Normalization of Autonomic Function in Children With Coarctation of the Aorta After Surgical Correction in Infancy

To the Editor:

Systemic hypertension affects ≥20% of patients with coarctation of the aorta (CoA) by adolescence, despite early surgical repair. This leads to premature death and is arguably the most important outcome variable in these patients. We have previously demonstrated reduced spontaneous baroreceptor reflex sensitivity (BRS) and heart rate variability (HRV) in preoperative neonates with CoA compared with age-matched controls, suggesting early autonomic dysfunction. Altered BRS has also been demonstrated in older children after late surgical repair, however, little is known about BRS and autonomic function in younger patients after successful neonatal repair. In the current study, we re-evaluated spontaneous BRS, HRV, and blood pressure (BP) variability (BPV) from our initial cohort at 5 years on to determine whether there was persisting abnormality of cardiovascular autonomic variables as a precursor to arterial hypertension.

We re-examined 6 of the 7 living CoA patients and 7 of the 12 living age- and sex-matched control patients from the initial cohort. The remaining 5 controls could no longer be traced, and 1 CoA patient was not included because of severe developmental delay. None of the subjects were taking medications. Somerset Research Ethics Committee approval was granted for the study, and informed consent was obtained.

Subjects were studied in a quiet room, lying supine on a hospital examination bed. Data acquisition was as reported previously. Briefly, continuous BP waveform was recorded from the middle finger of the right hand (Portapres Systems, FMS) and ECG recorded with a standard 3-lead configuration. Analogue output signals of BP and ECG were displayed and stored on computer with Spike 2 software (Cambridge Electronic Design). Right-arm BP was measured on 3 occasions with an automated oscillometric device (Dynamap PRO 300, Critikon Inc) in the sitting position after a period of rest. Assessments of spontaneous BRS, HRV, and BPV were carried out using sequence technique and time- and frequency-domain analysis protocols, respectively. Data are expressed as mean±SE. Comparisons were made using 2-tailed Student t tests for normally distributed data. Paired t tests were used when comparing changes within groups over the 5-year period.

There were no significant differences in age (5.3±0.3 years [CoA] versus 5.5±0.2 years; P=0.34), body surface area (0.73±0.03 m² [CoA] versus 0.82±0.04 m²; P=0.11), heart rate (97±4 bpm [CoA] versus 97±6 bpm; P=0.99), forearm systolic BP (106±4.3 mm Hg [CoA] versus 108±4.4 mm Hg; P=0.76), or diastolic BP (66±3.7 mm Hg [CoA] versus 65±4.7 mm Hg; P=0.89) between CoA and controls at follow-up. In both groups, BPV and HRV in frequency and time domains had increased with age. Interestingly, compared with neonatal levels, spontaneous BRS had reduced in the control group but was unchanged in the CoA group (Figure). Therefore, at 5-year follow-up, spontaneous BRS (9.8±1.0 ms/mm Hg [CoA] versus 9.3±1.0 ms/mm Hg; P=0.74), HRV, and BPV measurements were not statistically different between the 2 groups, despite significant differences in neonatal life (Table).

The major finding of our study is that patients with early CoA repair undergo normalization of noninvasively measured indicators of autonomic function by 5 years. These findings are consistent with a previously published report demonstrating normalization of BRS in a canine model after CoA repair. These authors argue that initial arterial hypertension proximal to the CoA site may lead to resetting of the arterial baroreceptor to operate at higher BP. Our data indicate that early repair with relief of upper body hypertension leads to re-establishment of BRS around normal BP levels within a 5-year postoperative period. The normalization of BRS may also be related to the beneficial effect of early surgical repair on arterial compliance, because increased arterial distensibility will increase baroreceptor responsiveness to changes in BP. In addition, early reduction in the pressure gradient across the coarctation may improve pressure-induced upper body shear stress, which is associated with generation of reactive oxygen species, leading to an increase in BRS under certain circumstances via a central mechanism. It is also possible that early upper body BP reduction may modulate brain stem angiotensin II type 1 receptor levels to increase BRS, although further studies are necessary to ascertain the exact mechanisms by which BRS is improved after CoA repair.

Because BP was not different at 5 years, we cannot ascertain which, if any, of our cohort will develop hypertension. However, further changes in BP control must take place to reflect the reported incidence of adolescent hypertension. The mechanisms driving hypertension in CoA patients remain unclear; however, it may be that progressive autonomic dysfunction occurs later in
childhood, given that baroreceptor impairment has been demonstrated in postcoarctectomy teenagers after later surgical repair. It is, therefore, important to continue our current longitudinal evaluation of autonomic function in growing children after early CoA repair to investigate whether progressive abnormality still occurs and how this relates to BP control.

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Disclosures
None.

Table. Paired Comparison Data Between CoA and Control Groups When Newborn and at 5 Years of Age

<table>
<thead>
<tr>
<th>Measured Variable</th>
<th>Control (Newborn to 5 y)</th>
<th>P</th>
<th>CoA (Newborn to 5 y)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRS, ms/mm Hg</td>
<td>14.7±1.5, 9.3±1.1</td>
<td>0.02</td>
<td>8.3±1.9, 9.8±0.98</td>
<td>0.56</td>
</tr>
<tr>
<td>HRV, SD, ms</td>
<td>38±3.5, 58.5±5.6</td>
<td>0.013</td>
<td>18.5±2.9, 61.7±7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HRV, TP, ms²</td>
<td>35±3.7, 120.5±12.7</td>
<td>0.001</td>
<td>17.8±5, 123.2±17.1</td>
<td>0.001</td>
</tr>
<tr>
<td>HRV, LF, ms²</td>
<td>10.1±0.9, 24.1±2.6</td>
<td>0.002</td>
<td>6.1±1.5, 23.1±2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HRV, HF, ms²</td>
<td>24.9±3.2, 78.6±9.2</td>
<td>0.003</td>
<td>11.7±3.6, 82.6±13.4</td>
<td>0.002</td>
</tr>
<tr>
<td>BPV, TP, mm Hg²</td>
<td>3±0.4, 12.2±1.5</td>
<td>&lt;0.001</td>
<td>4.1±0.5, 12.3±1.5</td>
<td>0.007</td>
</tr>
<tr>
<td>BPV, LF, mm Hg²</td>
<td>1±0.2, 2.9±0.3</td>
<td>0.001</td>
<td>0.9±0.2, 2.7±0.3</td>
<td>0.006</td>
</tr>
<tr>
<td>BPV, HF, mm Hg²</td>
<td>2±0.3, 6.5±0.9</td>
<td>&lt;0.001</td>
<td>3.3±0.4, 6.8±1.2</td>
<td>0.07</td>
</tr>
</tbody>
</table>

TP indicates total power; LF, low frequency; HF, high frequency.

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