Spontaneous fluctuation indices of the cardiovagal baroreflex accurately measure the baroreflex sensitivity at the operating point during upright tilt

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Am J Physiol Regul Integr Comp Physiol 304: R1107–R1113, 2013. First published April 10, 2013; doi:10.1152/ajpregu.00559.2012.—Spontaneous fluctuation indices of cardiovagal baroreflex have been suggested to be inaccurate measures of baroreflex function during orthostatic stress compared with alternate open-loop methods (e.g. neck pressure/suction, modified Oxford method). We therefore tested the hypothesis that spontaneous fluctuation measurements accurately reflect local baroreflex gain (slope) at the operating point measured by the modified Oxford method, and that apparent differences between these two techniques during orthostasis can be explained by a resetting of the baroreflex function curve. We computed the sigmoidal baroreflex function curves supine and during 70° tilt in 12 young, healthy individuals. With the use of the modified Oxford method, slopes (gains) of supine and upright curves were computed at their maxima (Gmax) and operating points. These were compared with measurements of spontaneous indices in both positions. Supine spontaneous analyses of operating point slope were similar to calculated Gmax of the modified Oxford curve. In contrast, upright operating point was distant from the centering point of the reset curve and fell on the nonlinear portion of the curve. Whereas spontaneous fluctuation measurements were commensurate with the calculated slope of the upright modified Oxford curve at the operating point, they were significantly lower than Gmax. In conclusion, spontaneous fluctuations in AP generate changes in R-R interval. These are known as closed loop, or spontaneous fluctuation methods, because they do not interrupt baroreflex feedback loops. Spontaneous fluctuation methods include measurements in the time domain, such as the sequence technique (27), and measurements in the frequency domain, such as transfer function analysis or autoregressive modeling (18). However, spontaneous measures generate information over a very narrow range of arterial pressures, and many investigators have questioned the ability of spontaneous measures to accurately represent baroreflex function (11, 19, 29), particularly during orthostatic stress in which spontaneous fluctuation techniques have demonstrated both a decrease (2, 3, 33, 37, 40) and an increase (2, 6, 8, 41) in cardiovagal baroreflex sensitivity when subjects are upright compared with supine. However, it has recently been shown that the cardiovagal baroreflex is shifted during orthostasis with no change in maximum sensitivity (35). The shift in the entire curve may account for the discrepancies in the literature, but this has not yet been investigated.

The entire idealized baroreflex curve (Fig. 1) represents baroreflex function. The slope at the centering point is the maximum slope or gain of the curve, often referred to as Gmax (17, 30), and is often assumed to best represent baroreflex function. The slope of the curve at any specific pressure corresponds to a gain or sensitivity at that particular point. Spontaneous indices can estimate the slope and baroreflex sensitivity measured at that specific operating point, but they are not necessarily representative of Gmax unless the operating point is close to the centering point. When the operating point is near the centering point (Operating Point 1 in Fig. 1), the slope of the curve approximates Gmax. Therefore, when the operating point is near the center of the baroreflex curve the sensitivity approximates Gmax, but if it is at any point away from Gmax the gain will be reduced.

When open loop methods are employed, Gmax is regarded as the measure of baroreflex function. If one equates baroreflex function entirely with Gmax, then spontaneous indices fail to estimate baroreflex function when the operating point is distant from the centering point. Baroreflex function, when considered in this context, often results in the misinterpretation that spontaneous indices are not valid methods, particularly during orthostatic stress (2, 19). Contrastingly, if baroreflex function is defined by the entirety of the baroreflex curve over a range of pressures, then spontaneous indices may indeed accurately reflect baroreflex slope (or gain) at the operating point even though it may be distant from the center and would be a valid measure of cardiovagal baroreflex function, albeit different from Gmax. This is an important distinction, and may offer

Open loop methods can be difficult to implement. Therefore, many investigators employ simpler techniques in which small, spontaneous fluctuations in AP generate changes in R-R interval. These are known as closed loop, or spontaneous fluctuation methods, because they do not interrupt baroreflex feedback loops. Spontaneous fluctuation methods include measurements in the time domain, such as the sequence technique (27), and measurements in the frequency domain, such as transfer function analysis or autoregressive modeling (18). However, spontaneous measures generate information over a very narrow range of arterial pressures, and many investigators have questioned the ability of spontaneous measures to accurately represent baroreflex function (11, 19, 29), particularly during orthostatic stress in which spontaneous fluctuation techniques have demonstrated both a decrease (2, 3, 33, 37, 40) and an increase (2, 6, 8, 41) in cardiovagal baroreflex sensitivity when subjects are upright compared with supine. However, it has recently been shown that the cardiovagal baroreflex is shifted during orthostasis with no change in maximum sensitivity (35). The shift in the entire curve may account for the discrepancies in the literature, but this has not yet been investigated.

