M-mode measurements of the left ventricle were performed according to recommendations of the American Society of Echocardiography to determine fractional shortening and left ventricular end-diastolic and -systolic diameters.

Anatomy and function of the mitral and aortic valve were assessed by 2D echocardiography, color flow mapping, and pulsed-wave and continuous-wave Doppler recordings. Morphology of the aortic arch was evaluated by 2D echocardiography and color-flow Doppler. Systolic peak flow velocities in the descending aorta were determined by the use of continuous-wave Doppler from a suprasternal or high right parasternal axis and the presence or absence of a “diastolic tail” was noted. M-mode tracings of the ascending and abdominal aortic wall motion were recorded simultaneously with an ECG in the left decubitus position at 2 different levels: level 1, proximal ascending aorta 5 mm superior to the sinotubular junction (parasternal long-axis view, the Figure), and level 2, descending abdominal aorta just proximal to the branching off of the celiac trunk (abdominal paramedian long-axis view). Attention was paid to setting the cursor line exactly perpendicular to the long axis of the aorta in views showing the largest aortic diameters. Sharp endothelial lines were used as additional indicators for the cursor line to cut the central line of the aorta. All images were digitally stored as raw data with the EchoPAC System, version 6.4.1 (General Electric Vingmed).

Throughout the echocardiographic examination, supine systolic and diastolic blood pressures were measured 3 times in the right arm and in the right leg by an automatic oscillometric device (Dinamap PRO 300, Critikon Inc) according to the recommendations of the American Heart Association. Right arm blood pressure was obtained during examination of the ascending aorta; blood pressure in the right leg was obtained during scanning of the abdominal aorta. For further calculations, the mean of the 3 measurements was taken. The difference between systolic and diastolic blood pressures was taken as an estimation of the aortic pulse pressure. Accuracy and reproducibility of this method have been demonstrated previously.

Length and weight were recorded for each subject. Current medication was noted from the patients’ charts. Written informed consent was obtained for all patients, and all data were handled according to the 1975 Declaration of Helsinki.

#### Determination of Aortic Elastic Properties

A software tool for automated and standardized calculation of aortic diameters was developed (C.B. and D.B.) as described elsewhere. In brief, M-mode tracings of the ascending (level 1) and descending (level 2) aortas of ≥5 heart cycles were uploaded. To detect the inner aortic wall contours, an image-processing algorithm ran on the images. From the computed aortic edge map, ascending and descending aortic outlines were calculated throughout the heart cycles. According to the usual aortic diameter measurements with the leading edge technique, the automatically detected inner diameter of the aorta was enlarged by the anterior aortic wall thickness.
TABLE 2. Blood Pressure and Left Ventricular Function in Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=17)</th>
<th>Control Subjects (n=17)</th>
<th>P*</th>
<th>P †</th>
<th>P ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>142±14</td>
<td>133±15</td>
<td>0.96</td>
<td>0.14</td>
<td>0.2</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right arm, systolic</td>
<td>91±22</td>
<td>93±13</td>
<td>0.2</td>
<td>0.02</td>
<td>0.96</td>
</tr>
<tr>
<td>Right arm, diastolic</td>
<td>52±14</td>
<td>56±10</td>
<td>0.5</td>
<td>0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Right leg, systolic</td>
<td>62±14</td>
<td>85±15</td>
<td>&lt;0.005</td>
<td>0.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Right leg, diastolic</td>
<td>39±10</td>
<td>52±13</td>
<td>0.01</td>
<td>0.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>20±7</td>
<td>20±4</td>
<td>0.14</td>
<td>0.17</td>
<td>0.5</td>
</tr>
<tr>
<td>FS, %</td>
<td>33±9</td>
<td>40±5</td>
<td>0.13</td>
<td>0.03</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LVEDd indicates left ventricular end diastolic diameter. Values are mean±SD.
*Preoperative vs control; †postoperative vs control; ‡preoperative vs postoperative.

Results

Study Population

There were no significant differences with regard to age at examination, weight, length, and gender between patients and control subjects (Table 1). Resting blood pressure in the right arm and heart rate did not differ significantly between patients and control subjects preoperatively, whereas postoperative systolic blood pressure in the right arm was significantly higher in patients (Table 2). Blood pressure in the right leg was significantly lower before the operation, whereas there was no difference postoperatively compared with that in control subjects.

