Cardiac Autonomic Nervous System Activity and Cardiac Function in Children After Coarctation Repair

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Background. Coarctation of the aorta (CoA) is one of the most common congenital heart defects. Most patients live into adulthood as a result of improved surgical techniques; however, late complications, including hypertension, recoarctation, and arrhythmias, are common. The autonomic nervous system (ANS) might play a role in the pathology. This study evaluated cardiac ANS activity and cardiac function in children after CoA repair and investigated the relationship between the two.

Methods. The study participants were 31 children after CoA repair and 62 healthy controls aged between 8 and 18 years. Ambulatory impedance cardiography was used to measure cardiac ANS activity and cardiac output for 24 hours. Transthoracic echocardiography and cardiac magnetic resonance imaging were used to measure cardiac function.

Results. No group differences were found in ambulatory cardiac ANS activity. However, ambulatory cardiac output and left ventricular function were significantly decreased in patients compared with controls.

Conclusions. Left ventricular function and ambulatory cardiac output are impaired in patients after CoA repair, despite unchanged cardiac ANS activity in this group. These results underscore the importance of clinical follow-up, even in patients without residual stenosis.

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Abbreviations and Acronyms

ANS = autonomic nervous system
CI = confidence interval
CO = cardiac output
CoA = coarctation of the aorta
E' = peak early velocity
ECG = electrocardiogram
GLS = global peak strain
HR = heart rate
ICG = impedance cardiogram
IQR = interquartile range
LV = left ventricle
MET = metabolic equivalent task
MRI = magnetic resonance imaging
PA = physical activity
PEP = preejection period
PNS = parasympathetic nervous system
PWV = pulse wave velocity
RSA = respiration sinus arrhythmia
RV = right ventricle
S' = peak systolic velocity
TDI = tissue Doppler imaging
TTE = transthoracic echocardiogram

Twenty-four hour ECG and ICG registration was done using the 5fs version of the Vrije Universiteit Amsterdam (VU) Ambulatory Monitoring System (VU-AMS; VU University, The Netherlands) [10]. A 1-lead ECG was derived from 3 pregelled Ag/AgCl (Kendal H124SG, Halberstadt, Germany) spot electrodes on the chest. Thoracic impedance (Z) was conducted by introducing a small alternating current (50 kHz, 350 mA) through the foot-to-foot transit-time method was used to setup data from the VU-AMS device, the 24-hour recording was divided into fixed periods, coded for activity. Ensemble-averaged ICG and ECG during these periods were analyzed. The mean heart rate (HR), RSA, PEP, and CO was ultimately calculated for each patient for sleeping (mean of all sleeping labels), sitting (mean of watching television, reading, computer), active sitting (class, crafts, homework), light physical activity (walking, chores), and heavy physical activity (cycling, gymnastics, playing). Participants were queried about their physical activity by the use of a short lifestyle interview because differences in ANS activity might partly be explained by physical activity level [17].

Cardiac Function and Structure

Supine resting transthoracic echocardiograms (TTE) were conducted by a pediatric cardiologist or an experienced technician (Vivid 9; General Electric Healthcare, Horten, Norway). Images were stored and analyzed offline using EchoPac 113 software (General Electric Healthcare). LV longitudinal global peak strain (LV GLS, %) was calculated as the average of the peak strain obtained from the apical 2-3- and 4-chamber view using speckle tracking strain analysis [18]. Biventricular performance was characterized using pulsed-wave tissue Doppler imaging (TDI) from an apical 4-chamber view. Myocardial velocity curves were obtained at the basal part of the left and right ventricular wall and the intraventricular septum. Peak systolic velocity (S') and peak early (E') diastolic velocities (cm/s) were assessed in 3 consecutive heart beats, and the average was used for analysis.

Cardiac magnetic resonance imaging (MRI) was done in an Ingenia 3T scanner (Philips Healthcare). Pulse wave velocity (PWV) and LV wall mass were assessed in patients only. Analyses were done offline using in-house developed MASS software (Leiden, The Netherlands). PWV was determined from 2 high-temporal one-directional velocity-encoded time-resolved MRI acquisitions, planned perpendicular to the aorta, 1 at the ascending aorta at the level of the pulmonary trunk and 1 at the abdominal aorta 3 cm below the diaphragm. Flow mapping was performed to obtain velocity-time curves. The PWV was determined over both the proximal aorta (ascending aorta plus aortic arch and thoracic descending aorta, Fig 1) as well as the distal descending aorta (Fig 1). The validated foot-to-foot transit-time method was used to define PWV [19].

