Vascular Dysfunction After Repair of Coarctation of the Aorta
Impact of Early Surgery

Marcello de Divitiis, MD; Carlo Pilla, MD; Mia Kattenhorn, BSc; Mariutzka Zadinello, MD; Ann Donald, AVT; Paul Leeson, MB, PhD; Sharon Wallace, BA, DipHE, RN; Andrew Redington, FRCP; John E. Deanfield, FRCP

Background—Patients with repaired coarctation are at increased risk of hypertension and cardiovascular disease despite successful repair. We studied the function of conduit arteries in upper and lower limbs of patients late after successful coarctation repair and its relation to age at surgery.

Methods and Results—Flow-mediated dilatation (FMD) and the dilatation after sublingual nitroglycerin (NTG, 25 μg) were measured by using high-resolution ultrasound in the brachial artery in 64 coarctation patients (44 males and 20 females, aged 19±10 years; median age at operation 4 months) and 45 control subjects (28 males and 17 females, aged 19±10 years) and in the posterior tibial artery in 37 patients and 22 control subjects. Arterial stiffness was determined by pulse-wave velocity (PWV) of the brachioradial and femoral-dorsalis pedis tracts. Patients, compared with control subjects, had lower brachial FMD (7.16±3.4% versus 8.62±2.3%, respectively; P=0.02) and NTG (11.46±4.3% versus 13.21±4.6%, respectively; P=0.046) and higher brachioradial PWV (9.17±3.1 versus 8.06±1.9 m/s, respectively; P=0.05). In contrast, posterior tibial FMD, NTG, and lower limb PWV were comparable. Age (months) at the time of repair was related to brachioradial PWV (r=0.42, P=0.002) but not to brachial FMD or NTG.

Conclusions—Patients with repaired aortic coarctation have impaired conduit artery function, with abnormal responses to flow and NTG, and increased vascular stiffness confined to the upper part of the body. Early repair is associated with preserved elastic properties of conduit arteries, but reduced reactivity remains. (Circulation. 2001;104[suppl I]:I-165-I-170.)

Key Words: coarctation ■ arteries ■ muscle, smooth ■ endothelium

Coarctation of the aorta is not simply a mechanical obstruction of the aorta. Life expectancy remains reduced in patients with coarctation of the aorta even after successful repair.1,2 Late arterial hypertension, more often systolic, which occurs in nearly one third of patients after repair, and atherosclerosis are the main determinants of cardiovascular events.1–3 Coronary heart disease, stroke, sudden cardiac death, and heart failure account for the majority of premature deaths,1–3 and prognosis is related to the age at intervention.1–3

Endothelial function of conduit arteries is now understood to be a key initiating event in atherogenesis,4 and increased stiffness and abnormal smooth muscle response of the arterial wall can contribute to the development of hypertension.5 However, little is known about vascular function and its determinants in patients after repair of coarctation, particularly in those who underwent surgery in the neonatal period and during infancy.6,7

Therefore, we have studied arterial stiffness and vascular responses to endothelium-dependent and -independent stimulators in upper and lower limb conduit arteries in patients late after repair of aortic coarctation performed at different ages. In particular, we set out to evaluate whether aortic coarctation represents an extensive arterial disease with abnormal vascular responses and whether late vasculopathy can be prevented by early repair. Our findings have potential implications for management strategies aimed at reducing late morbidity and mortality in this high-risk group.

Methods

Study Population
Clinical characteristics of the study population are shown in Table 1. We identified 280 patients, aged between 9 and 60 years, who had survived repair of isolated coarctation of the aorta at Great Ormond Street Hospital for Children between 1970 and 1998 (without major associated cardiovascular abnormalities, such as ventricular septal defect and aortic and mitral valve functional abnormalities). Those who had no evidence of recoarctation (>3.5-m/s velocity and/or >20 mm Hg pressure gradient at continuous Doppler in the aortic arch and the presence of a diastolic tail) and no evidence of aortic aneurysm at the last outpatient visit were invited by letter to

