Arterial baroreflex function in older adults with neurocardiogenic syncope

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Abstract

Purpose: Neurocardiogenic syncope (formerly vasovagal) accounts for large numbers of falls in older adults and the mechanisms are poorly understood. This study examined the differences in baseline arterial baroreflex function in older adults with and without a neurocardiovascular response to orthostatic stress.

Methods: Subjects were divided into two groups based on the presence (TT+ group) or absence (TT- group) of a neurocardiovascular response to upright tilting (70 degree head-up tilt for 10 minutes after 400 micrograms of sublingual nitroglycerin). A neurocardiovascular response was defined as presyncopal symptoms (lightheadedness) in association with at least a 30 mm Hg decrease in blood pressure. Before being divided into groups, baroreflex function was assessed using the spontaneous baroreflex method (baroreflex sensitivity, BRS). This method involves the analysis of “spontaneous” swings in blood pressure and heart rate that are mediated by the arterial baroreflexes.

Results: 42 older adults (mean age 70.3±0.7 yr) were recruited, of which 18 were in the TT+ and 24 were in the TT- group. At baseline, the TT+ group demonstrated increased arterial baroreflex sensitivity in response to negative blood pressure sequences only (BRS$_{\text{down}}$, 11.2±1.9 vs. 7.3±1.0 ms/mm Hg, $P=0.011$). During tilt, the TT+ group demonstrated a much larger decrease in overall arterial baroreflex sensitivity than the TT- group (-6.8±1.2 vs. –3.2±0.9 ms/mm Hg, $P=0.012$). There was a negative correlation between BRS$_{\text{down}}$ and length of tilt table test ($r=-0.329$, $P=0.041$) in the TT+ subjects.

Conclusion: Older adults with neurocardiogenic syncope have exaggerated arterial baroreflex sensitivity at baseline.

Neurocardiogenic syncope (NCS), formerly known as vasovagal syncope, was first defined as a constellation of “vagal” symptoms that includes a fall in blood pressure and a slowing of the ventricular rate. Although initially felt to be primarily a diagnosis in younger patients, the use of tilt-table testing has uncovered a more bimodal distribution for this condition. In fact, NCS has been found to account for 30 to 50 percent of syncopal spells in outpatient populations of older adults.

The mechanisms behind neurocardiogenic syncope remain poorly understood, and consequently there are few effective pharmacological treatments for this condition. Classical explanations invoking cardiac ventricular receptor stimulation due to venous blood pooling (the Bezold-Jarisch reflex) have been disproved in animal studies. An appropriate baroreflex response is vital to maintaining blood pressure in older subjects in the face of an orthostatic stressor.
Enhanced baroreflex sensitivity (BRS) has been shown to be a characteristic of young subjects with tilt-induced neurocardiogenic syncope.\textsuperscript{8, 9} Neurocardiogenic syncope remains common\textsuperscript{3} in older adults despite the fact that normal aging is associated with a reduction in BRS.\textsuperscript{10} This suggests that neurocardiogenic syncope in older adults might have a different mechanism; one in which altered arterial baroreflex function may or may not be playing a part. In the current study, we measured arterial baroreflex function both at baseline and during upright tilt in older adults with and without neurocardiogenic syncope. We hypothesized that exaggerated BRS would not be a predictor of vasovagal response to upright tilt, contrary to the results seen in younger adults.

\textbf{Methods}

\textit{Subjects (Table 1)}

Fifty older adults (30 male and 20 female, mean age 70.1±0.7 yr) were recruited ranging in age from 65 to 83 yr. All subjects had to be > 65 yr and were excluded if they had a history of angina, myocardial infarction, stroke, chronic pulmonary disease, or smoking in the last 5 yr. Since orthostatic hypotension is a separate condition from neurocardiogenic syncope, subjects with this condition were excluded during the initial screening visit by a series of five orthostatic maneuvers. Each orthostatic maneuver consisted of changing position from lying to standing for 3 min, and was followed by a 5-min rest period. Orthostatic hypotension was defined as a drop in systolic blood pressure > 20 mmHg during one of these maneuvers.\textsuperscript{11} Subjects were also excluded if they took beta-blockers, calcium channel blockers, or any other agent with the potential to influence autonomic function. Entry requirements also included a normal physical examination, normal resting electrocardiogram, normal hematocrit, fasting blood glucose, and creatinine. On this basis we excluded 8 subjects (n=42; 26 male and 16 female).

