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van den Bogaard, B.

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Chapter 6

Pulse wave reflection and response to pharmacological vasodilation in post-coarctectomy patients

Bas van den Bogaard
Paul Luijendijk
Gijs-Jan Mackaij
Berend E Westerhof
Jos op ’t Roodt
Gert A van Montfrans
Barbara JM Mulder
Berto J Bouma
Bert-Jan H van den Born

Submitted
ABSTRACT

Objectives. Post-coarctectomy (CoA) patients are thought to have enhanced pulse wave reflection, which is thought to contribute to cardiovascular disease in this patient group. We compared wave reflection in relatively healthy group of CoA patients without hypertension or recoarctation and matched controls and compared wave reflection responses to pharmacological vasodilation.

Methods. In step 1 we measured augmentation index (AIx), a measure of wave reflection, using applanation tonometry in thirty post-coarctectomy patients without hypertension or recoarctation (age 32±10 yrs, 18 males, blood pressure 127±10 / 69±9 mmHg) and control subjects (age 33±9 yrs, 18 males, blood pressure 122±11 / 69±8 mmHg). In step 2 we assessed Alx response to salbutamol and nitroglycerine in 7 post-coarctectomy patients and controls (both groups age 33±9 yrs, 5 males).

Results. Step 1: AIx was higher in CoA patients compared to controls (17±14 vs 9±14 %, p<0.01). Step 2: the mean decrease in AIx from baseline in response to salbutamol was 5±12 vs 3±3 % (p=0.54) for CoA patients versus control subjects and 24±7 % vs 14±7 % in response to nitroglycerine (p=0.04).

Conclusions. CoA patients without hypertension or recoarctation have higher AIx compared to matched controls. The decrease in AIx was similar after salbutamol, but was greater after nitroglycerine in CoA patients compared to controls. Although wave reflection is increased in CoA patients, it can be decreased pharmacologically.
INTRODUCTION

Aortic coarctation is a relatively common congenital heart defect characterized by a stenosis in the aortic arch. Despite successful surgical repair, adult post-coarctectomy (CoA) patients have an increased risk of cardiovascular disease and decreased life expectancy compared to the general population.1-4 Intra-arterial measurements have shown that blood pressure waves are altered in patients with aortic coarctation and that the change in pressure wave form may be explained by early and thus increased reflection of the pressure waves on the stenosis.5 In population studies the augmentation index (AIx), a measure of wave reflection, is a predictor of cardiovascular events and mortality independent of blood pressure.6 CoA patients have enhanced wave reflection even after surgical repair and it has been hypothesized that this might contribute to the development of cardiovascular disease in CoA patients.7 Two recent non-invasive studies assessing AIx using applanation tonometry gave conflicting results. In line with invasive data, Szczepaniak and colleagues found higher AIx in CoA patients,8 while Swan and colleagues found no difference.9 In CoA patients, enhanced wave reflection is thought to arise from early reflection of pressure waves on the reconstructed and scarred aorta.7 The reconstructed pre-stenotic aorta has indeed been shown to have reduced elastic properties,10,11 even when the coarctation is repaired in early childhood.12 Furthermore the type of surgical intervention and anatomy of the aortic arch may influence local arterial stiffness and increase wave reflection.12-14 Differences between CoA patients and controls may be caused by differences in age and blood pressure, which may act as possible confounders. Moreover, the question remains whether enhanced pulse wave reflection in CoA patients is related to anatomic or functional changes in the proximal aorta, and whether differences in wave reflection can be influenced by vasoactive substances. In normotensive and hypertensive subjects with a normal structure of the aorta, angiotensin II or noradrenalin induced vasoconstriction cause an increase in AIx,15 whereas vasodilators, such as nitroprusside and calcium channel blockers lower AIx.16 Since in CoA patients increased wave reflection might be caused by disturbances in the anatomy and functional properties of the proximal aorta, it is not known whether vasodilating drugs decrease wave reflection to the same extent as in persons with a normal anatomy of the aorta.

We set out to examine whether AIx is increased in a relatively healthy subgroup of CoA patients without hypertension or evidence of restenosis compared to controls. Finally we examined how AIx responds to endothelium dependent and independent vasodilation, using salbutamol and nitroglycerine, in CoA patients and controls.
METHODS

The study consisted of two parts. To assess differences in hemodynamics between CoA patients and controls we non-invasively assessed peripheral and central hemodynamics (step 1). We then examined differences in response to endothelium dependent and independent vasodilation in CoA patients and controls by determining wave reflection and central hemodynamics before and after salbutamol and nitroglycerine (step 2). The study protocols were approved by the medical ethics committee of the Amsterdam Medical Center and all participants gave informed consent.