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TABLE 1. Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=64)</th>
<th>Control Subjects (N=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>43/21</td>
<td>28/17</td>
<td>0.3</td>
</tr>
<tr>
<td>Age, y</td>
<td>19±9.9</td>
<td>20±8.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.5±0.3</td>
<td>1.55±0.2</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>21.2±3.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Right arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122±14</td>
<td>111±9</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67±9</td>
<td>61±9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>88±9</td>
<td>81±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>53±12</td>
<td>51±8</td>
<td>0.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±11</td>
<td>72±15</td>
<td>0.8</td>
</tr>
<tr>
<td>Right leg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>124±15</td>
<td>119±13</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>66±9</td>
<td>59±11</td>
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<tr>
<td>Mean blood pressure, mm Hg</td>
<td>84±14</td>
<td>81±12</td>
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<tr>
<td>Arm-leg systolic pressure, mm Hg</td>
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<td>−8.3±7</td>
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<td>Biochemistry</td>
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<td></td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.5±0.4</td>
<td>4.6±0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.0±1</td>
<td>4.01±1.2</td>
<td>0.3</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>0.91±0.4</td>
<td>0.73±0.2</td>
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</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.45±0.5</td>
<td>1.41±0.2</td>
<td>0.7</td>
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<tr>
<td>LDL, mmol/L</td>
<td>2.0±1.0</td>
<td>2.00±1.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are mean±SD or as indicated.

lesions or recoarctation (defined above). All subjects underwent noninvasive assessment of endothelium-dependent dilatation (flow-mediated dilatation [FMD]) and endothelium-independent dilatation (dilatation to sublingual nitroglycerin [NTG]) of the brachial artery. In 60 coarctation patients and 43 control subjects, vascular stiffness was assessed by measurement of brachial arterial pulse-wave velocity (PWV). Vascular studies were then performed in the lower limb. In 60 patients and 42 control subjects, PWV between femoral and dorsalis pedis arteries was measured, and in 37 patients and 24 control subjects, endothelium-dependent and -independent responses of the posterior tibial arteries were studied. These subgroups were comparable in age, sex, and body mass index. The institutional ethics committee approved the present study, and written informed consent was obtained from each subject.

FMD and NTG-Induced Dilatation in Upper and Lower Limbs

All subjects were studied while they were at rest in the supine position in a quiet air-conditioned room (22°C to 25°C). Vascular ultrasound assessment of the endothelium-dependent and endothelium-independent dilatation of the brachial artery was performed in all patients by using a technique developed by our group,5 which has been shown to be accurate and reproducible.10 A B-mode scan of the right brachial artery was obtained in longitudinal section between 5 and 10 cm above the elbow by use of a 7.0-MHz linear array transducer and an Acuson XP10 scanning system. The center of the artery was identified when the clearest picture of the anterior and posterior wall was obtained, and the transducer was kept at this point throughout the scan by a stereotactic clamp. Arterial flow velocity was obtained continuously during scanning by pulsed Doppler signal at 70° to the vessel with the range gate (1.5 mm) in the center of the artery. B-mode images were triggered to the ECG signal to obtain only end-diastolic frames and were acquired every 3 seconds on a personal computer by using a video frame grabber. B-mode images and flow velocity were also recorded throughout the study on an S-VHS video. In each study, the response of the brachial artery to increased flow (FMD) and NTG were evaluated. A pneumatic cuff was placed around the forearm just below the elbow. After 1 minute of acquisition for baseline vessel size, the cuff was inflated for 5 minutes at 300 mm Hg. It was then released to induce reactive hyperemia, and brachial artery diameter images were acquired for 5 minutes after the cuff was released. Seven minutes after cuff deflation, images were again acquired for 1 minute and then for 5 minutes after administration of 25 μg sublingual NTG. This dose was significantly lower than that used in previous studies6,9 and was selected to achieve a dilatation more closely related to that obtained for FMD.11

Analysis of Vascular Studies

Brachial artery diameter was measured offline by a semiautomatic edge detection system (Information Integrity).12 All analyses were performed by a single experienced operator (M.K.), who was unaware of the clinical status of the subjects. Baseline vessel size was taken as the mean of the measures obtained during the first minute. FMD was calculated as absolute and percentage maximum increase in vessel size from baseline. NTG response was also calculated as absolute and percentage maximum increase in vessel size from baseline. Flow velocity (the stimulus to the vessel dilatation) was calculated by measuring the brachial flow velocity time integral, offline, from video-recorded tapes at baseline and from 15 to 120 seconds after cuff release. Reactive hyperemia was calculated as the maximum percent increase in flow velocity after cuff release compared with baseline flow velocity and as the area under the curve of all velocity time integral values measured after cuff release.3,11

FMD and NTG were studied in the right posterior tibial artery with the subject in the supine position with the leg slightly externally rotated. The artery was scanned in the middle of the calf with the pressure cuff placed just above the ankle. The same imaging criteria,
acquisition, and analysis software were used as in the brachial artery studies.