LV wall mass was assessed from a cine multislice short-axis data set acquired with steady-state free-precession gradient echo. Epicardial and endocardial contours were drawn in every slice. The areas were subtracted, and the resulting areas were multiplied with slice thickness, number of slices, and the density of myocardium. Contours were drawn end-diastole and end-systole by
1 researcher and supervised by 1 radiologist. The average from the end-diastolic mass and end-systolic mass was used for analysis.

The TTE, cardiac MRI, and 24-hour monitoring were all obtained within 48 hours for all but 1 patient, for whom there were 7 days between the cardiac MRI and the TTE and 24-hour monitoring.

Statistical Analyses

IBM SPSS Statistics 23.0 software (IBM, Armonk, NY) was used for statistical analysis. Differences in HR, PEP, RSA, and CO between the healthy control and the patient group were studied by fitting a linear mixed model. Because RSA was skewed, its natural log transformation was used for further analysis. In the mixed model, we treated activity as a within-subject factor with 5 levels (sleep, inactive sitting, active sitting, moderate physical activity, heavy physical activity), and we treated group as a between-subject factor, with 2 levels (healthy control and CoA patient). In the model, a random intercept was allowed over persons. Weekly physical activity was included as a covariate in the analysis of ANS activity and additionally breathing frequency in the analysis of RSA.

Results

Table 1 summarizes the patient characteristics and weekly physical activity level. Resting systolic blood pressure was significantly higher ($p = 0.030$) in patients than in controls. The surgical technique used for CoA repair was end-to-end anastomosis in 28 patients and subclavian flap in 3. Time after operation averaged 12 years (range, 3.6 to 17.6 years). None of the patients had a clinically significant residual stenosis. Maximal flow velocity at the coarctation site averaged 2.3 (SD, 0.6) m/s. The aortic valve was bicuspid in 19 patients (59%). At the time of the study, 3 patients were using medication (labetalol or enalapril). Adjusted group means of HR, RSA, PEP, and CO in each of the 5 ambulatory activities are summarized in Table 2.

Results of the mixed linear modelling included a main effect of ambulatory activity on all 4 measures. For HR, no main effect of group was found ($F_{1,96} = 2.10$, $p = 0.15$), but there was an interaction effect between group and activity ($F_{4,91} = 2.74$, $p = 0.033$). HR was higher in healthy and mean arterial blood pressure in the analysis of PEP. Differences in patient characteristics between groups were evaluated by means of an independent t test. For comparison of the 7 cardiac function variables between groups, a multivariate analysis of variance was performed. In case of significance of the omnibus group effect ($p < 0.05$), post hoc testing on each separate variable used a Bonferroni correction of the overall $p$ value. Lastly, a correlation matrix was computed for the cardiac function variables, blood pressure, and ambulatory cardiac ANS variables, PEP, and RSA during sleep in the patient group.
controls during all periods except for sleep; however, univariate test results showed no significant differences. For PEP, no main effect of group ($F_{1,74} = 0.43, p = 0.515$) but an interaction effect between group and activity ($F_{2,81} = 4.55, p = 0.002$) was found. The adjusted mean for PEP was higher in patients during sleep and higher in healthy controls during periods of moderate or heavy physical activity. However, univariate tests did not show significant differences. RSA showed neither a group effect ($F_{1,95} = 1.09, p = 0.300$) nor an interaction of group-by-activity ($F_{4,97} = 1.04, p = 0.393$). Lastly, CO showed a main effect of group ($F_{1,98} = 8.06, p = 0.006$), which was due to lower CO in the CoA patients throughout the entire ambulatory recording period.

Cardiac function was significantly different between the two groups (Pillai’s trace, $V = 0.340$; $F_{2,74} = 5.46, p < 0.001$). Univariate tests showed a significantly lower peak S’ and E’ wave velocity in the LV wall and lower peak E’ velocity in the intraventricular septum in patients compared with controls (Table 3).

A significant correlation was found between basal RSA during sleep and LV GLS ($r = 0.51, p = 0.004$) and between basal RSA and PWV in the proximal aorta ($r = 0.47, p = 0.012$). Also significant were the correlations between basal PEP during sleep and LV GLS ($r = -0.45, p = 0.002$), between basal PEP and LV mass ($r = 0.55, p = 0.002$), and between basal PEP and peak S’ wave in the intraventricular septum ($r = -0.45, p = 0.010$). These associations were not found in the healthy control group. The correlation matrix can be found in Table 4.

