Evidence for Cardiovascular Autonomic Dysfunction in Neonates With Coarctation of the Aorta

Jaimie W. Polson, PhD; Naomi McCallion, MRCPI; Hidefumi Waki, PhD; Gareth Thorne, PhD; Mark A. Tooley, PhD; Julian F.R. Paton, PhD; Andrew R. Wolf, MD

Background—Coarctation of the aorta (CoA) is associated with hypertension and abnormalities of blood pressure control, which persist after late repair. Assumptions that neonatal repair would prevent development of blood pressure abnormalities have not been supported by recent data. We hypothesized that early pathological adjustment of autonomic cardiovascular function may already be established in the neonate with coarctation.

Methods and Results—We studied 8 otherwise well neonates with simple CoA and compared measures of spontaneous baroreflex sensitivity, heart rate variability, and blood pressure variability with 13 healthy newborn babies. Spontaneous baroreflex sensitivity was calculated with sequence methodology from an ECG, and noninvasive blood pressure was recorded with a Portapres. Heart rate variability was determined with time- and frequency-domain measures. Blood pressure variability was measured in the frequency domain. In comparison with normal controls, neonates with CoA had raised blood pressure (78.9 ± 3.8 versus 67.1 ± 2.1 mm Hg), depressed baroreflex sensitivity (8.7 ± 1.5 versus 13.8 ± 1.1 ms/mm Hg), reduced heart rate variability (total power 16.5 ± 3.1 versus 31.5 ± 2.2 ms²), and an increase in the high-frequency component of blood pressure variability (3.1 ± 0.3 versus 2.2 ± 0.2 mm Hg²). This is not the pattern expected if neonates with CoA simply had subclinical cardiac failure.

Conclusions—These data suggest that infants with CoA already show signs of pathological adjustment of autonomic cardiovascular homeostasis. Further longitudinal studies are required to determine whether these alterations play a role in the increased risk of late hypertension in these patients. (Circulation. 2006;113:2844-2850.)

Key Words: baroreceptors ■ heart defects, congenital ■ hypertension ■ nervous system, autonomic ■ pediatrics

Patients with untreated coarctation of the aorta (CoA) have poor outcomes, with a median life expectancy of 31 years due to hypertension-related pathology. Correction of the anatomic defect in childhood or adult life is not curative: Most of these patients have persistent abnormalities of cardiovascular regulation, significant long-term morbidity, and reduced life expectancy. It was hoped that early anatomic repair in the neonate could restore normal cardiovascular homeostasis, thereby ameliorating the incidence and severity of the problems associated with late repair. Early repair is now routinely performed in pediatric cardiac practice, but a recent study evaluating the results of CoA repair within the first few months of life showed disappointing results, with a 20% to 30% incidence of hypertension at 10 years' follow-up, despite good anatomic correction.

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The cause of late hypertension after CoA repair is not completely understood. Known associations with CoA include reduced responsiveness to vasoactive agents, increased arterial stiffness, abnormalities in aortic arch geometry, abnormalities in renal function with increased renin-angiotensin activity, and altered baroreflex function. A number of recent studies in both humans and animals indicate that reduced baroreflex reflex sensitivity (BRS) may play an important role in the pathogenesis of hypertension, and although reduced BRS has been reported in patients with postoperative CoA, it is unclear at what point in the disease process these autonomic abnormalities arise. If BRS is already abnormally low in the newborn infant with preoperative CoA, there may be long-term consequences for normal regulation of arterial pressure and, despite successful subsequent repair, an increased risk of hypertension in the long term. Alterations in baroreflex function have been demonstrated in animal models investigating the developmental origins of adult hypertension, but to date, there have been no human data describing baroreflex function in neonates awaiting CoA repair.

Measurement of heart rate variability (HRV) is another way of assessing autonomic function. Changes in the power of the high-frequency (HF) and low-frequency (LF) components of HRV are believed to correspond to alterations in...
parasympathetic and sympathetic outflow to the heart. Similarly, changes in beat-to-beat systolic blood pressure variability (BPV) can provide information on vascular autonomic control. These techniques have been used to evaluate cardiovascular autonomic function and have been shown to predict mortality outcome in patients with cardiovascular risk. In addition, recent studies show that normotensive patients with family history or predisposition to hypertension have altered HRV and BPV, which suggests that these indices of autonomic function may characterize early signs of altered cardiovascular homeostasis and subsequent risk of late hypertension. In infants, HRV is reduced in a number of conditions, including preterm birth, congenital heart defects, respiratory distress, and sudden infant death syndromes (see Rosenstock et al). HRV has not been assessed in neonates with CoA.