**PWV in Upper and Lower Limbs**

Brachioradial PWV (the velocity of propagation of the arterial pulse from the brachial to the radial probe) was measured by using a photoplethysmographic technique. Two photoprobe units, each containing an infrared-emitting diode and a phototransistor, were placed over the brachial and radial arteries and secured without compression. The infrared beam was scattered by the skin and other soft tissues and strongly absorbed by the blood as it flowed along the blood vessels. As the pulse wave passes along the vessel under the probe, the diameter of the vessel increases, so that more of the infrared signal is absorbed, and the reflected portion detected at the skin is reduced. The time-varying signals from the 2 probes were converted into pulse waveforms, and the transit time. The accuracy and reproducibility of photoplethysmographic assessment of PWV have been validated, and this measure is considered to be a robust index of arterial stiffness being inversely related to the square root of distensibility (PWV=1/√distensibility). Femoral-dorsalis pedis PWV was also assessed by similar methodology.

**Statistical Analysis**

Data analysis was performed by using the SPSS statistical package. Data are presented as mean±SD. Data not showing a normal distribution are presented as median (range). The comparison between groups of continuous variables was performed by the Student t test and, in case of a skewed distribution of a variable (as reactive hyperemia), by rank Mann-Whitney test. Categorical variables were analyzed by the χ² test. The relationships between clinical and functional variables were analyzed by the Pearson correlation test. Parameters not showing a normal distribution (such as age at the time of repair) were logarithmically transformed before the analysis. The independent determinants of brachial PWV were analyzed on the basis of the results of the Pearson test by multiple linear regression with a model including age, age at repair, and body mass index as independent variables. A value of P<0.05 was considered to be statistically significant.

**Results**

**Study Population**

None of the subjects recruited for the study (Table 1) showed significant residual obstruction at the coarctation site (mean pressure gradient in the descending aorta 10±3 mm Hg). Thirteen patients (20%) were hypertensive at rest.

**Upper Limb Vascular Phenotype**

There was no difference between baseline brachial artery diameter and flow between the patients and control subjects (Table 2). Peak flow increase during reactive hyperemia and the flow area under the curve were also comparable between patients and control subjects. However, brachial FMD was significantly lower in patients than in control subjects, as both absolute and percentage dilatations (Figure 1). Both absolute and percent dilatations to NTG were also reduced in patients with repaired coarctation (Figure 1 and Table 2).

Brachioradial PWV measurements were of adequate quality in 51 patients (85%) and 41 control subjects (95%). PWV was significantly higher in the coarctation patients (Table 2).

**Lower Limb Vascular Phenotype**

There was no difference in baseline posterior tibial artery diameter (2.4±0.5 versus 2.3±0.3 mm, P=0.3) and flow (0.04±0.03 versus 0.04±0.03 m, P=0.9) between the coarctation patients and control subjects, respectively. Peak flow increase during reactive hyperemia (598±366% versus 580±332%, P=0.74) and area under the curve of the velocity time integral (10.4±2.3 versus 11.3±5.6 m, P=0.6) were also comparable between patients and control subjects, respectively. Posterior tibial absolute FMD (0.2±0.10 versus 0.16±0.11 mm, P=0.3) and percentage FMD (8.56±5.2% versus 7.21±5.2%, P=0.37) were comparable between patients and control subjects, as were absolute NTG dilatation (0.34±0.09 versus 0.32±0.10 mm, P=0.6) and percent NTG dilatation (14.53±5.2% versus 14.0±5.1%, P=0.71) (Figure 2). Femoral-dorsalis pedis PWV, which was of adequate quality in 48 patients (80%) and 41 control subjects (95%), was also comparable (9.44±3.16 versus 9.11±2.99 m/s, respectively; P=0.8).

**Determinants of Vascular Responses**

There was no relationship between any vascular measure and resting blood pressure, arm-leg pressure gradient, or surgical technique of coarctation repair. In patients with repaired coarctation, univariate analysis showed that brachial FMD was related to baseline vessel diameter (r=-0.35, P=0.005). Brachial NTG response was related to age (r=-0.27, P=0.03), body mass index (r=-0.31, P=0.01), body surface area (r=0.29, P=0.02), and body mass (r=0.34, P=0.01).

