Age Matched Attenuation of Both Autonomic Branches in Chronic Disease: III. Coronary Artery Disease

Rohit R. Arora, MD; Samanwoy Ghosh-Dastidar, PhD; Joseph Colombo, PhD

BACKGROUND

All muscle in the body is controlled by nerves. The heart is no exception. The heart is controlled by both the parasympathetic and sympathetic (P and S) nervous systems. Heart muscle, of course, is unique. When considering heart muscle function there is: 1) the mechanical activity of the heart (i.e., muscles, valves, etc., as measured in echocardiograms, etc.), and 2) the electrical activity of the heart muscle (as measured by EKG, etc.). Neither of these functions consider the influence of the P and S nervous systems; a third feature of heart muscle function control. Historically, due to a lack of reliable P and S measures \[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16\], the nervous systems’ input to the heart has largely been assumed as represented in HR and BP levels and changes. However, these mixed measures are often misleading, since both P and S branches control both HR and BP.

Generally, in healthy, normal individuals, the parasympathetic input to the heart results in respiratory sinus arrhythmia, which causes higher HR variability (HRV). Parasympathetic input also causes lower mean HR and reduces contractility which reduces average BP. The sympathetic input to the heart results in the opposite: reduced HRV, higher HR, and higher BP \[17\]. P&S Monitoring, together with cardiac monitoring (EKGs, Stress testing, Imaging, Tilt-studies, etc.), unbundles muscle from nerve issues, providing more information to improve the differential diagnosis, quantify individual patient’s responses to disease and therapy, and improve outcomes.

Symptoms of abnormal sympathovagal balance (SB) and of autonomic neuropathy (i.e., cardiovascular autonomic neuropathy, or CAN) have been noted. Example affects include unexplained arrhythmia (reports of palpitations with negative 12-lead EKG), mitral valve prolapse syndrome (symptoms of mitral valve prolapse with negative auscultation), and abnormal baroreflex and vascular control. Treating to normalize SB and treating CAN \[18\] has been shown to slow the progression of autonomic decline and reduce morbidity and mortality \[19\]. Chronic disease increases the morbidity and mortality risk through accelerating P and S decline and the onset of CAN \[18,19,20,21,22,23,24\]. Patients with coronary artery disease (CAD) are investigated to determine if CAD follows the same pattern as other chronic diseases.
See “P&S Monitoring vs. HRV-alone” subsection in the “Introduction” of “Age Matched Attenuation of Both Autonomic Branches in Chronic Disease: I. Hypertension” for a short discussion of the background to independent, simultaneous P and S assessment. With independent, simultaneous measures of P and S activity, a causal relationship between CAD and autonomic dysfunction leading to autonomic neuropathy, and eventually CAN, may be possible. This study considers the relationship between the resting P and S activity and duration of CAD, a chronic disease.

METHODS

Serial P&S Monitoring (ANX-3.0 Autonomic Monitor, ANSAR Medical Technologies, Inc., Philadelphia, PA) was performed on 59 consecutive CAD patients (Females = 8; Age = 65.5 ± 13.3) from two large ambulatory cardiology clinics, one near Chicago, IL and the other near New York, NY. Patients were assessed as they were, with medication on board (including beta-blockers and anti-hypertensives) and with or without co-morbidities (Hypertension = 42; Diabetes = 25). The data were compared with preexisting data for 112 age-matched, normal controls (Ages 40-90) with no history of hypertension, diabetes, or cardiovascular and autonomic disorders. The controls are from a database that has been collected over the past decade. P&S Monitoring is based on patient responses to a standard clinical study that includes a 5-min resting baseline. Normal adult ranges for P and S are 1.0 to 10.0 bpm$^2$. Resting P or S levels below 1.0 bpm$^2$ indicate advanced autonomic dysfunction (see the broken horizontal line in the figure). Resting parasympathetic levels below 0.1 bpm$^2$ indicate cardiovascular autonomic neuropathy (CAN). CAN indicates risk of sudden cardiac death, and may be normal for geriatric patients, or post-MI and post-CABG patients. Normal SB is between 0.4 and 3.0. As Umetani, et al. indicate, more resting parasympathetic activity is beneficial for geriatric patients to reduce morbidity and mortality. This translates to low-normal SB as the recommended normal for geriatric patients (0.4 < SB < 1.0). CAN with high SB indicates high risk for sudden cardiac death. Low-normal SB minimizes morbidity and morality risk [18,19]. Patients with arrhythmia were excluded. Data were analyzed with SPSS 14.0.

RESULTS

A student T-test was performed given the low number of females in this cohort. The T-test finds that the females’ results are statistically similar to the males (p=0.051). Table 1 presents the average P and S responses, along with the respective standard deviations, for both the CAD patients and the normal subjects. These data are plotted in the figure: red is the respective average, resting sympathetic responses and blue are the parasympathetic responses. The acceleration in sympathetic decline causes the average 45-year-old CAD patients to be similar to the average 85-year-old normal subject. Table 2 presents the average (resting) sympathovagal balance responses and resting BP measures. Overall, the average SB for the patients is more than double that for the normal subjects, and the (medicated) patients’ resting BP is higher than that for the normal subjects.

Overall, resting P and S levels were found to be significantly reduced in chronic CAD patients compared to age-matched, normal controls (see Figure and Table 1). The normal subjects’ resting responses revealed that the P and S activity normally decreases with age. The differences between normal controls and CAD patients indicate that the patient demonstrates an accelerated decline over that of the normal subject. An age-distributed investigation revealed that P and S activity decreases with age, a trend similar to that of normal controls. However, these
differences between normal controls and CAD patients are much more marked in the younger population and gradually decrease with age. These trends were observed regardless of any co-morbidities or medications. The P and S values for 45-year-old CAD patients were similar in magnitude (or lower) than those of 85-year-old normal controls (see Table). The fact that the difference between the CAD patients and normals decreases seems to be due to the aging effect of the normals. The CAD patients’ average P and S levels remain much the same across the ages studied.

