Clinical research

Predicting the risk of early atherosclerotic disease development in children after repair of aortic coarctation

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Received 23 February 2004; revised 18 September 2004; accepted 1 October 2004; online publish-ahead-of-print 16 December 2004

Aims Increased cardiovascular morbidity is manifested a long time after the repair of aortic coarctation (CoA). By way of impaired flow-mediated vasodilation (FMD) and increased intima media thickness (IMT), surrogate parameters of atherosclerosis, cardiovascular risk factors (RFs) can be correlated with early vascular wall changes in children. This study investigated whether changes in arterial wall function and morphology are detectable in children after coarctation repair.

Methods and results We examined 28 children after successful repair of CoA vs. 30 control subjects. All children underwent identical screening, with a broad RF profile and FMD/IMT measurements. CoA-children presented significantly ($P < 0.001$) impaired FMD (4.87 ± 2.6 vs. 10.2 ± 3.1%) and higher IMT values ($P < 0.001$) than the controls (0.48 ± 0.08 vs. 0.38 ± 0.05 mm). The blood pressure during rest and exercise and the left ventricular mass were significantly elevated, but no additional RF could be identified in CoA-children. Only a remaining pressure gradient related significantly to FMD.

Conclusion This study documents early vascular wall changes in children after successful coarctation repair. Arterial hypertension and a resting pressure gradient are the major contributing factors to early atherosclerotic development and should be primary targets for therapy. Vascular status should be monitored regularly by FMD and IMT.

KEYWORDS
Atherosclerosis; Paediatrics; Aortic coarctation; Risk factors

Introduction

The long-term follow-up data subsequent to a successful surgical repair of aortic coarctation (CoA) show cardiovascular morbidity and mortality at a considerable period of time after surgery. Systemic hypertension during rest and exercise seems to be the major adverse prognostic factor.1,2 The cause-and-effect correlation of hypertension and vascular changes after CoA repair is still a subject of dispute. A number of subjects who present no stenosis or just mild residual stenosis and who are normotensive at rest have elevated blood pressure (BP) during exercise or daily life activities.3 These observations have clinical relevance, as 24 h ambulatory BP and BP during exercise have a greater impact on
cardiovascular outcome than resting BP. Early vascular abnormalities have been detected in young adults and children even after successful and early CoA repair.\textsuperscript{4,5}

CoA might not be simply a mechanical obstruction of the aorta, but more likely a generalized disease of the cardiovascular system. The task of the clinician dealing with these patients is to assess the individual risk and to provide strategies of preventive therapy (e.g., release of restenosis, anti-hypertensive medication). Growing knowledge about new risk factors (RFs), such as insulin resistance, lipoprotein a, and chronic inflammation, make the picture of the pathological process of atherosclerosis more complete and has to be taken into account. With new diagnostic tools, such as flow-mediated vasodilation (FMD) and by measuring the intima media thickness (IMT), it is now possible to detect vascular changes at an early stage. FMD can be assessed non-invasively in either the brachial or the radial artery. This technique has been reported to be accurate and reproducible and serves as a useful surrogate measure of the endothelial function in coronary arteries.\textsuperscript{6–8}

A number of studies have quantified the association of IMT of the extracranial carotid arteries and the status of coronary atherosclerosis. Moreover, they have demonstrated a pronounced, gradual correlation between enhanced IMT and a greater incidence of myocardial infarction and stroke.\textsuperscript{9–11}

Both FMD and IMT have been shown to be related to several cardiovascular RFs.\textsuperscript{12–14} These proceedings would make it possible to define the potential role of different RFs and to calculate the individual risk involved, even with young patients.

We investigated whether children already show vascular wall changes after CoA repair and if there are any additional factors that influence the development of cardiovascular disease in these patients, when compared with non-CoA subjects.