Study population and design

We used the CONgenital CORvitia (CONCOR) database, the Dutch national registry of patients with congenital heart disease, to recruit CoA patients from the Academic Medical Center and two participating tertiary referral centers. Control subjects were recruited via advertisement and among hospital staff. All measurements were conducted in a quiet, temperature-controlled room. Participants were asked to visit the research facility after an overnight fast. Measurements were performed in supine position in the morning after a 15 minute rest. All hemodynamic measurements were performed by a single investigator (BvdB).

Step 1 In 30 CoA patients without hypertension and without recoarctation, which was ruled out by cardiac magnetic resonance imaging, and in 30 control subjects matched for age and gender, peripheral and central hemodynamics and arterial stiffness were measured. Brachial systolic and diastolic blood pressure (SBP, DBP) were measured 3 times at 1-minute intervals using a validated oscillometric device (Omron 705IT) with an appropriately sized cuff. We used the average of the last two readings for the calibration of central hemodynamic measurements and further analyses. Central hemodynamics and pulse wave velocity (PWV), as a measure of arterial stiffness, were performed using the SphygmoCor system (Atcor Medical Pty Ltd, West Ryde, Australia).17 By using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Texas, USA) peripheral pressure waveforms were recorded from the radial artery of the right arm. Using the brachial blood pressure for calibration and with the use of a validated generalized transfer function a corresponding central (aortic) waveform was generated. Central DBP, SBP, mean arterial pressure (MAP), pulse pressure, reflection time (Tr) and Alx were calculated by further analysis of the central waveform. The Alx is the difference between the second and first systolic peaks divided by the pulse pressure and is reported as a percentage and was corrected for heart rate of 75 beats per minute.

First we tested the validity of the radial to aortic transfer function in CoA patients by measuring radial and carotid artery waveforms in a group of 37 CoA patients with and without hypertension (unpublished data). The aortic Alx derived from waveforms at the right radial artery correlated significantly with right carotid artery Alx (R=0.72, p=<0.001). This is similar
to previous findings by Segers and colleagues reporting a correlation of 0.75 between aortic AIx derived from the radial artery and carotid AIx in middle-aged normotensive and mildly hypertensive subjects free from cardiovascular disease.\textsuperscript{18} Because radial measurements are easier to perform and are more reproducible we decided to calculate aortic waveforms from radial artery measurements. Carotid-femoral PWV was assessed using the foot-to-foot method. Measurements were done in duplicate and means were used for analysis.

**Step 2** In 7 CoA patients and 7 age and gender matched control subjects, wave reflection response to endothelium dependent vasodilation and endothelium independent vasodilation with salbutamol and nitroglycerine (NTG) was determined by applanation tonometry of the right radial artery as described previously.\textsuperscript{19} After calibration with brachial blood pressure, baseline applanation tonometry measurements were performed. Thereafter, 400 μg salbutamol (Pharmachemie BV, Haarlem, the Netherlands) was inhaled by the participant under supervision of the investigator. Applanation tonometry measurements were repeated after 5, 10, 15 and 20 minutes. After a 10 minute interval the next baseline measurement was taken and immediately followed by administration of 400 μg sublingual nitroglycerine spray (Sandoz BV, Almere, the Netherlands). After 3, 5, 10, 15 and 20 minutes measurements were repeated. We calculated AIx at baseline and at time of maximum response to salbutamol or NTG. To further examine the effect of salbutamol and NTG on peripheral and central pressure waves we used a model of the arterial system to calculate central pressure and flow from the peripheral pressure waves allowing separation into backward and forward waves by waveform analysis as previously described.\textsuperscript{20,21}

**Statistical analysis.**

Data are presented as mean±standard deviation (SD) for continuous variables and n (%) for categorical variables. Comparisons of variables between groups were made by unpaired Student’s \textit{t}-tests for continuous variables in the step 1 analysis; in the step 2 analysis because of the limited sample size we used the non-parametric Mann-Whitney test. Categorical variables were compared by \( \chi^2 \)-test. A \( p \) value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 16.0, Chicago, Illinois, USA).