DISCUSSION
Excess S activity relative to P activity at rest (high sympathovagal balance [SB=S/P]) is associated with CAD and heart disease [25]. Even with cardiac medication on board, and their BPs controlled (average BP for the cohort was less than 153/89), the CAD presented at ages 45 and 55 with advanced autonomic dysfunction, with P and S levels continuing to decline until age 75, on average.

Throughout most of the CAD population, resting sympathetic activity is nearly double that of the resting parasympathetic activity. High sympathetic activity relative to parasympathetic is also known to be a risk factor for mortality [24]. The geriatric cardiology literature indicates that more parasympathetic activity relative to sympathetic activity at rest is associated with improved outcomes, and lower morbidity and mortality [19,20,24]. In these data “more parasympathetic activity” [24] is represented by the relative parasympathetic dominance (over sympathetic) in the normals ages 75 and 85. This relationship between P & S is reverse in the CAD population throughout the decades (see Table 2). The greater, resting sympathetic excess (SE) as compared with age-matched patients diagnosed with hypertension [26] and diabetes [27] may be a reason for the higher mortality and morbidity rates in the CAD patients.

CONCLUSION
Early resting SE (relative to resting parasympathetic levels, or high SB) is the autonomic condition associated with CAD patients. Between these two cohorts, both P and S activity appear to be significantly decreased in chronic CAD patients as compared with age-matched normal controls. Whether these observations suggest autonomic decline as the effect of CAD, or as a cause of CAD, still remains to be established. These data suggest that autonomic assessment can guide therapy. Therapy based on sympathetic blockade (i.e., beta-blockers or anti-hypertensives) reduces sympathetic activity relative to parasympathetic activity, thereby reducing SB. Reducing SB in CAD patients (on average) helps to establish and maintain normal autonomic balance. Normalizing autonomic balance earlier can reduce morbidity and mortality in the CAD patient, thereby reducing hospitalizations and health care costs.
**Figure:** Baseline (Bx, or resting) autonomic changes with age in CAD patients. The broken curves represent age matched normals. The solid lines represent the CAD patients. The red lines represent average resting sympathetic activity (in bpm²) within the cohort. The blue lines represent average resting parasympathetic activity (in bpm²) within the cohort. The horizontal broken line indicates advanced autonomic dysfunction.

**Table 1:** Baseline (Bx, or resting) autonomic changes with age in (medicated) patients with CAD and in Normals.

<table>
<thead>
<tr>
<th>Mean Age</th>
<th>CAD S</th>
<th>CAD P</th>
<th>Norms S</th>
<th>Norms P</th>
<th>N</th>
<th>S</th>
<th>P</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>43.0</td>
<td>1.10±0.33</td>
<td>0.65±0.09</td>
<td>3.58±0.24</td>
<td>3.64±0.52</td>
<td>5</td>
<td>3.58±0.24</td>
<td>3.64±0.52</td>
<td>28</td>
</tr>
<tr>
<td>54.3</td>
<td>0.87±0.39</td>
<td>0.59±0.19</td>
<td>2.73±.36</td>
<td>2.68±0.41</td>
<td>19</td>
<td>2.73±.36</td>
<td>2.68±0.41</td>
<td>18</td>
</tr>
<tr>
<td>62.9</td>
<td>0.91±0.50</td>
<td>0.35±0.14</td>
<td>1.94±.40</td>
<td>1.92±0.47</td>
<td>14</td>
<td>1.94±.40</td>
<td>1.92±0.47</td>
<td>15</td>
</tr>
<tr>
<td>74.2</td>
<td>0.52±0.22</td>
<td>0.35±0.09</td>
<td>1.21±.36</td>
<td>1.39±0.33</td>
<td>11</td>
<td>1.21±.36</td>
<td>1.39±0.33</td>
<td>8</td>
</tr>
<tr>
<td>83.2</td>
<td>0.49±0.25</td>
<td>0.46±0.31</td>
<td>0.54±.35</td>
<td>1.00±0.14</td>
<td>10</td>
<td>0.54±.35</td>
<td>1.00±0.14</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 2: Average resting BP changes with age in (medicated) patients with CAD and in Normals.

<table>
<thead>
<tr>
<th>Mean Age</th>
<th>CAD SB</th>
<th>CAD BP</th>
<th>Normals SB</th>
<th>Normals BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>43.0</td>
<td>1.74</td>
<td>133/88</td>
<td>1.63</td>
<td>129/79</td>
</tr>
<tr>
<td>54.3</td>
<td>1.85</td>
<td>129/76</td>
<td>0.93</td>
<td>123/79</td>
</tr>
<tr>
<td>62.9</td>
<td>6.38</td>
<td>127/71</td>
<td>0.87</td>
<td>127/78</td>
</tr>
<tr>
<td>74.2</td>
<td>1.34</td>
<td>130/75</td>
<td>0.87</td>
<td>128/78</td>
</tr>
<tr>
<td>83.2</td>
<td>2.12</td>
<td>118/54</td>
<td>0.77</td>
<td>114/64</td>
</tr>
</tbody>
</table>

18 Vinik AI, Murray GL. Autonomic neuropathy is treatable. US Endocrinol. 2008; 2: 82-84.
27 Vinik AI, Arora RR, Colombo J. Age matched attenuation of both autonomic branches in chronic disease: II. Diabetes Mellitus. Cleveland Clinic Heart Brain Summit Cleveland Clinic Lou Ravo Center for Brain Health, Las Vegas, NV, 23-24 September, 2010.