**Figure 1.** Percentage brachial artery FMD and nitroglycerin (GTN) dilatation in patients with repaired coarctation (Coa) and control subjects (Ctrl). Horizontal line indicates mean.
Figure 2. Percentage posterior tibial artery FMD and nitroglycerin (GTN) dilatation in coarctation (Coa) and control (Ctrl) groups. Horizontal line indicates mean.

Area ($r=0.35, P=0.001$), and baseline vessel diameter ($r=-0.53, P=0.0001$). Brachial FMD ($r=0.02, P=0.86$) and NTG ($r=-0.15, P=0.22$) were not related to the age at the time of repair and were not related to systolic, diastolic, and pulse pressure measurements. In contrast, brachioradial PWV showed a positive correlation with age at surgical repair ($r=0.45, P=0.01$) (Figure 3), body mass index ($r=0.44, P=0.02$), and age ($r=0.28, P=0.55$) but not with systolic blood pressure ($r=-0.07, P=0.6$).

At multilinear regression analysis, age at surgical repair and body mass index predicted brachioradial PWV independently of age (Table 3). In the 32 patients who underwent repair in the first 4 months of life, FMD was reduced for both absolute dilatation ($0.22 \pm 0.08$ versus $0.28 \pm 0.10$ mm, $P=0.002$) and percent dilatation ($6.87 \pm 2.5\%$ versus $8.7 \pm 2.3\%$, $P=0.002$) compared with control FMD. Absolute NTG response was also reduced in patients with early repair compared with control subjects ($0.37 \pm 0.11$ versus $0.43 \pm 0.14$ mm, $P=0.05$), whereas the percent dilatation was lower, but the difference did not reach statistical significance ($11.7 \pm 4.42\%$ versus $13.36 \pm 4.5\%$, respectively; $P=0.1$). There was no difference in brachioradial PWV between the patients repaired at <4 months and the control subjects ($8.3 \pm 1.9$ versus $8.1 \pm 2.9$ m/s, respectively; $P=0.5$).

In the posterior tibial artery, there was an inverse correlation between FMD and the duration of follow-up ($r=-0.32, P=0.04$). Posterior tibial NTG was inversely related to basal diameter ($r=-0.52, P=0.001$) and body surface area ($r=-0.36, P=0.035$).

In the control subjects, brachial absolute FMD was related to basal diameter ($r=0.36, P=0.02$), body mass index ($r=0.37, P=0.019$), age ($r=0.32, P=0.04$), and body surface area ($r=0.35, P=0.026$), whereas percentage FMD showed an inverse correlation with basal diameter ($r=-0.32, P=0.04$). Percent NTG dilatation also was inversely correlated with basal diameter ($r=-0.42, P=0.005$) and body surface area ($r=-0.32, P=0.042$).

**Discussion**

The present study shows that in patients with repaired coarctation of the aorta, vascular reactivity and mechanical properties of large conduit arteries are impaired even late after successful repair (absence of residual obstruction and/or aortic aneurysm). Vascular function is different in the upper and lower limbs. Reduced FMD and NTG responses and a higher PWV were observed in the upper limb. In contrast, lower limb arteries showed preserved FMD and NTG responses and normal PWV. The timing of operation has a selective impact on the different measures of vascular function, so that patients who underwent repair of aortic coarctation in the first 4 months of life had normal arterial stiffness (PWV) but impaired reactivity of the brachial artery (reduced brachial FMD and NTG responses). This pattern of persistent abnormalities of conduit arteries in the upper limb during long-term follow-up suggests that aortic coarctation is associated with extensive arterial dysfunction and that, at least in part, vascular changes are acquired as a result of the abnormal hemodynamics present in the upper part of the body before surgery.