**RESULTS**

**Step 1** Table 1 shows baseline and hemodynamic parameters of CoA patients and controls. Patients and controls were well matched for age, gender and body mass index. Peripheral SBP and DBP were not significantly different between CoA patients and controls, although PP tended to be higher in CoA patients, 58±12 vs 53±9 mmHg, (\( p=0.06 \)). AIx was increased in CoA patients compared to controls, 17±14 vs 9±14 % (\( p<0.01 \)). There was a trend towards
a higher central SBP (110±12 vs 104±11 mmHg, \(p=0.06\)), while central DBP was similar. The central PP was significantly higher in CoA patients, 40±8 vs 34±6 mmHg (\(p<0.01\)). PWV did not differ between the two groups, 5.9±0.8 vs 6.1±1.1 m/s for CoA patients compared to controls (\(p=0.24\)).

**Step 2** Mean age was 33±9 years for both the CoA patients and controls subjects, both groups consisted of 2 males and 5 females. One subject in each group used antihypertensive medication. At baseline, CoA patients had higher SBP and similar DBP compared to controls (125±7 / 71±4 vs 116±6 / 68±5 mmHg, \(p=0.02 / p=0.33\)). Baseline Alx values for CoA patients were higher before salbutamol (22±16 vs 2±6 %, \(p=0.01\)) and NTG administration (25±13 vs -2±11 %, \(p=0.11\)). The decrease in Alx from baseline for salbutamol was similar for CoA patients and controls (5±12 vs 3±3 %, \(p=0.54\), while in CoA patients the decrease in response to NTG was larger (24±7 % vs 14±7 %, \(p=0.04\)). Figure 1 shows the response of the peripheral pressure waves to salbutamol and NTG administration in CoA patients and controls. Figure 2 shows the response of the central aortic pressure waves. After NTG the decrease in central systolic peak significantly differed between CoA patients and controls with a central SBP decrease of 7.4 mmHg in CoA patients and 3.0 mmHg in controls (\(p=0.01\)), while peripheral SBP was similar between CoA patients and controls in
response to salbutamol and NTG. When separated in forward and backward waves, the late systolic part of the forward wave and to a lesser degree the backward wave decreased after NTG compared to baseline in both groups, but this effect was more evident in the CoA group than in controls. Because of the combined decrease in forward and backward pressure waves, the resultant reduction in AIx, central SBP and PP was therefore significantly larger in CoA patients compared to controls.

Figure 1 Radial pulse waves at baseline (solid lines) and after administration (dotted lines) of salbutamol (panel A and B) and NTG (panel C and D) in CoA patients and controls.
This study shows that CoA patients without hypertension or recoarctation have an increased AIx compared to age and gender matched healthy controls. CoA patients compared to control subjects had similar AIx response to endothelium dependent vasodilation with salbutamol, while endothelium independent vasodilation with NTG caused a greater decrease in AIx and central systolic pressure in CoA patients.

For a long time it has been recognized that in case of a coarctation of the aorta the decrease in diameter and elasticity of the proximal aorta reduces the cushioning function resulting
in a change of the pressure wave because of early reflection on the coarctation site. This is supported by a report showing a decrease, but not a complete normalization, of the AIx after successful balloon dilatation of the aortic stenosis. Previous invasive measurements in CoA patients have demonstrated that wave reflection remains enhanced after successful surgical repair. Important determinants of AIx are age and blood pressure, but even in normotensive CoA patients AIx was higher compared to age matched controls. In comparison with the report by Murakami and colleagues, we found a smaller difference in wave reflection between CoA patients and controls despite a higher average age of our study population. However, our patients exhibited no sign of clinically relevant recoarctation and were free of hypertension,
whereas Murakami’s study consisted of a more heterogeneous group of CoA patients, two of whom had a pressure gradient over the coarctation site. Also, we used healthy normotensive controls free of cardiovascular disease that were individually matched for age and gender with CoA patients, whereas the control group of Murakami’s study consisted of subjects who had catheterization for various cardiac or aortic diseases and were assumed to be normal controls.

Our data of increased Alx in CoA patients are in line with previous intra-arterial studies, but also with one non-invasive study using applanation tonometry. A second study using applanation tonometry, however, found no difference in Alx between normotensive CoA patients and controls with similar age as in our study, but comparable to us they did find increased central PP. Furthermore, in the study of Szczepaniak and colleagues Alx was increased in CoA patients with and without residual stenosis of the aorta, suggesting that the function of the proximal aorta is impaired irrespective of residual stenosis of the aorta.