This study was approved by the Human Subjects Committee of the University of British Columbia, and all subjects gave written informed consent.

\textit{Study Design}

Each subject participated in two separate data collection sessions. The first (Session #1) allowed us to measure baseline arterial baroreflex function. The second (Session #2) allowed us to divide the subjects into two groups based on the presence (TT+ group) or absence (TT- group) of a neurocardiovascular response to upright tilting. Since baseline arterial baroreflex function (Session #1) was determined before Session #2 (tilt-table session), both the subject and the technician responsible for measuring arterial baroreflex measures were blinded as to subject group. Since baseline arterial baroreflex function data was analyzed after both sessions were complete, both the subject and technician were blinded as to each subject’s arterial baroreflex function during Session #2.

During both sessions, the study room was temperature-controlled (25 ± 1°C). All study sessions were performed between 9 AM and noon for all subjects to avoid bias due to circadian rhythms. Each subject was supine for 45 min prior to the start of data collection in order to reach steady state. Subjects were fasting, had refrained from the consumption of alcohol or caffeine, and had not exercised for the 24 hours prior to each session.

\textit{Session #1—Baseline Arterial Baroreflex Function}

Session #1 was performed with the subject supine. Twenty minutes of resting heart rate and blood pressure data was collected after a 45-min resting period prior to data collection in order to reach a steady state. Heart rate was monitored continuously using a 3 lead-electrocardiogram. Blood pressure was monitored using a Finometer (Finapres Medical Systems, The Netherlands). The Finometer measures beat-to-beat blood pressure noninvasively using infrared plethysmography through a finger-cuff. Use of the Finometer...
and infrared plethysmography for monitoring blood pressure changes has been well established as a non-invasive measure of beat-to-beat blood pressure\textsuperscript{12}, has been extensively validated against intra-arterial blood pressure monitoring in older adults\textsuperscript{13}, and is validated for the assessment of arterial baroreflex function.\textsuperscript{14} The Finometer uses waveform filtering, level correction and an additional return-to-flow calibration to reconstruct brachial artery pressures.\textsuperscript{15}

**Session #2—Tilt Table Testing**

After receiving 400 $\mu g$ nitroglycerin (GTN) sl, each subject was placed in a 70° head-up tilt for 10 min. Since there is no recognized gold standard for tilt table testing\textsuperscript{16}, this protocol was chosen because, unlike other drug provocation agents, GTN produces a positivity rate in older adults similar to younger age groups.\textsuperscript{17} A 10 min tilt time was selected because this duration has higher specificity for neurocardiogenic syncope than tilt-table tests of longer duration.\textsuperscript{16} The tilt table test was considered positive if the subject demonstrated presyncopal symptoms (lightheadedness or ‘dizziness’) in association with $>30$ mm Hg drop in blood pressure compared with baseline, or developed outright syncope. Heart rate and blood pressure were monitored continuously as described above in Session #1.