Recently, spontaneous BRS has been measured in the neonate by adapting a noninvasive device designed for the adult that measures the continuous blood pressure (BP) waveform (Portapres systems: Finapres Medical Systems, Amsterdam, the Netherlands). In the present study, we have used this technique to compare spontaneous BRS in newborn infants with CoA and normal controls. We have also measured HRV and BPV to determine whether these characteristics are altered in neonates with CoA before surgical repair.

Methods

We recruited 10 term infants with CoA before they underwent surgical repair and 20 healthy term infant controls. Patients with CoA were recruited consecutively on admission to hospital on the basis of the clinical assessment that the patient was otherwise well and did not have significant cardiac, respiratory, or renal dysfunction. This determination was based on the infant being managed without the need for inotrope, respiratory, or renal support. Patients treated with prostaglandin E2 were excluded from the study. We used a Portapres monitor (Portapres systems: Finapres Medical Systems, Amsterdam, the Netherlands). In the present study, we adapted for use in the infant by placing the cuff around the wrist. Continuous BP waveform was measured with the Portapres model 2, calibrated for use in the infant by adapting a noninvasive device designed for the adult that measures the continuous blood pressure (BP) waveform (Portapres systems: Finapres Medical Systems, Amsterdam, the Netherlands). In the present study, we have used this technique to compare spontaneous BRS in newborn infants with CoA and normal controls. We have also measured HRV and BPV to determine whether these characteristics are altered in neonates with CoA before surgical repair.

Assessment of Spontaneous BRS

Spontaneous BRS was determined from the spontaneous changes in systolic BP (SBP) and the interval between peaks in the R-wave of the ECG (RR interval) by a time-series analysis procedure similar to that described previously. Briefly, spontaneously occurring changes in SBP, over a period of 4 or more beats, were identified, and relationships with the corresponding RR intervals, with delays of 3, 4, and 5 beats, were plotted. These delays were based on preliminary observations that there was a delay of ~2 seconds for heart rate (HR) to change in response to a spontaneous change in pressure and that the neonatal HR is ~2 beats per second. The slope and r² value of the linear regression for these plots were calculated. A baroreceptor-mediated change in HR was considered to have occurred when the slope was positive and r² was >0.8 for each delay. On fulfillment of these criteria, the 3 slopes were averaged to give a value for BRS. We have previously shown that this protocol measures BRS accurately in animals compared with standard pharmacological techniques.

Assessment of HR and BPV

HRV was calculated with time- and frequency-domain methodology. Time-domain analysis was performed on ECG recordings over a period of exactly 15 minutes. The following 3 measures were calculated: SD of the normal-to-normal (NN) RR intervals, square root of the mean squared differences of successive NN intervals, and the number of successive NN intervals greater than 5, 10, 20, 30, 40, and 50 ms, expressed as a ratio of the total number of NN intervals (pNN50). A family of pNN values, rather than only pNN, provides better separation between groups, particularly for short RR intervals, such as those occurring in neonates. Frequency-domain analysis of HRV and BPV was performed with a custom-made program (developed in collaboration with Tears Computer Co, Tokyo, Japan; see Waki et al). Peak detection on ECG and BP signals was used to create RR interval and SBP sequences. These were resampled at 5 Hz, and linear trend removal and fast Fourier transform (256 point, Hanning window) with 50% overlap were performed. Spectral bands for HRV and BPV were defined at 0.04 to 0.15 Hz for LF and 0.15 to 1.1 Hz for HF (based on respiratory rates in infants at 0.5 to 1 Hz). The total frequency band was defined as the range between 0.04 and 1.1 Hz. The very-low-frequency band was not analyzed because of probable slow trend artifacts.

Statistical Analysis

Data are expressed as mean±SE unless otherwise noted. Data were tested for normality with a Shapiro Wilks test. The accuracy of the Portapres in measuring BP was evaluated by the extent of agreement with measurements from an arterial line. Bias was defined as the average of the difference between Portapres and arterial line values. The SD of the bias is an index of intrapatient variation. Comparisons between CoA and controls were made with unpaired 2-tailed t tests for normally distributed data and Mann-Whitney rank sum tests for data that were not normally distributed. Differences were considered significant at P<0.05.

Results

The postmenstrual age (gestation age plus postnatal age) of the CoA group was ~2 weeks greater than that of the control group.
In 5 infants, we compared simultaneous recordings of BP measured from the Portapres and via an arterial cannula. When the cuff was positioned correctly around the infant’s wrist, a good BP waveform was obtained, with good similarity between the 2 signals (Figure 1). However, the Portapres signal fluctuated considerably with movement and became less accurate in time, possibly because of the cuff loosening signal fluctuated considerably with movement and became less accurate in time, possibly because of the cuff loosening.