Similar FMD findings have been demonstrated in other cohorts of young subjects with coronary risk factors such as hypercholesterolemia, cigarette smoking, and diabetes. FMD has been shown to reflect endothelium-derived NO bioavailability in conduit arteries, and reduced brachial artery FMD has been related to adverse cardiovascular outcome in coronary patients. However, the FMD findings must be interpreted with caution in coarctation patients, in view of the reduced dilatation to NTG (NO donor) even at the low dose used (25 μg). This may be due to reduced capacity for relaxation of vascular smooth muscle cells and/or to structural changes in the arterial wall that limit its ability to dilate. The latter is supported by the increase in PWV in the brachioradial tract, indicating an increase in resting arterial stiffness. The vascular responses in the upper limb may have hemodynamic consequences for blood pressure regulation. In a previous report, we have demonstrated a relationship between brachial NTG response and peak systolic blood pressure on dynamic exercise in patients who had their

**TABLE 3. Independent Predictors of Brachioradial PWV Analyzed by Multiple Regression Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Standard Error</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age at operation</td>
<td>0.58</td>
<td>0.24</td>
<td>0.10–0.16</td>
<td>0.02</td>
</tr>
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<td>Body mass index</td>
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<td>0.13</td>
<td>0.03–0.56</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>−0.05</td>
<td>0.06</td>
<td>−0.18–0.06</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Units for regression coefficient are m/s per unit change in explanatory variable. $R^2=0.54$. 
coarctation repaired relatively late, and we have recently shown a relationship between brachial NTG response and 24-hour systolic blood pressure (authors’ unpublished data, 2000). Arterial stiffness affects the ability of the large arteries to act as a cushion for cardiac output and is an important determinant of the vascular load on the heart. It is now evident that aortic stiffness in healthy children predicts systolic blood pressure, and because subjects tend to remain in the same decile of systolic blood pressure over the decades of follow-up (tracking). Furthermore, aortic PWV has been shown to be an important prognostic factor in subjects with essential hypertension. Another potential mechanism by which vascular stiffness in healthy children predicts systolic blood pressure, and because subjects tend to remain in the same decile of systolic blood pressure over the decades of follow-up (tracking), arterial stiffness in part determines your future cardiovascular profile.

The distribution of vascular functional changes found in our patients may be the consequence of structural abnormalities of the arterial wall of the type reported by Sehested et al. They found an increase in collagen and a decrease in smooth muscle content in the aortic segment above the coarctation compared with young transplant patients with comparable histological findings in the lower aorta in the 2 groups. In an experimental study in dogs by Ghaleh et al, supravalvular aortic banding resulted in impairment of coronary endothelial function assessed by both response to flow and acetylcholine. This blunted vascular reactivity was associated with morphological abnormalities in the vessel wall, which included intimal and medial thickening, malalignment of endothelial cells, and disruption of the internal elastic lamina. The number of smooth muscle cells was increased in the media, and there was additional disarray, with the cells oriented at an oblique angle to the adjacent layer.

The present study is the first to examine the late vascular phenotype in patients who have undergone coarctation repair as neonates or in infancy. Early repair of coarctation appears to preserve arterial elastic properties, thus preventing an increase in later arterial stiffness over the pattern found in normal subjects. In contrast, age at repair was not related to later arterial reactivity with responses to both flow and NTG; in fact, they were impaired, even in patients who had their operation in the first few months of life. This suggests very early “programming” of vascular reactivity, which may be determined by the abnormal hemodynamics in prenatal development or in the first few weeks after birth. Our previous data suggest that vascular reactivity is influenced by intrauterine factors, such as birth weight.

Arterial stiffness, measured as arterial distensibility, has not been related to prenatal factors but to environmental influences, such as LDL cholesterol as early as the first decade of life. The abnormal increase in arterial stiffness in coarctation patients also seems to develop during this period, and irreversible changes do not appear to develop in utero or in the first few months after birth. These vascular abnormalities are likely to represent a mechanism for the relationship between age at repair of coarctation and the development of arterial hypertension. Therefore, careful long-term follow-up is indicated even in subjects who underwent repair at a very early age because the functional significance of this pattern of vascular responses remains uncertain.

Clinical Implications
Aortic coarctation is associated with persistent abnormalities of arterial function during long-term follow-up even in subjects with apparently successful repair. These abnormalities are likely to contribute to the development of late systolic hypertension, through both direct effects on the vessels and effects on baroreflex sensitivity, and therefore may contribute to atherosclerosis, which is responsible for reduced life expectancy and morbid events. Early repair may preserve the elastic properties of conduit arteries, and this may explain, at least in part, the known relationship between the timing of repair and prognosis. However, both endothelial and smooth muscle functional abnormalities persist despite early repair, so that careful long-term surveillance of coarctation patients is desirable.

Acknowledgment
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References
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