Advances in the management and surveillance of patients with aortic coarctation
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Chapter 8

Pulse wave analysis using applanation tonometry in patients with successfully repaired aortic coarctation

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Submitted for publication
Abstract

Background:
Aortic coarctation poses a lifelong high cardiovascular risk, despite successful invasive management. Premature atherosclerosis in this patient population cannot be solely explained by the presence of restenosis and hypertension but may also be caused by unfavorable aortic flow characteristics.

Methods:
Aortic pressure waveforms of normotensive patients following successful coarctation management were obtained with pressure tonometry at radial, carotic and femoral arteries. These waveforms were compared between 11 patients and 14 healthy controls. Age, blood pressure and body mass index were comparable between groups. Patients with aneurysm formation and recoarctation diagnosed by MRI were excluded from the study. Various timing and pressure variables were defined in the aortic pressure waveform.

Results:
Time between first systolic inflection and start of the reflected wave was significantly shorter for patients (33.2 ± 2.50 ms) than for controls (39.5 ± 8.13 ms, p = 0.020). The Central Sub-Endocardial Viability Ratio, a measure of the relationship between myocardial blood flow and oxygen demand, was lower for patients (1.43 vs 1.60; p=0.043). Both central systolic pressure and pressure at inflection point appeared to be significantly higher in patients. The Effective Reflection Distance, defining the timing of forward and backward travelling aortic pressure waves, was found to be 21.3 ± 5.35 cm versus 28.3 ± 5.96 cm (p=0.0056).

Conclusions:
The early return of aortic wave reflection in these patients unfavorably augments the maximum systolic pressure and lengthens the systolic period. This provides an additional explanation for high cardiovascular complication rates, despite anatomically satisfactory coarctation management.
Introduction

In subjects with successful repair of aortic coarctation, there is a high incidence of various atherosclerotic late-term complications including accelerated coronary artery disease.\textsuperscript{1-3} Persistent hypertension at rest, during 24-hr ambulatory monitoring or during exercise in more than 50% of postoperative patients, is likely to contribute to this observation.\textsuperscript{4} The underlying causes of the increased prevalence of cardiovascular disease and hypertension in this patient group are not entirely clear. Restenosis or residual stenosis accounts for only a minority of cases of postoperative hypertension. Additionally, normotensive patients are also at high cardiovascular risk.\textsuperscript{5} To offer an explanation other than hypertension, it has been hypothesized that aortic coarctation leads to degeneration of the aortic segment proximal to the coarctation before repair which may not be reversible. Sehested et al. found an increased collagen content and decreased smooth muscle in the precoarctation aortic arch, which leads to increased stiffness and diminished reactivity to pharmacological agents.\textsuperscript{6} Since structural abnormalities have also been found proximal and distal to the coarctation, some of these abnormalities may be determined by alterations in hemodynamics.\textsuperscript{7} Applanation tonometry is a simple, non-invasive and generally available technique that provides insight in structural and functional properties of the arterial tree. Aortic pulse wave velocity (PWV), central blood pressure and augmentation pressure or index can be derived from pulse wave analysis (PWA). These variables are associated with the presence of cardiovascular disease or risk factors. PWV and augmentation index predict cardiovascular outcome in general and various cardiovascular target populations.\textsuperscript{8-11} We hypothesized that abnormalities in vascular function and structure of the aorta, including the precoarctation segment, can be identified using applanation tonometry in patients with a successfully repaired aortic coarctation.

Materials and methods

Subjects

Informed consent has been obtained from all subjects. We examined a group of 11 patients following surgical coarctation repair (n=8) and balloon angioplasty (n=3) for native coarctation of the aorta. Surgery comprised resection and end-to-end anastomosis (6/8) or patch aortoplasty (2/8). Balloon angioplasty was performed without the use of endovascular stents. Inclusion criteria were a successful repair of aortic coarctation, systolic blood pressure below 150 mmHg at rest, with or without medication, and absence of aneurysm formation or recoarctation. An aneurysm was defined as an aortic ratio > 1.5, measuring aortic diameters at the coarctation repair site and thoracic aorta at the level of the diaphragm. Recoarctation was defined as 1) systolic blood pressure difference > 20 mm Hg between upper and lower extremities and/or 2) direct visualization of collateral vessels by MRI and/or 3) an increase in flow from proximal to distal descending thoracic aorta as measured...
by velocity-encoded cine MRI. This criterium is based upon the observation that blood flow is directed away from the aorta through the intercostals in the normal circulation, so flow decreases in the distal thoracic aorta. In the presence of collateral circulation, blood flows towards the thoracic aorta through the intercostals, so flow increases distally. Aortic diameters at the repaired aortic segment were measured in aortic reconstructions, based on gadolinium-enhanced MR angiography in oblique sagittal plane in the patient group. The control group comprised 14 subjects without cardiovascular disease.