**Derived Measurements**

All post-collection analysis of the data was done in a blinded fashion. Before all derived measurements, each segment of raw blood pressure and electrocardiogram signal was manually examined in order to exclude artifacts. Two measures of arterial baroreflex function were determined using a custom-written software program (Matlab Release 13, 2002). Arterial baroreflex function was measured by the sequence method, which provides baroreflex sensitivity (BRS, in ms/mm Hg) and baroreflex effectiveness index (BEI, percent). Both the BRS\textsuperscript{18} and BEI\textsuperscript{19} have been used previously to examine baroreflex function in older adult subjects and are well validated against traditional measures such as the Oxford method.\textsuperscript{20}

**The Sequence Method of Assessing Arterial Baroreflex Function**

This involves the analysis of “spontaneous” swings in blood pressure and heart rate that are mediated by the arterial baroreflexes. Data is examined for progressive increases in both systolic blood pressure (SBP) and RR-interval (RRI) or progressive decreases in SBP and RRI. BRS is defined as the mean slope of the regression lines for all these baroreflex-mediated sequences (+RRI/+SBP or –RRI/-SBP) and is measured in ms/mm Hg.\textsuperscript{20} This method of baroreflex assessment has the advantage that it can be performed noninvasively and can provide multiple sequential observations (as opposed to methods that involve the direct intravenous injection of vasoactive medications).\textsuperscript{21}

Parameters used for our spontaneous baroreflex analysis were the inclusion of all baroreflex-mediated sequences of 3 or more beats that had a correlation coefficient $>0.80$, a threshold of blood pressure change of 1 mm of Hg, and a threshold for change in RR-interval of 4 msec. For the purpose of our analysis there is a $+1$ shift between the SBP data and the RRI data (the SBP pulse is plotted against the following RRI for the purpose of regression analysis). This set of conditions for spontaneous baroreflex is standard for the literature\textsuperscript{20}, has been shown to maximally correlate with the bolus intravenous phenylephrine method\textsuperscript{22} and has high intrasubject reproducibility.\textsuperscript{18} Spontaneous baroreflex measures allows for a separate examination of arterial baroreflex sensitivity for sequences characterized by a decrease (BRS\textsubscript{down}) or increase (BRS\textsubscript{up}) in blood pressure. As used previously\textsuperscript{23} this method allows the comparison of BRS regardless of the length of the data segment.\textsuperscript{24} This method allows us to compare BRS at baseline (20 min data collection) with the last 2 min of tilt\textsuperscript{25}.

The sequence technique also allows the calculation of the BEI, an alternative noninvasive measure of...
the arterial baroreflex. The BEI quantifies the number of times the arterial baroreflex is activated in response to non-baroreflex influences that create swings in blood pressure. This is assessed by the ratio of the number of baroreflex-mediated sequences (+RRI/+SBP or –RRI/-SBP) to the total number of all significant swings in blood pressure (+SBP or –SBP). The BEI has been shown to be specific for detection of arterial baroreflex dysfunction and is thought to be complementary to the calculation of BRS \(^{26}\), examining the interaction between the arterial baroreflex and other nonbaroreflex mechanisms controlling the sinus node. \(^{26}\)

**Statistical Analysis**

Data analysis was done in a blinded fashion. Results are expressed as the mean ± standard error. Given that we had four primary outcomes measures (BRS, BRS\(_{\text{down}}\), BRS\(_{\text{up}}\) and BEI), a value of \(P<0.013\) was considered significant after Bonferroni correction for multiple comparisons. \(^{27}\) Mean values for each variable were determined for each minute of upright tilt. A one-way Analysis of Variance (ANOVA) was used to compare our primary outcomes at baseline between the TT+ and TT- groups. Two-way ANOVA with repeated measures was used to compare alterations in BRS with upright tilting seen in the TT+ group with the TT- group. The Pearson correlation coefficient was used to evaluate the relationship between BRS\(_{\text{down}}\) and tilt table test duration.

## Results

### Subject Characteristics

The subjects had an overall average age of 70.3±0.7 yr. Overall mean weight (82.9±2.3 kg) and mean height (166.7±1.9 cm) resulted in a subject population that was mildly overweight but not obese \(^{28}\) with a mean body mass index of 29.5±0.7 kg/m\(^2\). Of the 42 subjects studied, 18 had a positive tilt-table test (TT+ group) and 24 had a negative tilt-table test (TT- group). The TT+ group had an average tilt-table tolerance of 5.14±0.36 min, ranging from 2.52 to 8.39 min. Baseline characteristics for both the TT+ and TT- groups showed no difference with the exception of BMI which tended to be higher in the TT- group (see Table 1).