**Methods**

**Study design**

We identified 45 consecutive patients undergoing repair of CoA in the Department of Cardiac Surgery at the University of Rostock. Patients with associated cardiovascular abnormalities were excluded. Twenty-eight patients with isolated, successfully treated CoA (group 1) and a median age of 12 years (range 6–17 years) were included. Surgery had been performed 5–16 (median 9) years ago between the second week and the 11th year of life. The characteristics of group 1 are shown in Table 1. Patients with a bicuspid aortic valve had no significant aortic valve stenosis. A number of studies have quantified the association of IMT of the extracranial carotid arteries and the status of coronary atherosclerosis. Moreover, they have demonstrated a pronounced, gradual correlation between enhanced IMT and a greater incidence of myocardial infarction and stroke.\textsuperscript{9–11}

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**Measurement of risk factors**

During a 2 day stay, anamnestic and anthropometric data were reviewed. Body fat in percentage of body weight was measured by bioelectrical impedance (Data Input inc. Frankfurt, Germany).\textsuperscript{16} A venous blood sample was collected after overnight fasting. Insulin resistance was calculated by using the homeostasis model assessment.\textsuperscript{17}

Resting BP was measured at all extremities by an automatic oscillometric cuff device (Dinamap, Critikon Inc., Tampa, FL, USA). The 24 h ambulatory BP was measured on the right arm (Space Labs Inc., Issaquah, WA, USA). BP measurements were recorded automatically every 15 min from 8:00 a.m. to 20:00 p.m. (daytime BP) and every 30 min from 20:00 p.m. to 8:00 a.m. (night-time BP). BP studies were excluded if there was an interval of >2 h of invalid or absent measurements. Hypertension was defined as 24 h systolic and/or diastolic BP (sBP/dBP) over the 95th percentile of the reference values provided by Soergel et al.\textsuperscript{18} Patients on anti-hypertensive medication were considered to have hypertension by way of the same criteria.

For the evaluation of exercise parameters, the spiroergometry equipment (Oxycon Alpha, Jaeger, Germany) was used. All children underwent a cycle exercise test using a modified Bruce protocol with continuously increased strain loads and

<table>
<thead>
<tr>
<th>Table 1 Characteristics of study population (group 1 n = 28)</th>
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<tr>
<td>Coarctation patients (n)</td>
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<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Aortic hypoplasia</td>
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<tr>
<td>Age at surgery</td>
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<tr>
<td>&lt;1 month</td>
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<td>1–12 months</td>
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<td>Primary procedure</td>
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<td>End-to-end</td>
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<td>Subclavian flap</td>
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<td>Restenosis treatment</td>
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<td>Balloon angioplasty</td>
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<td>Re-operation</td>
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<tr>
<td>Patch</td>
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<td>Tube graft</td>
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<td>Pharmacotherapy</td>
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<td>Beta-blocker</td>
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\( n \), number of subjects; end-to-end, resection and end-to-end anastomosis; tube graft, tube graft interposition.
were exercised to the point of exhaustion. Hypertension during exercise was considered prevalent if the blood pressure, measured at 2 watt/kg strain, exceeded 180 mmHg.

Echocardiography and vascular measurements were taken with a Hewlett-Packard Sonos system (Sonos 5500, Philips Int.). The ascending aorta and the aortic arch were visualized by means of high, long axis view and suprasternal view. Left ventricular measurements were taken from two-dimensional guided M-mode tracings, as recommended by the American Society of Echocardiography. Parameters measured by echocardiography were pressure gradient throughout the former coarctation region and the left ventricular and aortic morphology. Left ventricular mass (LVMMI) was calculated using the Devereux-modified American Society of Echocardiography cube equation.20

**Vascular measurements**

**FMD**

Endothelium-dependent responses of the right radial artery were measured for each patient, subject to the guidelines of the International Brachial Artery Reactivity Task Force.21 Subjects were in the supine position with their forearm comfortably placed and fixed in a semi-open splint. The radial artery was imaged 5 cm distal of the antecubital fossa in the longitudinal plane. A small blood pressure cuff was placed distal on the wrist to create a flow stimulus by reactive hyperaemia. A baseline rest image was acquired and the blood flow velocity was estimated by time-averaging the Doppler signal from a mid-artery sample volume. After a 5 min interval of ischaemia, cuff deflation was followed by a brief high-flow state. The image of the artery and the Doppler signal was recorded alternately in 20 s intervals up to 5 min after cuff deflation. Images were stored on a magnet-optical disc and analysed after the procedure. Distance measurements of the artery are taken at the mid-artery sample volume. After a 5 min interval of ischaemia, maximal systolic extension.