**Pulse wave analysis**

ECG-tracing and arterial pulse waveforms at the right radial artery were simultaneously recorded in all subjects in supine position following 10 minutes of rest. Blood pressure at the right brachial artery was taken prior to these measurements by use of an automatic pressure cuff. Radial waveforms were recorded by use of a SPT-301B Millar pencil-type tonometer (AtCor Medical SphygmoCor system). The radial waveform was calibrated using systolic and diastolic pressure values from the cuff measurement. Real-time display of pressure waveform facilitated the operator to optimize recordings in order to capture at least 10 seconds of reproducible data. Central aortic waveforms were subsequently derived by previously validated, mathematical transfer functions and displayed graphically and numerically. The transfer function enables assessment of the central systolic and diastolic blood pressure. The technique that we used for pulse wave analysis has been described before. The derived aortic pressure waveforms were analysed to determine ejection duration (used as a measure of systolic function), augmentation pressure (the pressure increase due to the reflected components of the original pressure pulse generated by ventricular ejection, resulting in a systolic shoulder on the ascending limb pressure curve that coincides with peak flow) and augmentation index, the latter being defined as the ratio of the augmentation pressure to the pulse pressure. The augmentation index was adjusted so that assessment thereof was performed at a projected heart rate of 75 beats per minute. Additionally, a measure of the relationship between myocardial blood flow and oxygen demand (subendocardial viability ratio) was determined by calculating the ratio between the integral of pressure and time during diastole (Diastolic Pressure Time Index) and systole (Systolic Pressure Time Index). Various timing variables, determined from differentials mathematically, were computed. Figure 1 represents the flow waveforms in which time variables are indicated. The first inflection point represents the time at peak of the pressure wave generated by ventricular ejection, in the absence of wave reflection. The time of return of the reflecting wave is defined as the subsequent concavity in the wave. This second inflection represents the time at the foot of the reflecting wave. The central systolic pressure is indicated as the following pressure peak or shoulder. The summated forward-moving and backward-moving pressure waves reach their maximum at this moment. The incisura indicates the end of systole.
Pulse wave analysis after successfully repaired aortic coarctation

Pulse wave velocity
Pulse waveforms were recorded at the carotid and femoral arteries during ECG tracing. The carotid-femoral distance was assessed by subtracting the distance between the suprasternal notch and the carotid artery measurement site from the distance between the suprasternal notch and the femoral artery measurement site. An algorithm was used in which the foot of the tonometer waveform was identified as the point at which the first derivative is a maximum in the pressure wave contour of at least three
pairs of data at the proximal and distal recording sites. $^{16}$ PWV, expressed in meters per second, could be calculated by dividing distance with the transit time. The Effective Reflecting Distance (ERD) was calculated by the formula: ERD = PWV x time between the wave foot and return of the reflected wave (see Figure 1).

**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 as appropriate. Categorical variables were compared between groups using $\chi^2$-test or Fisher’s exact test. Correlation was tested by calculating Pearson correlation coefficients. Differences between groups were analysed by two-sample Kolmogorov-Smirnov test and independent samples T-test or Mann-Whitney U test subsequently, as appropriate. All p-values were based on two-sided comparisons, and a value of <0.05 was considered significant.

**Results**

**Patient characteristics**
The mean age was 38.8 ± 7.05 years for patients and 39.4 ± 4.50 years for controls. Six patients and four controls were male. Brachial systolic and diastolic blood pressure were 129 ± 9.66 and 74.8 ± 9.64 mmHg in patients and 128 ± 10.2 and 77.9 ± 7.45 mmHg in controls. Body mass index was 26.1 ± 4.05 kg/m² for patients and 25.9 ± 2.94 kg/m² in controls. Coarctation treatment had been performed 5.6 to 26 years before investigation. Four patients were treated by antihypertensive medication, comprising angiotensin-converting-enzyme inhibitors in all of them. Minimal aortic diameter at coarctation site ranged from 14 to 31 mm in the patient group (mean 19.0 ± 5.70 mm).

**Pulse wave analysis**
The pressure waveform recordings could be successfully acquired in all patients. Results of timing and pressure variables derived from the central aortic pressure waveforms are displayed in Tables 1 and 2, respectively.