TABLE 1. Comparison of BP Measurements Obtained With Portapres and Arterial Line

<table>
<thead>
<tr>
<th>BP Measurement</th>
<th>Gain, mm Hg/mm Hg</th>
<th>Bias</th>
<th>SD of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>0.97±0.02</td>
<td>1.71±1.69</td>
<td>4.20±0.31</td>
</tr>
<tr>
<td>DBP</td>
<td>1.06±0.02</td>
<td>-2.28±0.76</td>
<td>2.67±0.49</td>
</tr>
<tr>
<td>Change SBP</td>
<td>0.91±0.10</td>
<td>0.04±0.02</td>
<td>1.12±0.13</td>
</tr>
</tbody>
</table>

Gain indicates slope of linear regression of BP measured from arterial line and Portapres; Bias, mean of the difference in BP measurements; DBP, diastolic blood pressure; and change SBP, beat-to-beat change in SBP.

The total number of pressor and depressor events were 17.0±1.8 (range 10 to 25) and 19.3±2.0 (range 11 to 27), respectively, in CoA and 14.5±2.7 (range 2 to 32) and 17.1±2.7 (range 7 to 39) in controls. This equated to a total frequency in events of 2.8±0.4 events per minute in CoA and 2.8±0.3 events per minute in control infants (P=0.93). Spontaneous BRS was calculated for pressor events, depressor events, and total number of events. All measurements showed that infants with CoA had a significant reduction in spontaneous BRS of ~40% (Figure 2). The correlation between SBP and BRS was poor in both the control (r=0.12) and CoA (r=0.29) groups.

**HR and SBP Variability**

Although HR was similar in the 2 groups, variability in HR was dramatically reduced in CoA (Figure 3A). We found a significant reduction in the 3 time-domain measurements of HRV examined (Table 2; Figure 3B), and consistent with this, frequency-domain analysis showed a decrease both in total power and in the power in the LF and HF bands (Table 3). The ratio of LF to HF power was not different between the groups (P=0.3). There was a strong correlation between SBP and BRS very accurately. The mean change in SBP was not different between the 2 measures (Portapres 1.71±0.65 mm Hg versus arterial line 1.76±0.4 mm Hg, P=0.68), with limits of agreement of ~2 mm Hg (Table 1).

With the Portapres, infants with CoA demonstrated a significantly higher average SBP than controls (78.9±3.8 versus 67.1±2.1 mm Hg, respectively; P<0.01). HR and RR intervals were not different (Table 2).

**Spontaneous BRS**

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HRV and BRS in infants with CoA ($r=0.78$ to $0.89$), whereas the correlation was only moderate in controls ($r=0.47$ to 0.52). There was no clear relationship between HRV and age; some measures showed a trend for HRV to increase with age, whereas others showed a trend for HRV to decrease. The correlation was poor in all cases ($r=0.14$ to 0.27). In contrast to HRV, BPV showed an increase in power in the HF range in the CoA group (Table 3). We also noted a trend toward an increase in total power in BPV in the CoA group, although this was not significant ($P=0.11$). Although there was no change in absolute LF power ($P=0.8$), when expressed in normalized units, a reduction was observed.

Discussion

There is increasing interest in the role of the autonomic nervous system in cardiovascular disease, with accumulating evidence that autonomic dysfunction may play a role in its etiology.8–11,16,17 The results of the present study appear to demonstrate that infants with CoA have established autonomic dysfunction, in terms of reduced BRS and HRV, and increased BPV in early postnatal life before corrective surgery. This suggests that even in the very early stages of the disease process, pathological alterations in autonomic function have occurred, which may have deleterious consequences much later in life despite early correction of the aortic pathology. Elucidation of the mechanisms of this process could help in understanding why some but not all CoA patients develop hypertension in the long term.

Portapres Validation

Raised BP in the right arm, proximal to the lesion, is expected in CoA,1 and the results of the present study demonstrated an increase in average SBP of $12 \text{ mm Hg}$ compared with controls. However, a recent study found considerable variation in BP measurements between a Finapres and arterial line, with considerable variation in bias and limits of agreement.25 The present data are consistent with this report, which suggests that the Portapres has limited value in estimating absolute BP. The increase in right arm pressure observed in the CoA group exceeded the confidence intervals, which suggests that upper body BP was indeed higher in this group, even though the infants in the study were considered to have adequate circulation distal to the coarctation. However, interpretation of this result remains limited because of the inaccuracy in measuring absolute BP with the Portapres.