### Baseline Arterial Baroreflex Function (Figure 1)

Subjects with positive tilt table tests (TT+ group) demonstrated increased arterial baroreflex sensitivity

<table>
<thead>
<tr>
<th>TABLE 1. Subject Characteristics</th>
<th>TT + Group n=18</th>
<th>TT - Group n = 24</th>
<th>All Subjects n = 42</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>70.1±1.1</td>
<td>70.4±1.1</td>
<td>70.3±0.7</td>
<td>0.451</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>80.0±2.4</td>
<td>86.5±4.2</td>
<td>82.8±2.3</td>
<td>0.165</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>168.7±2.0</td>
<td>166.7±1.9</td>
<td>166.7±1.9</td>
<td>0.224</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m(^2))</strong></td>
<td>28.3±0.6</td>
<td>31.2±1.2</td>
<td>29.5±0.7</td>
<td>0.029*</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mm Hg)</strong></td>
<td>142±5</td>
<td>149±4</td>
<td>145±3</td>
<td>0.292</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mm Hg)</strong></td>
<td>86±3</td>
<td>86±2</td>
<td>86±2</td>
<td>0.784</td>
</tr>
<tr>
<td><strong>Mean Blood Pressure (mm Hg)</strong></td>
<td>104±3</td>
<td>107±3</td>
<td>106±2</td>
<td>0.480</td>
</tr>
<tr>
<td><strong>Heart Rate (beats per minute)</strong></td>
<td>68±3</td>
<td>63±2</td>
<td>66±3</td>
<td>0.162</td>
</tr>
<tr>
<td><strong>Glycosylated Hemoglobin (Percent)</strong></td>
<td>6.9±0.2</td>
<td>6.6±0.1</td>
<td>6.7±0.2</td>
<td>0.320</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mmol/L)</strong></td>
<td>5.2±0.3</td>
<td>4.6±0.3</td>
<td>5.0±0.2</td>
<td>0.176</td>
</tr>
<tr>
<td><strong>Total Cholesterol/High Density Cholesterol</strong></td>
<td>3.4±0.2</td>
<td>3.4±0.2</td>
<td>3.4±0.2</td>
<td>0.827</td>
</tr>
</tbody>
</table>

Demographic data for subjects with a positive tilt table (TT+ group), subjects with a negative tilt table (TT- group) and all subjects is shown as mean±standard error. \(P\) values are shown for differences between the two groups (independent t-test). \(P<0.05\) is indicated by *. 

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in response to negative blood pressure sequences (BRS<sub>down</sub>, P=0.011). The TT+ group demonstrated a nonsignificant trend toward overall higher baroreflex sensitivity (P=0.037) but no difference in BRS<sub>up</sub>. There was no difference in baroreflex effectiveness between the TT+ and TT- groups (0.384 vs. 0.386). During baseline rest, there was no difference in the number of detectable blood pressure swings between the TT+ and TT- groups (387±21 vs. 400±41). There was also a weak but significant negative correlation between BRS<sub>down</sub> and tilt table test duration (r=-0.329, P=0.041) in the TT+ subjects.

Changes in Arterial Baroreflex Function During Upright Tilting

Upright tilting resulted in an overall decrease in arterial baroreflex sensitivity when all subjects were examined together. As shown in Figure 2, BRS (P<0.001), BRS<sub>up</sub> (P<0.001) and BRS<sub>down</sub> (P<0.001) all demonstrated an overall decrease in sensitivity. BEI did not show any change with upright tilting (P=0.603). The TT+ group demonstrated a much larger decrease in overall arterial baroreflex sensitivity (P=0.012) mainly due to a much larger decrease in BRS<sub>down</sub> (P=0.005). The response of BRS<sub>up</sub> to upright tilting was no different between the TT+ and TT- groups.