The heart rate and ejection duration were not different significantly between patients and controls. The time at the first inflection point and the interval between the first inflection point and the start of the reflected wave were significantly shorter in patients. Peak systolic pressure was reached earlier in patients, while the subendocardial viability ratio was lower mainly due to a decrease in the diastolic pressure time index. Despite similar brachial systolic pressure, central systolic pressure was higher in patients. No significant differences in other pressure variables were observed between the groups. Noteworthy was the large variability in augmentation pressure in the patient group.
Table 1. Pulse wave analysis: timing data.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=11)</th>
<th>Controls (n=14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (beats/min)</td>
<td>65.4 ± 3.85</td>
<td>64.1 ± 10.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Ejection Duration (ms)</td>
<td>329 ± 22.7</td>
<td>330 ± 19.6</td>
<td>0.86</td>
</tr>
<tr>
<td>Time to first systolic inflection (ms)</td>
<td>106 ± 9.64</td>
<td>118 ± 14.9</td>
<td>0.028*</td>
</tr>
<tr>
<td>Time to return of the reflected wave (ms)</td>
<td>139 ± 11.4</td>
<td>158 ± 21.0</td>
<td>0.015*</td>
</tr>
<tr>
<td>Time between first systolic inflection and start of the reflected wave (ms)</td>
<td>33.2 ± 2.50</td>
<td>39.5 ± 8.13</td>
<td>0.021*</td>
</tr>
<tr>
<td>Time to peak pressure (ms)</td>
<td>213 ± 19.2</td>
<td>223 ± 16.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Systolic pressure-time index</td>
<td>2406 ± 322</td>
<td>2330 ± 385</td>
<td>0.29</td>
</tr>
<tr>
<td>Diastolic pressure-time index</td>
<td>3414 ± 437</td>
<td>3629 ± 267</td>
<td>0.044*</td>
</tr>
<tr>
<td>Subendocardial viability ratio</td>
<td>1.43 ± 0.189</td>
<td>1.60 ± 0.285</td>
<td>0.043*</td>
</tr>
</tbody>
</table>

The subendocardial viability ratio is the diastolic pressure-time index divided by the systolic pressure-time index. *: p<0.05.

Table 2. Pulse wave analysis: pressure data.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=11)</th>
<th>Control group (n=14)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central systolic pressure (mmHg)</td>
<td>125 ± 15.1</td>
<td>109 ± 8.73</td>
<td>0.009*</td>
</tr>
<tr>
<td>Central diastolic pressure (mmHg)</td>
<td>74.8 ± 9.64</td>
<td>77.9 ± 7.46</td>
<td>0.37</td>
</tr>
<tr>
<td>Central Pulse pressure (mmHg)</td>
<td>50.0 ± 11.8</td>
<td>31.7 ± 6.45</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Augmentation pressure (mmHg)</td>
<td>10.4 ± 8.61</td>
<td>5.44 ± 3.55</td>
<td>0.39</td>
</tr>
<tr>
<td>Augmentation index (corrected for heart rate @ 75/min)</td>
<td>19.6 ± 12.9</td>
<td>14.0 ± 8.30</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*: p<0.05.

Figure 2. Box and Whisker diagrams for the Effective Reflection Distance. The Effective Reflection Distance was found to be significantly shorter for patients (21.3 ± 5.35 cm versus 28.3 ± 5.96 cm), indicating the early return of aortic wave reflection in patients.
Pulse wave velocity

No significant difference in PWV was observed in patients (6.40 ± 1.45 m/s) and controls (7.21 ± 0.948 m/s) (p = 0.11). The Effective Reflection Distance was found to be significantly shorter for patients (21.3 ± 5.35 cm versus 28.3 ± 5.96 cm) (p<0.01) (Figure 2).

No significant correlation was observed between aortic diameter and PWV (Pearson correlation coefficient < 0.6; p = 0.09) or between aortic diameter and augmentation index (@HR 75) (Pearson correlation coefficient < 0.6; p = 0.08).