Rerunning the analyses without the 3 patients who were taking medication did not alter the pattern of results.

### Table 3. Cardiac Structure and Function Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure of</th>
<th>Related to</th>
<th>CoA Patients Mean (SD)</th>
<th>Healthy Controls Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV GLS, %</td>
<td>LV global function</td>
<td>Contractility</td>
<td>17.9 (2.4)</td>
<td>18.2 (2.2)</td>
</tr>
<tr>
<td>Tissue Doppler imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV S’, cm/s</td>
<td>Systolic function</td>
<td>Contractility</td>
<td>8.7 (3.1)*</td>
<td>10.8 (3.0)</td>
</tr>
<tr>
<td>LV E’, cm/s</td>
<td>Diastolic function</td>
<td>Contractility</td>
<td>15.0 (4.6)*</td>
<td>19.4 (3.7)</td>
</tr>
<tr>
<td>Septum S’, cm/s</td>
<td>Systolic function</td>
<td>Contractility</td>
<td>6.9 (1.0)</td>
<td>7.2 (1.0)</td>
</tr>
<tr>
<td>Septum E’, cm/s</td>
<td>Diastolic function</td>
<td>Contractility</td>
<td>12.6 (2.3)*</td>
<td>14.0 (2.1)</td>
</tr>
<tr>
<td>RV S’, cm/s</td>
<td>Systolic function</td>
<td>Contractility</td>
<td>13.0 (2.2)</td>
<td>12.3 (1.8)</td>
</tr>
<tr>
<td>RV E’, cm/s</td>
<td>Diastolic function</td>
<td>Contractility</td>
<td>16.0 (3.4)</td>
<td>14.8 (3.3)</td>
</tr>
<tr>
<td>PWV proximal aorta, m/s</td>
<td>Aortic stiffness</td>
<td>Blood pressure</td>
<td>4.9 (1.3)</td>
<td>...</td>
</tr>
<tr>
<td>PWV distal aorta, m/s</td>
<td>Aortic stiffness</td>
<td>Blood pressure</td>
<td>3.9 (0.8)</td>
<td>...</td>
</tr>
<tr>
<td>LV mass, grams</td>
<td>Hypertrophy</td>
<td>Afterload</td>
<td>85 (27)</td>
<td>...</td>
</tr>
</tbody>
</table>

* Significant difference between groups after Bonferroni correction for multiple comparisons ($p < 0.007$).

CoA = coarctation of the aorta; E’ = peak early velocity; GLS = global longitudinal strain; LV = left ventricle; PWV = pulse wave velocity; RV = right ventricle; S’ = peak systolic velocity.
blood pressure relative to the coarctation, decreased elastic wall properties [20], systemic blood pressure. Also, increased pressure proximal to the coarctation could activate the renin-angiotensin system to increase systolic velocity.

Kim and colleagues [9], who showed reduced longitudinal LV strain; LV GLS = left ventricle; PEP = preejection period; RSA = respiration sinus arrhythmia; RV = right ventricle; S = peak systolic velocity.

Table 4. Correlation Between Cardiac Autonomic Nervous System and Cardiac Function and Structure in the Coarctation of the Aorta Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>PEP (sleep)</th>
<th>RSA (sleep)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV GLS</td>
<td>0.54 (0.34 to 0.70)</td>
<td>0.51 (0.08 to 0.36)</td>
</tr>
<tr>
<td>Tissue Doppler imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV S'</td>
<td>-0.31 (-0.67 to 0.05)</td>
<td>0.04 (-0.33 to 0.42)</td>
</tr>
<tr>
<td>LV E'</td>
<td>-0.25 (-0.62 to 0.12)</td>
<td>0.10 (-0.29 to 0.48)</td>
</tr>
<tr>
<td>Septum S'</td>
<td>-0.45 (-0.78 to -0.11)</td>
<td>0.23 (-0.13 to 0.59)</td>
</tr>
<tr>
<td>Septum E'</td>
<td>-0.23 (-0.60 to 0.15)</td>
<td>0.06 (-0.32 to 0.44)</td>
</tr>
<tr>
<td>RV S'</td>
<td>-0.04 (-0.42 to 0.34)</td>
<td>-0.14 (-0.52 to 0.24)</td>
</tr>
<tr>
<td>RV E'</td>
<td>-0.01 (-0.38 to 0.37)</td>
<td>0.04 (-0.34 to 0.41)</td>
</tr>
<tr>
<td>Cardiac output (sleep)</td>
<td>-0.09 (-0.47 to 0.29)</td>
<td>-0.03 (-0.41 to 0.35)</td>
</tr>
</tbody>
</table>

* Significant correlation (p < 0.05).