All subjects were examined in a quiet, temperature-controlled room. The procedure was carried out during the morning after exercise was considered prevalent if the blood pressure, measured at 2 watt/kg strain, exceeded 180 mmHg.

**IMT**

A high-frequency (15 MHz) vascular linear transducer was used for imaging the carotid arteries. Sonography and reading was carried out by trained and certified sonographers. Intra- and inter-observer variability (mean bias) were 0.2 and 1.2%, respectively. Patients were examined in the supine position, with the head turned 45° away from the side being scanned. Three segments were identified on each side: the distal 1.0 cm of the common carotid artery, the bifurcation itself, and the proximal 1.0 cm of the internal carotid artery. Five measurements were taken at 2 mm intervals at near and far wall in each of the three segments. Maximal and mean IMT were calculated separately for each side of each segment.

**Statistical methods**

All data were stored and analysed using the SPSS statistical package 11.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for variables of interest. The statistics computed included mean and standard deviations of continuous variables, frequencies and relative frequencies of categorical factors.

Our significance tests were two-sided, in the sense that sufficiently large departures from the null hypothesis, in either direction, will be judged significant. Bonferroni correction was made to control experimental type I error. That means that we work with a lower critical significance probability (for parameters in Table 2, differences would be significant only if $P < 0.05/13 \approx 0.004$ and in Table 3 only if $P < 0.05/8 = 0.00625$).
For the comparison of independent group means we used the Mann-Whitney U test, as described in the notes of Tables 2 and 3. Due the small case number, no further analysis of subgroups was performed.

Correlations between variables were calculated by Spearman’s rank correlation coefficient.

The sample size that was used is in rough accordance with recommendations in guidelines of the International Brachial Artery Reactivity Task Force. The authors recommend an intervention study of 20-30 patients in a crossover design and 40-60 patients in a parallel-group design study in total. They write that in studies of this size the minimal statistically significant difference that can be detected is an absolute change in FMD of 1.5-2%. We followed their recommendations in our study design.

Results

Risk profile

There were no significant differences in the data of the laboratory risk profile between groups 1 and 2 (Table 2).

Adequate 24 h BP recordings were obtained in 96% of all subjects. sBP, dBP, and mean BP during daytime and night-time were significantly elevated in group 1. Fifteen (54%) of 28 subjects of group 1 presented systolic and diastolic hypertension in the 24 h measurement. BP load was between 32 and 76% of daytime and night-time measurements. For four (14%) of the group 1 subjects, the sBP ranged between the 90th and 95th percentiles. Ten (36%) presented hypertension during exercise. None of the control subjects had elevated BP.

There was no strong correlation between mean 24 h sBP measurements and pressure gradient throughout the former coarctation region (r = 0.11). sBP during exercise and LVMMI were significantly different in group 1 and group 2 (Table 2). A pressure gradient in excess of 16 mmHg (Doppler and BP measurements) throughout the former coarctation region had no significant influence on sBP during exercise (P = 0.24) and LVMMI (P = 0.18).

A positive correlation could be found between sBP at 2 watt/kg strain load during exercise and LVMMI (r = 0.53). Subjects of group 1 with BP >180 mmHg at 2 watt/kg strain load during exercise showed an obviously elevated LVMMI (111 ± 17.5 vs. 87.7 ± 25.2 g/m², P = 0.028, not significant by using Bonferroni correction). No correlation was found between the other parameters (e.g. 24 h BP gradient, anti-hypertensive medication, and rate of LVMMI).

Vascular measurements

Group 1 presented significantly reduced FMD in comparison with group 2 (4.87 ± 2.6 vs. 10.2 ± 3.1%) (P < 0.001). Time to maximal dilation was between 40 and 80 s after cuff release. There was no correlation between maximal FMD and time to maximal dilation and no significant difference of time to maximal dilation between the two groups.

Subjects from group 1 with arterial hypertension showed a greater reduction in FMD (4.7 ± 2.5%) than those with normal BP (5.15 ± 2.7%), but this was not statistically significant (P = 0.52). Patients with hypertension during exercise showed a slightly more impaired FMD (4.5 ± 2%) than those with no exercise hypertension (5.1 ± 2.9%). These differences in FMD were not statistically significant (P = 0.47).