Mean left ventricular end-diastolic diameter did not differ between patients and control subjects preoperatively or postoperatively. Fractional shortening of the left ventricle was higher in patients after surgery compared with control subjects. Seven of the 17 patients had bicuspid aortic valves. None of them had a hypoplastic ascending aorta (Table 3).

There was no evidence of residual obstruction at the coarctation site after surgery, defined as the systolic blood pressure gradient from the right arm to right leg <20 mm Hg (8±13 mm Hg) and continuous-wave Doppler peak velocity at the coarctation site <3.5 m/s (2±0.5 m/s). In addition, none of the patients showed a diastolic tail at continuous-wave Doppler examination.

Aortic Elastic Properties

Cross-sectional distensibility of the ascending aorta was significantly reduced in the patient group both before and after the operation compared with control subjects. Wall stiffness index correspondingly was increased in patients in both situations. No significant changes concerning the ascending aorta occurred within the patient group before or after the operation (Table 4).

Distensibility and wall stiffness index of the descending aorta did not differ between patients and control subjects before or after the operation. In the patient group, wall

TABLE 3. Diastolic and Systolic Diameters of the Ascending Aorta in Patients Preoperatively

<table>
<thead>
<tr>
<th>Patient</th>
<th>BSA</th>
<th>Diastolic Diameter, mm</th>
<th>Systolic Diameter, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.20</td>
<td>5.9</td>
<td>7.7</td>
</tr>
<tr>
<td>2</td>
<td>0.34</td>
<td>11.6</td>
<td>14.2</td>
</tr>
<tr>
<td>3</td>
<td>0.22</td>
<td>9.7</td>
<td>10.2</td>
</tr>
<tr>
<td>4</td>
<td>0.22</td>
<td>6.9</td>
<td>8.8</td>
</tr>
<tr>
<td>5</td>
<td>0.26</td>
<td>10.8</td>
<td>12.9</td>
</tr>
<tr>
<td>6</td>
<td>0.21</td>
<td>8.3</td>
<td>10.1</td>
</tr>
<tr>
<td>7</td>
<td>0.21</td>
<td>9.3</td>
<td>9.9</td>
</tr>
<tr>
<td>8</td>
<td>0.21</td>
<td>6.9</td>
<td>7.2</td>
</tr>
<tr>
<td>9</td>
<td>0.22</td>
<td>10.9</td>
<td>12.2</td>
</tr>
<tr>
<td>10</td>
<td>0.20</td>
<td>10.9</td>
<td>12.5</td>
</tr>
<tr>
<td>11</td>
<td>0.19</td>
<td>7.4</td>
<td>7.8</td>
</tr>
<tr>
<td>12</td>
<td>0.22</td>
<td>9.8</td>
<td>11.3</td>
</tr>
<tr>
<td>13</td>
<td>0.24</td>
<td>8.5</td>
<td>10.6</td>
</tr>
<tr>
<td>14</td>
<td>0.27</td>
<td>10.4</td>
<td>11.9</td>
</tr>
<tr>
<td>15</td>
<td>0.22</td>
<td>9.2</td>
<td>9.8</td>
</tr>
<tr>
<td>16</td>
<td>0.22</td>
<td>7.9</td>
<td>9.1</td>
</tr>
<tr>
<td>17</td>
<td>0.20</td>
<td>6.4</td>
<td>7.9</td>
</tr>
</tbody>
</table>

BSA indicates body surface area.
stiffness index was significantly lower after the operation compared with preoperatively; differences in distensibility were not statistically significant.

The subgroup of the 7 patients with bicuspid aortic valve did not differ from the 10 patients with tricuspid aortic valves in terms of distensibility and stiffness index in the ascending aorta preoperatively (Table 5).

Discussion

Our data show that the aortic elastic properties of the ascending aorta are primarily impaired in newborns with coarctation and remain unchanged after successful operation. This gives more evidence to the assumption that coarctation is not only a localized mechanical problem of the aortic isthmus but also a systemic vascular disease of the precoarcational arteries.