CI = confidence interval; E' = peak early velocity; GLS = global longitudinal strain; LV = left ventricle; PEP = preejection period; RSA = respiration sinus arrhythmia; RV = right ventricle; S' = peak systolic velocity.

aged 8 ± 7 years. The results from our study are in line with these results. We did not replicate Van der Ende and colleagues [9], who showed reduced longitudinal LV strain despite normal ejection fraction in their pediatric cohort after CoA repair. In the current study, longitudinal LV strain was not different between patients and controls.

Before intervention, the decreased blood pressure in the lower part of the body—including the kidneys—may activate the renin-angiotensin system to increase systemic blood pressure. Also, increased pressure proximal to the coarctation, decreased elastic wall properties [20], and secondary flow patterns [21] in the aortic arch may alter baroreceptor function. After intervention, ANS may be altered by damage to the ANS nerves travelling along the aorta. To our knowledge, the current study is the first to measure cardiac ANS activity in an ambulatory setting for a prolonged period and did not find differences in cardiac ANS regulation between healthy controls and children after CoA repair. In addition, in patients operated on at age 1 year (n = 8) vs patients operated on before 1 year (n = 23), no difference was found in ANS activity or when patients were divided into neonatal (operated in the first month of life; n = 15) or nonneonatal repair (operated after the first month of life; n = 16) as suggested by Klitsie and colleagues [7] (data not shown).

Kenny and colleagues [22, 23] studied cardiac ANS activity in CoA patients by measuring (15-minute supine) heart rate and blood pressure variability and baroreceptor sensitivity and did not find a difference between patients and controls. In contrast, Beekman and colleagues [24] and Millar and colleagues [25] reported decreased heart rate variability and baroreceptor function after repair in their pediatric cohorts. In adults after CoA repair, Moutafi and colleagues [26] found no differences in autonomic activity between patients and controls.

The current study finds a positive relationship between PWV (a measure of artery stiffness) in the proximal aorta and basal RSA during sleep (a heart rate variability measure of cardiac PNS activity). The only study investigating the relationship between PWV and cardiac PNS regulation in CoA patients found a negative relationship between baroreceptor sensitivity and aortic PWV [23]. The authors argued that hypertension becomes manifest once the ANS fails to compensate adequately in these patients. Although plausible, more research is necessary on this topic.

The current study also finds a positive relationship between basal RSA during sleep and LV longitudinal strain. The positive relationship between longitudinal strain and basal cardiac PNS regulation is in line with the suspected protective effect of vagal activity on the heart [27]. The protective effect of vagal activity has especially been investigated in its role in sudden cardiac death [28] but may also improve LV function [29, 30].

A negative relationship was found between basal PEP during sleep and septal peak systolic velocity (S') and between basal PEP and longitudinal LV strain. This validates the PEP as an index of cardiac sympathetic activity, with shortened PEP reflecting the increased contractility also indicated by higher S' and strain. However, PEP is known to be sensitive to the effect of aortic pressure (afterload), which is in turn a function of mean arterial blood pressure. When the heart has to pump against a high afterload, more time will be required to build up enough force to open the aortic valve. Hence, afterload may prolong PEP independent of cardiac inotropic drive [31, 32]. In keeping with these afterload effects, we found a positive relationship between basal PEP and LV mass. Increased afterload on the heart may, over time, cause LV hypertrophy and deterioration of LV function.

Hypertension is a well-known and common complication in CoA patients [3]. We reconfirmed this, with resting blood pressure being higher in patients than in controls (Table 1). Therefore, the use of PEP as a measure of sympathetic nervous system activity in this patient group is a limitation of the current study. A difference in PEP between the two groups could be the result of a difference in contractility due to sympathetic nervous system activity but may also be the result of a difference in afterload. We attempted to correct for afterload effects by including resting mean arterial blood pressure as a covariate in the model. However, we did not have 24-hour blood pressure measurements and were therefore unable to correct for the blood pressure during different activities during the day.

In conclusion, despite no differences in cardiac ANS activity between children after successful CoA repair and healthy peers, ambulatory CO and LV function were significantly decreased in these young patients. These
results underline the importance of life-long follow-up in CoA patients, even after successful repair, because none of the patients included in this study had a residual stenosis. Also, altered cardiac ANS function might still play a role in the long-term complications at older age, and this should be addressed in future studies.

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References