In patients presenting a pressure gradient >16 mmHg throughout the former coarctation region, FMD was significantly more impaired (4.2 ± 3.1%) in comparison with patients without any pressure gradient (FMD 5.97 ± 1.54%) (P = 0.03).

Age at surgery (≥1 year/<1 year, P = 0.42), time from surgical correction (≥10 years/<10 years, P = 0.56), pre-operative pressure gradient (≥40 mmHg/<40 mmHg, P = 0.49), and pre-operative sBP (≥140 mmHg/<140 mmHg, P = 0.23) were not statistically significant in relation to FMD and IMT. No correlation could be found between age at study (r = 0.01), pubertal stage (Tanner) (r = 0.12), and vascular measurements.

The measurements of IMT were adequate for all children in the segments of the common carotid artery and the carotid bifurcation. Images of the internal carotid artery did not satisfy the quality criteria in each case. In these segments, there were significant differences for near and far walls between groups 1 and 2 (P < 0.001). The IMT measurements from the two groups are shown in Table 3.

A statistically significant impact of parameters such as elevated BP during rest (P = 0.47) and exercise (P = 0.45) and a pressure gradient >16 mmHg (P = 0.57) on IMT could not be found.

Discussion

This study involved traditional and new RFs and early abnormalities in arterial physiology and structural wall changes in children following CoA repair. Previous studies have demonstrated hypertension at rest and during exercise as well as the adverse effects in these subjects.1-3,22

Impaired FMD, as a parameter of endothelial function, is even detectable in children after the CoA repair. Our measurements are in the range described in several studies on children at risk from the early development of atherosclerosis for different reasons and for normal controls.7,12-14

The measurements of the IMT of the carotid artery showed highly significant differences between children after CoA repair, compared with children without detectable RFs. These findings are reproducible for mean and maximal values of IMT in all vascular segments being scanned. There is still a lack of standards for IMT in children, so that a cut-off for clear pathology in IMT in children does not exist. The fact that IMT increases with age and with the progression of atherosclerotic disease has already been proved.23 Our IMT measurements in the patients’ group are admittedly elevated, but they are still well below those described as

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9. This study involved traditional and new RFs and early abnormalities in arterial physiology and structural wall changes in children following CoA repair. Previous studies have demonstrated hypertension at rest and during exercise as well as the adverse effects in these subjects.1-3,22

10. Impaired FMD, as a parameter of endothelial function, is even detectable in children after the CoA repair. Our measurements are in the range described in several studies on children at risk from the early development of atherosclerosis for different reasons and for normal controls.7,12-14

11. The measurements of the IMT of the carotid artery showed highly significant differences between children after CoA repair, compared with children without detectable RFs. These findings are reproducible for mean and maximal values of IMT in all vascular segments being scanned. There is still a lack of standards for IMT in children, so that a cut-off for clear pathology in IMT in children does not exist. The fact that IMT increases with age and with the progression of atherosclerotic disease has already been proved.23 Our IMT measurements in the patients’ group are admittedly elevated, but they are still well below those described as
pathological in adults by other authors. However, this significant increase in IMT with our young CoA-patients is likely to progress with age and can potentially evolve towards a high risk level.

The results of IMT and FMD confirmed that after the repair of CoA, children have detectable vascular wall changes, termed as early stages, as they progress towards manifesting atherosclerosis.

The laboratory risk profile, familial history of atherosclerosis, and anthropometric data gave no evidence of being responsible for the differences in the vascular status.

The major problem for children after the repair of CoA seems to be the persistence of arterial hypertension. CoA-children showed a more greatly impaired FMD if there was arterial hypertension during rest and exercise. A persistent pressure gradient throughout the former coarctation region had a significant influence on FMD. Yet patients with persisting hypertension and those with a pressure gradient were not identical. Vascular changes were even found after CoA repair in normotensive children, who presented no evidence of residual aortic arch obstruction. This supports the assumption that there are other, additional abnormalities that trigger the development of atherosclerosis and hypertension.