It is well known that in addition to the intrinsic gene-regulated processes of vascular development, normal blood flow is required for adequate intrauterine growth. There are increasing insights into the genetic regulation of these intrauterine angiogenic and vasculogenic pathways and their disorders. It may be speculated that a primary genetic defect accounts for both the development of coarctation and the disturbances in the elastic properties that we found in the ascending aorta in these patients. On the other hand, it is possible that impaired intrauterine flow conditions in coarctation patients secondarily lead to altered gene expression and regulation and consequently to disturbed endothelial function in fetal and early postnatal life.

Since the late 1970s, it has been known that, in the coarctation syndrome, functional abnormalities in the vascular bed of the upper body exist even after successful surgical correction. Meanwhile, similar findings were demonstrated with different diagnostic methods such as nuclear perfusion scanning, measurement of vascular resistance, 2D echocardiography, and measurement of flow-mediated dilatation or analysis of pulse-wave velocity. However, almost all previous studies investigated patients substantially later after surgical correction without any preoperative data.

In addition to the functional data on elastic properties, histological findings support the assumption of a systemic vascular disease of the prestenotic arteries. Volumetric analysis of prestenotic aortic tissue showed significantly more collagen and less smooth muscle mass compared with the poststenotic aorta. Very few data exist on the morphology of the aortic wall in neonates with coarctation. The data available on a few patients (2 patients <24 hours postpartum and 8 patients <6 weeks of age) suggest that medial abnormalities within the stenotic aortic segment in terms of cystic medial necrosis are present at or shortly after birth. These findings support the theory that, in patients with coarctation, morphological changes in the aortic wall develop in utero. Our data confirm the functional abnormalities early after birth as well. The mechanism responsible for these morphological and functional abnormalities remains unclear.

Other authors have shown the influence of the timing of the surgical correction on the preservation of vascular function in coarctation patients. de Divitiis et al demonstrated a benefit of early repair (median age at operation, 4 months) on the elastic properties of brachioradial arteries, although reduced reactivity to vasodilatation persists. In contrast to their findings, in a much older population (mean age, 19 years), we found impaired elastic properties even in neonates early after surgery (mean age at operation, 24 days). Surgical correction did not influence elastic properties in the short term. Because we do not yet have any data on mean or long-term outcome in our population, the question of whether elastic properties can be restored later in life is still unanswered.

Recent studies on adults with coarctation repair have proved that age and bicuspid aortic valve are the main risk factors for wall complications in the long-term follow-up period. Analysis of the subgroup of patients with bicuspid aortic valves in our series showed no difference compared with patients with tricuspid aortic valves. A longer longitudinal follow-up of a larger group of patients could determine whether having a bicuspid aortic valve is an independent risk factor.

### TABLE 4. Comparison of Aortic Distensibility and Wall Stiffness Index Between Patients Preoperatively and Postoperatively and Normal Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Ascending aorta</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Distensibility, 10⁻³ kPa⁻¹</td>
<td>79±58</td>
<td>65±24</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>5.2±4.4</td>
<td>4.0±1.6</td>
</tr>
</tbody>
</table>

### TABLE 5. Comparison of Elastic Properties of the Ascending Aorta: Patients With Bicuspid Versus Patients With Tricuspid Aortic Valves Preoperatively

<table>
<thead>
<tr>
<th></th>
<th>Bicuspid Valve</th>
<th>Tricuspid Valve</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distensibility, 10⁻³ kPa⁻¹</td>
<td>83±65 (62)</td>
<td>76±57 (59)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stiffness index</td>
<td>4.9±3.0 (3.8)</td>
<td>5.4±5.4 (3.9)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Values are mean±SD. Numbers in parentheses are medians.
In our series, we used M-mode tracings of the ascending and descending aortas, together with noninvasive blood pressure measurement, to calculate wall stiffness index and distensibility of the prestenotic and poststenotic aortic walls. The advantage of this method is that it can be performed easily at any age with low costs using a standard echo machine and a routine echo modality with no side effects. Because the method is standardized, it may also be used for the individual long-term follow-up of aortic wall elasticity in patients as it has been described earlier in patients with Marfan syndrome.28

Conclusions
Neonates with coarctation of the aorta have impaired elastic properties before and early after successful operation in the ascending aorta, whereas the descending aorta seems not to be affected.

References
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