BRS Changes in Human Infants

In contrast, we found the Portapres measured beat-to-beat changes in BP with high accuracy, consistent with Andriessen et al.25 This makes the Portapres well suited for determination of BRS, which compares relative changes in BP to changes in HR. Other investigators using the sequence technique in the healthy term neonate have determined values lower than those reported here (8.94 and 10.23 versus 13.8 ms/mm Hg).23,24 This may be due to differences in the algorithm for the calculation of BRS. In particular, these investigators did not implement a delay when plotting SBP against the corresponding RR interval. In our experience, in infants, there is a delay of $\approx 2$ seconds (3 to 5 cardiac cycles) between a change in BP and the corresponding change in HR. It may be that a lower value for BRS is calculated when a delay is not incorporated into the algorithm. This is consistent with a recent study using transfer function analysis of the LF bands of HRV and BPV to calculate spontaneous BRS, which found BRS to be 15.0 ms/mm Hg in the term neonate, with a delay (phase difference) of 2.6 seconds.31 We believe that the inclusion of a delay may provide a more accurate measure of BRS in the neonate; however, this requires further verification.

BRS Changes in Human Infants With CoA

We found BRS to be significantly lower in CoA infants than in controls. The 2-week difference in postmenstrual age is unlikely to underlie this difference, because BRS does not
change significantly in the first 2 postnatal weeks. Moreover, any change due to age differences would more likely cause an increase in BRS in the CoA (older) group. An inherent limitation of spontaneous BRS techniques is that they measure only around the operating point of BP. Therefore, if BP in CoA infants is higher, the observed reduction in BRS may be due to the baroreflex operating at a different (nonlinear) part of the baroreflex function curve. We cannot discount this possibility; however, we found no difference in BRS determined from pressor events versus from depressor events, which suggests that in both CoA and control groups, the BP operating point was on the linear part of the baroreflex function curve, supporting our conclusion that its sensitivity is reduced in CoA.

It is also possible that the medications with which the CoA infants were being treated may have altered BRS directly or indirectly via interactions with cardiorenal mechanisms. We cannot exclude this possibility, although evidence in canine animal models indicates that intravenous administration of prostaglandin E2 at a comparable dose does not cause baroreflex inhibition, whereas the mineralocorticoid receptor antagonist spironolactone has been reported to improve baroreflex function and HRV in cardiac patients. It has been shown previously that BRS is reduced in older hypertensive children with repaired CoA. The present work extends this finding by showing that BRS is already reduced in the early neonatal period. The cause of reduced BRS is not known, and there are a number of possible explanations. First, as mentioned above, we found that CoA neonates already had raised BP, which may cause resetting or desensitization of the baroreceptors. We cannot exclude this possibility, but we found a poor correlation between BP and BRS in both groups, which suggests that the low BRS was not directly related to the degree of hypertension in CoA. Another possible explanation is that the reduced BRS may be due to increased arterial stiffness, particularly proximal to the coarctation. This increased stiffness would result directly in a reduction in the transduction of BP changes into changes in afferent baroreceptor activity and a consequent reduction in BRS. Finally, it is possible that BRS may be reduced due to changes in the central processing of the baroreflex, secondary to the circulatory changes from the CoA. A potential mechanism for this is a renal hypertensive-induced rise in renin and angiotensin II, which can act at the area postrema and nucleus tractus solitarii to reduce BRS. Whatever the mechanism, the present data raise the possibility that reduced BRS may play a role in the development of hypertension in the long term in this patient group. This hypothesis is supported by recent clinical reports that indicate that BRS is reduced in normotensive patients with an increased risk of developing hypertension. Although traditional dogma maintains that the baroreflex is important only in the short-term regulation of BP, recent animal studies clearly demonstrate a crucial role for the baroreflex in the long-term regulation of BP.

Studies using animal models of developmentally programmed hypertension also have observed changes in baroreflex function, even before the onset of hypertension. There is a possibility that programmed hypertension in these animal models and late hypertension associated with CoA may have similar origins.