Pressure waves generated by contraction of the left ventricle (forward waves) travel down the aorta with a certain speed (pulse wave velocity), where they reflect at points where there is a discontinuity (reflection points) and travel back to the heart (backward waves). Pressure waves measured anywhere in the arterial system are the result of the interaction between forward and backward waves. It has been hypothesized that the increased wave reflection observed in CoA patients is caused by reflection of the forward pressure wave on the reconstructed aorta. Our findings of an increased Alx and a shorter reflection time support these observations. In general the Alx is principally determined by heart rate, aortic stiffness and reflection site.

Heart rate did not differ between CoA patients and controls, and correction for heart rate did not change the observed differences between the two groups. We found no differences in carotid-femoral PWV, a marker of the global aortic stiffness, between CoA patients and controls. However, this may not exclude local differences in aortic distensibility. Previous ultrasound and magnetic resonance studies have shown that the proximal aorta is less distensible even after correction of the coarctation. It is known that the pressure wave (and thus PP) arises from the interaction of left ventricular ejection and compliance of the arterial system, which is mainly determined by the aorta. Indeed we and others have shown increased central aortic PP in CoA patients. Because the increase in Alx could not be explained by differences in heart rate or global aortic stiffness in our study, the loss of elasticity in the reconstructed aorta and subsequent changes in reflection site is the most likely explanation for the observed differences in wave reflection.

In order to assess whether wave reflection can be pharmacologically modified in coarctation patients we used salbutamol and nitroglycerine, which are thought to affect pulse waveforms by decreasing the magnitude of wave reflection from peripheral sites through vasodilation. The Alx is for a large part determined by backward waves arising from the lower body, so the change in Alx in response to salbutamol and nitroglycerine would mainly result from dilatation of the post-coarctation vascular bed. At baseline and after endothelium dependent (salbutamol) and endothelium independent vasodilation (nitroglycerine), Alx remained higher in CoA
patients. Although it has been shown that pre-stenotic arteries have abnormal vasodilation, post-stenotic arteries indeed had normal vascular response to glyceryl trinitrate.\textsuperscript{28} It is likely that the increased wave reflection seen in CoA patients is partially caused by factors which cannot be influenced by pharmacologically induced vasodilation, such as anatomical or functional properties of the aortic arch.

The mean decrease in wave reflection for salbutamol was comparable between the groups. However, nitroglycerine reduced wave reflection to a larger degree in CoA patients than in control patients. Our wave separation analysis model showed that not only the backward but also the forward contributes to this. This suggests that in CoA patients reducing preload would effectively reduce wave reflection.

**Limitations** Our study was cross-sectional and has all the inherent limitations. Since we did not measure aortic length in patients or controls we cannot exclude that differences in aortic path length contribute to the early wave reflection. Because height was similar in CoA patients and controls, we consider it unlikely that the small surgically resected part of the aorta could explain the increased wave reflection. Furthermore there was no association between height and AIx in CoA patients (data not shown), suggesting that differences in aortic path length that result from differences in height are not an important determinant of wave reflection. The number of CoA patients and controls in the salbutamol and nitroglycerine study was small. We may therefore have missed small differences in response to vasodilation between groups. The decrease in AIx for CoA patients and controls after salbutamol and nitroglycerine was, however, comparable to normotensive healthy controls in a previous study.\textsuperscript{19}

**Conclusions** Wave reflection is increased in normotensive CoA patients without recoarctation compared to age and gender matched controls. The increased AIx observed in CoA patients before and after pharmacologically induced vasodilation gives further support to persistent anatomical and functional disturbances in the aorta as a cause of early wave reflection. We show, however, that wave reflection can be modified pharmacologically by vasodilating drugs and that the effect of nitroglycerine on wave reflection and central systolic pressure was larger in CoA patients than in controls.

**Perspectives** Increased AIx and central pressures are independent predictors of cardiovascular disease in the population. Antihypertensive drugs, preferably those with vasodilating capacities should be assessed for their ability to lower AIx and central pressure in CoA patients. It has not been determined though whether AIx and central pressures longitudinally predict cardiovascular events in CoA patients. Prospective follow-up studies would need to be designed to answer this question. In the mean time a first step would be to assess whether the AIx or central pressures are associated with organ damage in this specific patient group.
REFERENCES


