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Chapter 9

Assessment of proximal and distal aortic properties with magnetic resonance after successful coarctation management in adults

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Submitted for publication
Abstract

Background:
Aortic coarctation poses a lifelong high cardiovascular risk, despite successful surgical or percutaneous management.

Objective:
To investigate whether an abnormal aortic function is involved in the higher cardiovascular risk in patients after correction of aortic coarctation.

Methods:
We recorded aortic pressure waveforms and elastic properties by MRI in 13 patients with normal blood pressure following successful intervention for coarctation in adolescence, with or without the use of medication. Findings were compared to 13 age- and blood pressure-matched controls. Age, blood pressure and body mass index were comparable between a group of 13 patients and 13 control subjects, who underwent cardiac MR imaging for conditions other than aortic pathology. Patients with aneurysm formation and recoarctation were excluded.

Results:
Aortic distensibility appeared to be significantly lower for patients \(14.5 \times 10^{-3} \pm 7.82 \times 10^{-3} \text{ kPa}^{-1}\) as compared to controls \(30.9 \times 10^{-3} \pm 1.99 \times 10^{-3} \text{ kPa}^{-1}\) \((p = 0.01)\) in the ascending aorta, whereas it was not significantly different at the site of coarctation and at the level of the diaphragm. Pulse wave velocity (PWV) in the ascending aorta was calculated to be significantly higher for patients \((4.71 \pm 1.17 \text{ m/s})\) compared to controls \((3.65 \pm 0.965 \text{ m/s}; p = 0.0187)\). No significant differences were found for PWV of distal aortic segments. Indexed left ventricular mass was found to be \(75.6 \pm 39.7 \text{ g/m}^2\) in patients and \(42.6 \pm 10.4 \text{ g/m}^2\) in controls \((p=0.0141)\).

Conclusion:
These data show abnormal proximal aortic properties in subjects with normal blood pressure following successful coarctation management in adolescence with or without antihypertensive medication. This finding may contribute to the high cardiovascular burden upon these patients.
Aortic flow measurements in adults after coarctation repair

Introduction

Aortic coarctation poses a lifelong high cardiovascular risk, despite successful management by surgical repair or balloon angioplasty. Late or persistent hypertension at rest or during exercise, even present without residual aortic narrowing, can lead to an elevated cardiovascular risk in a high proportion of patients. An abnormal central aortic vascular structure and function have also been implicated as a mechanism of hypertension in these patients. Increased central aortic stiffness has been found in patients in whom coarctation and interruption of the aortic arch were managed surgically at neonatal age. Effects of antihypertensive medication tend to be smaller and take longer if coarctation repair is carried out at increasing age. Whether an abnormal aortic function could contribute to hypertension in patients that are managed for coarctation in adolescence or adulthood was object of this study. We recorded aortic pressure waveforms of normotensive patients following successful intervention for coarctation in adolescence. Aortic function in the pre-coarctation segment was investigated by MRI in this subset of patients and compared to age- and blood pressure-matched subjects without aortic pathology.

Methods

Subjects
We included 13 consecutive eligible adult patients visiting our outpatient clinic for regular control following coarctation management in our institution. Inclusion criteria for patient selection were a successful management of native coarctation in adolescence or adulthood, absence of other (congenital) cardiac conditions (including aortic valve dysfunction), systolic right brachial blood pressure below 150 mmHg at rest and absence of recoarctation or aneurysm formation. The use of antihypertensive medication was tolerated. Recoarctation was defined as the presence of one or more of the following: 1) systolic blood pressure gradients between upper and lower extremities exceeding 20 mmHg, 2) direct visualization of collateral vessels by MRI, 3) increase in flow from proximal to distal descending thoracic aorta as measured by velocity-encoded cine MRI and 4) a ratio of the aortic diameters at the level of coarctation repair and the level of the diaphragm below 0.7. An aneurysm at the coarctation repair site was defined as a ratio > 1.5 of the aortic diameter at the coarctation repair site compared to the aorta at the level of the diaphragm. The control group comprised 13 consecutive subjects in the patient’s age group, who underwent cardiac MR imaging for conditions other than aortic pathology. These included screening for myocardial ischemia (five), surveillance of known ischemic heart disease (three), hypertrophic cardiomyopathy (two), scheduled pulmonary vein isolation procedure (one), sarcoidosis (one) and corrected muscular ventricular septum defect (one).
Cardiac magnetic resonance acquisition and imaging