Impaired FMD is known to be an early sign of endothelial dysfunction, the key initiating event of atherogenesis. In CoA-children it may be the consequence of a reduced capacity for relaxation on the part of vascular smooth muscle cells and/or a tendency towards structural wall changes that limit the ability to dilate. An altered composition of the arterial wall in the pre-coarctation vascular bed, with an increased content of collagen and a reduced number of smooth muscle cells, could be an explanation for this phenomenon. Reduced endothelial-independent vasodilation by glycerol nitrate has previously been shown in older patients after CoA repair and has been discussed as a marker of impaired smooth muscle function and structural abnormalities. Endothelial-independent vasodilation was not evaluated in our population. Our detection of increased IMT in the carotid artery seems to confirm the assumed structural vascular changes. However, by measuring IMT, we are not able to define the histological changes in the vascular wall.

Functional abnormalities, such as an impaired function of vascular baroreceptors that show reduced distension and sensitivity to a certain BP are still the focus of discussion. Impaired vascular response has an impact on blood pressure regulation, even during exercise. Furthermore, enhanced arterial stiffness affects the ability of the large arteries to act as a cushion for cardiac output. It is, therefore, an important determinant factor in respect of the vascular load on the heart and has a vital impact on the future cardiovascular profile.

Elevated measurements of LVMMI are known themselves to be a RF for a cardiovascular outcome in the general population. In our patients, a strong correlation between LVMMI and sBP in the ambulatory measurement could not be proved, but the correlation between LVMMI and sBP during exercise was proved. Elevated LVMMI might be influenced by a persistent pathological response to BP elevations during daytime activities and increased aortic stiffness after CoA repair.

As others have reported in the literature, we found vascular changes even in children with early and apparently successful CoA repair, irrespective of the time of surgery. This suggests a very early impact on the development of vascular reactivity and changes in the arterial wall. Otherwise, pre-operative parameters such as pre-stenotic BP and pressure gradient throughout the CoA region had no influence on late post-operative vascular abnormalities in our population. Arterial hypertension and impaired endothelial function in CoA-patients might possibly be a congenital phenomenon in the arteries of those patients.

Bhat et al. showed a significant decrease in BP depending on the post-surgery time interval. Our data showed no effects from the post-surgery time interval on BP, LVMMI, FMD, or IMT. The abnormalities detected in the pre-coarctation vascular bed were prevalent many years after CoA repair and may not be reversible.

The most important finding in the present study was that early vascular changes are already detectable in children after apparently successful and early repair of CoA.

One of the major problems seems to be persistence of arterial hypertension during daytime activities and the remaining pressure gradient throughout the former CoA region. Regular aftercare, including the measurement of BP during exercise, 24 h BP monitoring and LVMMI and a consistent course of therapy for even mild hypertension seems to be important to lower the risk of atherosclerotic development.

Therapeutic options are re-interventions in cases of significant residual gradients and a tube graft bypass in older children with tubular aortic hypoplasia. ACE-antagonists have been shown to be effective not only in lowering arterial BP, but also in improving impaired endothelial function, and in reducing left ventricular hypertrophy. The therapeutic approach towards children after CoA repair requires further investigation. Nevertheless, lowering arterial BP during daily activities and during exercise is difficult to accomplish in these patients. Leading a healthy lifestyle and preferring an anti-atherogenic nutrition are additional options for lowering the risk of late complications in these high-risk patients. FMD and IMT seem to be further suitable instruments for the clinician to decide whether therapy is necessary and to monitor vascular development during follow-up and therapeutic actions.

Limitations

The mean age of the control group was higher than that of the CoA patients. Assuming that atherosclerosis develops in relation to age, then the results of the vascular measurements are even more significant. A statistically significant influence of age or pubertal development on FMD, IMT, and risk profile could not be found. There were more male subjects in the CoA group, but a significant difference in FMD and IMT could...
not be found between females and males in the CoA or control group. The control group consisted of patients with minor orthostatic complaints or dizziness. Morphological and functional cardiovascular abnormalities had been ruled out in this control population. Nevertheless, this group is only partly representative of the general healthy population of children.

Consideration has to be given to a certain influence of anti-hypertensive medication on BP and LVM/HMI in some of our patients. A significant influence on FMD and IMT could not be proved.

References