### HRV and BPV

Both time- and frequency-domain measures showed a large reduction in HRV in the CoA group. Reduced HRV is commonly observed in diseases that involve autonomic dysfunction, both in the adult and the infant. The present HRV data therefore provide additional evidence for autonomic dysfunction in CoA patients. Although it was not possible to obtain 24-hour ECG recordings for time-domain analysis, we were careful to ensure that our analysis was performed over precisely the same time period in each infant (15 minutes), which allowed us to compare relative differences between healthy neonates and those with CoA. We examined 3 time-domain measures: SD of the NN RR intervals gives a measurement of the overall variability, whereas square root of the mean squared differences of successive NN intervals and pNN50 are short-term measures. We did not calculate long-term measures of HRV because of the short time period over which we recorded ECG. Our frequency-domain analysis gave similar results to the time-domain analysis, with reductions in total power and in the HF and LF bands in the CoA group. There was no difference in the ratios of HRV power, expressed as normalized units, which suggests that the overall reduction in HRV power may reflect a generalized reduction in vagal activity in CoA patients, particularly because the vagus has a greater influence on HRV in the infant. It is possible that this may simply illustrate the compromised nature of the CoA infant rather than a specific autonomic defect. However, these patients were assessed as being otherwise well and did not
have increased HR or respiratory rate. Furthermore, these patients did not have increased LF/HF ratio, indicative of raised cardiac sympathetic nerve activity, which is typically observed in heart failure. However, we cannot exclude this possibility, and further studies may be appropriate. Finally, we found a strong correlation between BRS and HRV, consistent with the baroreflex being one of the major influences on cardiac vagal activity.

The increase in BPV in the HF range in CoA contrasts with the data in heart failure, which show a trend toward reduced BPV. The presence of patent ductus arteriosus in most of the CoA group (confirmed in 5 of 8 infants) may account for the increased HF BPV. This is believed to occur because of arteriolar and capillary recruitment during inspiration that produces a net increase in vascular capacitance in these patients: The subsequent mechanical effects increase HF BPV. There is general consensus that the HF component of BPV is related to the mechanical influences of respiration on stroke volume rather than to autonomic factors. However, recent reports indicate that the vagus plays an important role in moderating HF BPV under normal conditions.

Therefore, it is possible that the increased HF BPV in CoA may also be due in part to a reduction in vagal activity (as discussed above), which suggests the possibility of an attenuation of a fast-acting (vagal) buffering system for BP providing further evidence for possible early dysfunction in BP regulation in CoA.

In addition to providing information on autonomic function, reduced HRV power is known to be associated with cardiac and all-cause mortality, whereas increased BPV is associated with increased risk of end-organ damage. With this in mind, the present findings suggest that it may be useful clinically to measure these variables in CoA patients as an index for predicting severity of the disease.

Conclusions

Despite early successful repair, 20% to 30% of patients with neonatal CoA develop late hypertension. The present data show low BRS, low HRV, and increased BPV in infants with CoA, which indicates that alterations in BP regulation have taken place in fetal or very early neonatal life. We do not know whether infants undergoing early surgical CoA repair maintain altered BRS afterward, but failure of this reflex to normalize could cause long-term impediments to normal BP control. Animal studies show that specific interventions during fetal development, such as maternal undernutrition, can cause derangement in autonomic cardiovascular regulation and lifelong hypertension (developmentally programmed hypertension). In CoA, similar developmental autonomic abnormalities may occur that may have lifelong sequelae, even after the structural defect is corrected, resulting in increased cardiovascular morbidity. Further studies are required to determine whether BRS abnormalities persist in those CoA patients who go on to develop hypertension and whether such abnormalities have a causative role in the etiology of hypertension in this patient group. If such a case can be proven, new techniques of fetal detection of CoA and assessment of fetal HRV open up the possibilities of detecting and even treating those patients most at risk of developing late-onset hypertension after CoA repair.

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Disclosures

None.

References

Uncorrected coarctation of the aorta is associated with early death due largely to the consequences of hypertension. It is now possible to perform a surgical repair of the defect in infancy, and it had been hoped that this would provide a “cure” of the condition. However, recent data indicate that the coarctation patient is predisposed to hypertension, even after effective anatomic correction of the defect in infancy. One possibility is that changes in the central nervous system control of the cardiovascular system occur in coarctation, within the fetal or neonatal period, that manifest in hypertension in later years. Recently, our understanding of the importance of the autonomic nervous system in the long-term regulation of blood pressure and cardiovascular function has advanced substantially, and there is good evidence for underlying links between hypertension and increased sympathetic activity and/or reduced baroreflex sensitivity. In this study, we show that newborn infants awaiting coarctation repair have abnormalities in cardiovascular autonomic regulation, in terms of altered baroreflex function, heart rate variability, and blood pressure variability, that are conducive to the long-term development of hypertension. It is interesting to speculate whether these abnormalities resolve in those patients with good longer-term outcomes but not in those who develop late hypertension and whether intervention with antihypertensive agents in infancy could prevent these changes. Moreover, it is possible that this may reflect a more generalized phenomenon, whereby events that occur during development may produce alterations in autonomic function that predispose the healthy individual to increased risk of hypertension in later life.
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