All subjects underwent cardiac MRI using a 1.5 Tesla MRI scanner (Intera, Philips Medical Systems, Best, the Netherlands). The MR protocol applied has been advocated for follow-up of repaired coarctation. Informed consent was obtained in all subjects. Retrospective triggering was applied, using vector cardiography with fiber optic leads. A sensitivity encoding array coil was used to increase imaging acquisition speed. Blood pressure recording was performed at 2-minutes intervals. The MRI-protocol included anatomic assessment (turbo spin echo sequence) to evaluate LV anatomy and valvular morphology in short- and long-axis, as well as transversal plane. Aortic anatomy was assessed subsequently (balanced turbo field echo sequence, repetition time 3.0 ms, echo time 1.5 ms, matrix 256x256 mm; field of view 400 mm; slice thickness 8.0 mm) in transversal and sagittal oblique planes. Velocity-encoded cine MRI measurements were performed with “through-plane” scanning direction, perpendicular to the long axis of the aorta (fast field echo sequence, repetition time 5.0 ms, echo time 2.6 ms, flip angle 15°, field of view 350 mm, slice thickness 8.0 mm, velocity encoding up to 200 cm/s, gradually increasing Venc until aliasing was eliminated). Forty measurements per beat-to-beat-interval were performed, corresponding to temporal resolution between 20 (at 50 beats per minute) and 30 ms (at 75 beats per minute). Distinct oblique scanning planes were applied for each aortic cross-section. Magnitude images were used to trace minimal and maximal aortic areas at each aortic cross-section. The protocol was completed by 3D contrast enhanced angiography in oblique sagittal scanning plane (fast field echo sequence, repetition time 5.2 ms, echo time 1.5 ms, flip angle 40°, matrix 512x512, field of view 400 mm, slice thickness 4.0 mm), preceded by 2D bolus tracking.

Aortic distensibility

Aortic distensibility (ΔV/VΔP, where V is volume and P is pressure) can be represented as ΔA/AΔP (where A is area) for the distensibility at any particular aortic section. Distensibility was derived from the systolic distension (difference between peak systolic and end-diastolic intravascular cross-sectional area) and simultaneously recorded pulse pressure (ΔP) for each beat. Maximal and minimal aortic areas at the aortic sections were used to determine ΔA. The following formula was applied in calculating distensibility: distensibility = ΔA (mm²) / (diastolic area (mm²) x pulse pressure (mmHg)). Pulse pressure was based on brachial measurements. This technique has been reported before.9,10

Aortic Pulse Wave Velocity

PWV was computed based on the upstroke difference of initial flow acceleration between different aortic levels: the ascending aorta at the level of the pulmonary bifurcation, the descending aorta at the site of the repaired coarctation and the descending aorta at the level of the diaphragm. The following formula was used: PWV=Δx/Δt, where Δx is the distance between aortic levels. These distances were calculated from aortic source images, loaded in an off-line analysis program (EasyVision, Philips Medical Systems, Best, The Netherlands) in which tracking of
distances between different aortic levels could be performed three-dimensionally. Δt is the time difference of initial flow acceleration between different aortic levels. This interval was measured between normalized flow curves that were constructed using the χ2 minimization technique. Curves were drawn automatically (Microsoft Excel, Microsoft Corporation, Redmond, WA, United States of America). Time distances were measured between 0.2 and 0.5 on the y-axis, in the upstroke portion of the curve. Time intervals could be read out directly between the plotted curves. Components of the technique that we used for assessment of PWV have been described before.5,11,12 See Figure 1.