Discussion

Older adults with a neurocardiovascular response to upright tilt have exaggerated arterial baroreflex sensitivity in response to downward blood pressure sequences (BRS<sub>down</sub>) at baseline. Upright tilting itself also results in a decrease in BRS, which was exaggerated in the TT+ group due to a larger magnitude decrease in BRS<sub>down</sub>.

Previous investigations of young subjects have suggested that patients with NCS might have an enhanced arterial baroreflex response to changes in blood pressure, which might explain the large swings in blood pressure and heart rate observed during one of these episodes. Congruent with our study of older adults, young adults suffering from NCS demonstrate a larger BRS<sub>down</sub> when compared to normals, but no difference in baseline BRS<sub>up</sub>, overall BRS or BEI. This was further supported in the present study by the fact that there was a negative correlation between BRS<sub>down</sub> and tilt table test duration in TT+ subjects.

With respect to the effects of upright tilting itself on arterial baroreflex function, this has also only been examined in younger populations. As shown in Figure 2, upright tilting itself results in a decrease in BRS in older adults, and this decrease is augmented in TT+ subjects. The TT+ group decreased BRS by approximately 60% compared with a 45% decrease in the TT- group. Several previous investigations in young subjects with NCS demonstrated a decrease in arterial baroreflex sensitivity both during augmented (nitroglycerin) and unaugmented tilt table tests, congru-
ent with the results of the present study. To our knowledge, we are the first to demonstrate that older subjects with NCS have exaggerated arterial baroreflex function at baseline, and that upright tilting itself results in a decrease in BRS in older adults.

Possible Mechanisms

The mechanisms underlying NCS remain poorly understood. The classical explanation for NCS suggested that orthostatic stress produces reduced cardiac filling and increased sympathetic stimulation resulting in the stimulation of ventricular mechanoreceptors. However, subsequent work has shown that even entirely empty dog hearts on bypass do not demonstrate a Bezold-Jarish response, and NCS persists even after complete denervation of the heart. Disproof of ventricular mechanoreceptor stimulation as the inciting event for NCS has consequently led investigators to examine central alterations in cardiovascular control, possibly involving either opioid or serotonin pathways. Short-term decreases in blood pressure changes are buffered primarily by the arterial baroreflex, suggesting that NCS may be due to centrally mediated alterations in arterial baroreflex function either at baseline or during upright tilting. Our study provides support for a central as opposed to a peripheral alteration in arterial baroreflex function since we demonstrated no difference in baroreflex effectiveness (BEI) between the TT+ and TT- groups.

Clinical Implications

NCS is a common cause of fall-related morbidity and mortality in the older adult population. Although previously felt to be rare in older adults, an examination of syncope patients presenting to the emergency room has demonstrated a second peak incidence of NCS over the age of 70 yr. The results of our current study reinforce these findings, demonstrating that TT+ patients in the older population demonstrate similar alterations in arterial baroreflex function (both at baseline and during upright tilt) as their younger counterparts. The higher BRS seen in older TT+ adults also suggests that measures of arterial baroreflex function could be predictive of a future positive tilt table test. Although this requires much further study, perhaps this measure could eventually be used to replace tilt-table testing in frail older adults with contraindications such as severe coronary disease or cerebrovascular stenosis.

Limitations

Further research is needed to determine the clinical significance of the relationship between an exaggerated arterial baroreflex and a positive tilt-table test. It is possible that this baseline change in arterial baroreflex function is merely an epiphenomenon as opposed to a causal factor in the initiation of the NCS re-
response. Further study is needed to determine the exact mechanism behind the decrease in arterial baroreflex sensitivity with upright tilting and whether or not this could constitute a possible avenue of treatment for NCS.

Conclusions

Older adults with neurocardiogenic syncope demonstrate exaggerated arterial baroreflex sensitivity at baseline. Arterial baroreflex sensitivity decreases with upright tilting, and this decrease was amplified in older adults with NCS.

Acknowledgements

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References


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