Discussion

The main finding of our study is that abnormalities in pulse wave characteristics recorded by radial artery applanation tonometry are present in this patient group. Central systolic blood pressure and pulse pressure were increased in our patient group compared to controls. Augmentation pressure and augmentation index both appeared to be higher for patients, although this difference was not significantly different. Of the timing variables investigated, both time at the first inflection and start of the reflected wave were significantly shorter for patients as compared to controls. The subendocardial viability ratio (SEVR), also known as Buckberg Index (normal value >100%), was another timing variable found to be significantly different between groups. These data indicate that, even following successful coarctation repair, the heart is exposed to an increased pulsatile load. This may explain persistent cardiovascular complications, increased left ventricular hypertrophy and increased carotid intima-media thickness that are observed in normotensive subjects following successful aortic coarctation repair.1,2,16-19 Our findings were obtained by the non-invasive, relatively simple technique of applanation tonometry, which appears to be a potential tool to identify patients that are at the highest risk to develop complications following successful coarctation repair.

The rationale for calculating the subendocardial viability ratio (SEVR) in this study is its quality to represent the relationship between the work of the heart and its oxygen consumption and the pressure and time for coronary perfusion. Accordingly, it has been described as a measure of the propensity for myocardial ischemia on the basis of altered hemodynamic forces.14 A value < 100% has been shown to be associated with insufficient subendocardial perfusion.10 The ratio between diastolic and systolic integrals of time and pressure is a heart rate-dependent variable. The systolic period in hypertensive and elderly persons is found to be relatively long, not decreasing appropriately with tachycardia, thus reducing the diastolic time index and SVER. The average heart rate in our patient population exceeded that of the controls. Therefore, the difference found appears to be robust and may illustrate the hemodynamic burden of the successfully managed coarctation, although the average SEVR-value itself is within the normal range.

The exclusion of hypertensive patients, anti-hypertensive treatment in some patients
and the small sample size may underlie the relatively small difference in augmentation of pressure between our study groups. Murakami et al did find significantly higher augmentation indices invasively, in children that had a significantly higher systolic blood pressure than age-matched controls.21

No significant difference in pulse wave velocity was found between patients and controls in this study. In a previous study, pulse wave velocity assessed by MRI was increased in patients following successful coarctation repair.22 Possible factors to explain this discrepancy with our study are the difference in technique (MRI versus applanation tonometry in our study) and age of the study population (three decades younger than our patients). Age has been shown to be an important determinant for changes in vascular tree characteristics.23 In addition, small difference in pulse wave velocity in the aortic segment proximal to the coarctation repair site may have been obfuscated by compensatory effects in the segment distal to this site. Indeed, aortic stiffness was only increased in the precoarctation segment by analysis of MRI-acquired pulse waves.22 Finally, the small study group may have precluded detection of small differences in pulse wave velocity.

Aortic dimensions or flow velocities and pulse wave characteristics were not found to be strongly correlated. Recoarctation, based on anatomic and physiologic parameters, was excluded in the study group. We consider the aortic diameter, at least in the range investigated, unlikely to exclusively account for differences in pressure wave characteristics between patients and controls. Other aspects of the aortic anatomy, such as the presence of prosthetic interposition grafts, transsection of vasa vasorum by the surgical or endovascular procedure or changes in the composition of the aortic wall, probably cause the local aortic properties to alter in such way that the reflection point is displaced proximally, as is illustrated by the shorter effective reflection distance in the patient group. This distance is a measure of the timing of forward and backward travelling pressure waves at the level of the central arteries and may contribute to the increased central systolic pressure observed in our patient group.24

There are several study limitations. In addition to its small sample size, the study group is heterogenous, including patients with and without antihypertensive medication and following different types of coarctation management. Although the patient diversity may have attenuated differences between patients and controls, these patients represent a “real-life” population. We consider this of advantage in evaluating the role of non-invasive arterial applanation tonometry as screening tool. Besides this quality of our study population, its sample size prevented us from investigating the role of anti-hypertensive medication or different coarctation management types in subgroup analysis. Secondly, it cannot be excluded that aortic interventions per se cause vascular abnormalities in the aortic segments, independent of the underlying cause and resulting in the observed abnormal pulse wave characteristics, rather than coarctation-related effects on the vasculature. Such difference, although interesting with respect to pathophysiology, does not seem to have clinical consequences, since the diagnosis of coarctation in adults will lead to its invasive management commonly. Therefore, we think that this limitation does not undermine the methods and observations of this study.
In conclusion non-invasive arterial applanation tonometry demonstrate specific abnormalities in the pulse wave contour following coarctation repair compared to matched controls. These differences include premature reflection of the aortic pressure wave which may contribute to cardiovascular complications. This technique may be an additional tool to identify patients with successfully repaired coarctation that are still at increased cardiovascular risk.

References

Pulse wave analysis after successfully repaired aortic coarctation