**LV mass**
Short axis cine loops LV epicardial and endocardial contours were manually traced to compute LV mass as the end-diastolic myocardial volume (i.e., epicardial - endocardial volumes) multiplied by myocardial density (1.05 g/ml), using the standard disc-summation technique.13

**Statistical analysis**
All of the statistical analyses were performed using SPSS software package (SPSS for Windows, 14.0, SPSS Inc, Chigago IL, USA). Data are expressed as mean ± standard deviation or range (minimal-maximal) as appropriate. Categorical variables were compared between groups using χ2-test or Fisher’s exact test. Correlation was tested by calculating Pearson correlation coefficients. Differences between groups were analysed by independent samples T-test or Mann-Whitney U test as appropriate. All p-values were based on two-sided comparisons, and a value of <0.05 was considered significant.
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Results

Patient characteristics
Table 1 depicts the characteristics of patients and control subjects. Coarctation treatment had been performed 4.1 to 26 years before investigation at a median age of 20.6 years of age (range: 15.1 to 55.5 years). Surgery comprised resection and end-to-end anastomosis (6/13) or PTFE patch aortoplasty (3/13). Balloon angioplasty was performed in 4 patients. No stents were used.

Table 1. Characteristics of patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=13)</th>
<th>Controls (n=13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.1 ± 9.94</td>
<td>39.4 ± 9.82</td>
<td>0.66</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Brachial systolic blood pressure (mmHg)</td>
<td>130 ± 9.62</td>
<td>139 ± 17.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Brachial diastolic blood pressure (mmHg)</td>
<td>79.7 ± 8.91</td>
<td>85.0 ± 7.64</td>
<td>0.20</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>6/13</td>
<td>5/13</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Betablocker</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Combination ACE-inhibitor &amp; betablocker</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Aortic elastic properties for patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distensibility ascending aorta (E-3 kPa-1)</td>
<td>14.5 ± 7.82</td>
<td>30.9 ± 19.9</td>
<td>0.0108</td>
</tr>
<tr>
<td>Distensibility repaired coarctation segment(E-3 kPa-1)</td>
<td>12.0 ± 13.0</td>
<td>21.2 ± 14.1</td>
<td>0.0978</td>
</tr>
<tr>
<td>Distensibility descending aorta (E-3 kPa-1)</td>
<td>32.9 ± 26.5</td>
<td>30.6 ± 20.6</td>
<td>0.806</td>
</tr>
<tr>
<td>Pulse Wave Velocity ascending aorta - coarctation segment (m/s)</td>
<td>4.71 ± 1.18</td>
<td>3.65 ± 0.965</td>
<td>0.0187</td>
</tr>
<tr>
<td>Pulse Wave Velocity coarctation segment - descending aorta (m/s)</td>
<td>5.15 ± 2.24</td>
<td>6.49 ± 2.30</td>
<td>0.145</td>
</tr>
<tr>
<td>Pulse Wave Velocity ascending - descending aorta (m/s)</td>
<td>4.79 ± 1.30</td>
<td>4.51 ± 1.89</td>
<td>0.570</td>
</tr>
<tr>
<td>Difference between peak systolic and end-diastolic intravascular cross-sectional area (ΔA) (cm2)</td>
<td>1.07 ± 0.931</td>
<td>1.76 ± 1.01</td>
<td>0.080</td>
</tr>
</tbody>
</table>

Aortic elastic properties
Elastic properties of both study groups at different aortic levels are summed up in table 2. Distensibility of the ascending aorta was significantly lower in patients than controls. A significant difference was not found in the distal aortic segments. See Figures 2 & 3. PWV in the ascending aorta was calculated to be significantly higher for patients. This was not found for PWV in the descending aorta and for the combined aortic tracts. See Figures 4 & 5.
Aortic flow measurements in adults after coarctation repair

Figure 2. Box-and-Whisker diagrams for proximal aortic distensibility in patients and control subjects.

Figure 3. Box-and-Whisker diagrams for distal aortic distensibility in patients and control subjects.

Figure 4. Box-and-Whisker diagrams for proximal pulse wave velocity in patients and control subjects.
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Left ventricular mass and function

Left ventricular mass, indexed for body surface area, was significantly higher for patients (79.3 ± 41.7 g/m²), compared to controls (44.8 ± 10.9 g/m², p = 0.0141). Left ventricular ejection fraction was 57.1 ± 10.2 % for patients and 58.3 ± 11.1 % for controls (p = 0.785).

Discussion

The main finding of our study is that the ascending aorta of patients, following successful repair of native coarctation at adult age, demonstrates lower distensibility and higher pulse wave velocities than in control subjects with comparable age and blood pressure. A significant difference in unfavourable elastic properties was not found in the descending aorta. These observations demonstrate that an abnormal aortic function persists, despite performance of a successful surgical or percutaneous repair of aortic coarctation in adolescence or adulthood.

The role that aortic elasticity may play in the adult age group has not been well defined before in literature. Except a few individual cases, both histological and functional data on abnormal ascending aortic anatomy are limited to patients managed at neonatal age. Different from these patients, aortic arch or ishmus hypoplasia are usually not present at the adult age and cardiac malformations are rarely associated in patients that present with symptoms after childhood. Coarctation in adult patients generally constitutes the isolated type of coarctation, classified according to surgical nomenclature. Furthermore, the benefit of coarctation repair in that age group is less clear than in infants, because poor resolution of systolic hypertension in “adult” type coarctation has been reported. Despite this variation in coarctation morphology and severity at different ages, our study results demonstrate the same decrease in aortic compliance proximal to the coarctation as described in patients with repair at younger age.
**Left ventricular mass**
Although lower than 95% upper limit values of 74.7 g/m² (women) and 95.0 g/m² (men) in a hypertension free cohort with mean age 17 years higher than in our population, left ventricular mass index was significantly higher for patients than control subjects in this study. This finding suggests an increased cardiac workload following successful coarctation management and has been reported before. PWV was also found to be higher in patients. This can be adequately explained by the observation that arterial stiffness, directly measured by aortic PWV, is the final common pathway on which cardiovascular risk factors, including blood pressure, operate.

**Hypertension**
To identify aortic abnormalities beyond those that were caused by long-standing hypertension, we used a control group of subjects referred for routine MRI-investigation within the patient's age and blood pressure range, including several individuals managed by antihypertensive medication. Additionally, left ventricular systolic function did not differ between patients and controls. We therefore consider the differences that we found to be robust and related to coarctation and/or coarctation management, instead of just being compatible with the cardiovascular risk of our patients based on their blood pressure, ranging in the high-normal to moderately elevated values. Nevertheless, hypertension and left ventricular mass were found to be associated with aortic distensibility in other patient populations. These factors probably played a role in this study, although the influence thereof may differ between patients and controls. Whether the loss of distensibility is related causally to duration of hypertension, postoperative aortic morphology or both, is difficult to differentiate. Causality probably can only be demonstrated in a randomized, prospective study design. This will be hampered by the effort to correct this condition as soon as possible following diagnosis in adolescence or adulthood and the probable relationship between the coarctation severity and the age at which it will be diagnosed.

**Study limitations**
Differences between aortic flow characteristics in patients and controls were found in a small number of subjects in this study. Probably more different variables would have been found in a larger study population. Another limitation may be caused by the use of brachial instead of central aortic blood pressure. The latter would necessitate invasive pressure measurements, which we could not justify technically and ethically.

**Conclusions**
Functional aortic measurements by MRI demonstrate specific abnormalities following coarctation repair in adult patients, compared to matched controls. These differences include lower distensibility and higher pulse wave velocity of the ascending aorta. This unfavourable alteration has been described before in those surviving neonatal coarctation repair. This study demonstrates that this phenomenon is also seen in patients.
in whom coarctation has been managed successfully after childhood. The vascular
dysfunction demonstrated probably accounts for a part of the high cardiovascular
burden upon these patients.

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