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average body mass index (BMI) was 23 kg/m². Subjects were free from all cardiorespiratory, autonomic, and systemic illnesses. Subjects were not taking medications and were nonsmokers. There were no subjects with diabetes, hypertension, or history of arrhythmias, and all were free from all cardiorespiratory, autonomic, and systemic illnesses. Subjects were not taking medications and were nonsmokers. There were no subjects with diabetes, hypertension, or history of arrhythmias, and all were free.

The baroreflex sensitivity between the SAP and R-R interval was calculated using four methods. The sequence method was calculated in the time-domain, by using sequences of three or more consecutive beats where both SAP and R-R interval either increased or decreased. The modified Oxford method produced a range of SAP of Δ27–71 mmHg supine and Δ20–74 mmHg upright. After a 30-min rest period subjects were tilted to 70° upright for 10 min. HR, R-R interval, and AP data were taken during minutes 1–5 following tilt and used for the calculation of upright spontaneous baroreflex sensitivity. The modified Oxford method was then administered at 5 min following tilt using the methods described above. The modified Oxford method could be used only once to avoid patient syncope. After upright HR and AP returned to near pre-Oxford levels, subjects were returned to the supine position. All subjects were able to tolerate the 10-min tilt and none reported symptoms of presyncope.

Data analysis. Approximately 4 min of baseline data were analyzed preceding performance of the modified Oxford method in the supine position. Upright baseline data were obtained during minutes 1–5 of HUT to avoid the hemodynamic equilibration phase that occurs during the first minute of tilt. Data were collected continuously during the hypotensive and hypertensive phases of the modified Oxford method in both supine and upright positions and included ECG, CO, SAP, diastolic arterial pressure (DAP), and mean arterial pressure (MAP) calculated using the Finometer calibrated against oscillometric cuff pressure. Total peripheral resistance (TPR) was computed using the formula TPR = MAP/CO (mmHg·l⁻¹·min⁻¹). R-R interval and HR were calculated from the ECG data. Data were sampled at 200 Hz using custom signal processing software and analyzed off-line.

Modified Oxford method. R-R intervals were plotted as a function of SAP to generate the cardiovagal baroreflex response during the modified Oxford method. Because using all corresponding R-R interval and SAP values from the onset of decrease in SAP until maximum SAP introduces hysteresis (38), we adopted the strategy of Hunt and Farquhar (16) who restricted data acquisition to the rising arm of SAP (i.e., from the minimum until the maximum SAP was achieved). The SAP and corresponding R-R intervals were sorted from smallest to largest pressure. Pressures were arranged in bins of 1 mmHg. We then averaged all of the R-R interval point values corresponding to the SAP binned pressures to obtain an averaged bin R-R interval. We performed a weighted least squares fit of R-R interval against SAP where the weights were the number of points that fell into a specific bin divided by the total number of points in all bins.

Cardiovascular baroreflex curves were constructed for each subject while supine and during HUT by plotting R-R interval on the ordinate and SAP on the abscissa during the modified Oxford maneuver. A sigmoidal curve was fitted for each subject while supine and for each subject during HUT using the Levenberg-Marquardt nonlinear least squares algorithm (22). An $r^2$ of 0.85 or greater was obtained with each fit. Maximum baroreflex gain, $G_{\text{max}}$, was obtained at maximum slope of the generated sigmoid curve for each subject, supine and upright. The operating point was determined by the initial SAP and R-R interval of the subject prior to administration of SNP or phenylephrine. The slope at the operating point was calculated from the sigmoid fit for comparison with spontaneous fluctuation slopes (gains). The baroreflex threshold was identified as the minimum R-R interval of the sigmoid curve and the saturation was identified as the maximum R-R interval on the curve. The response range was calculated as the difference between the threshold and maximum (Fig. 1).

Spontaneous cardiovagal baroreflex indices. To measure spontaneous cardiovagal baroreflex function, the slope corresponding to spontaneous fluctuations in SAP and R-R intervals were calculated during supine and 70° HUT before the administration of SNP and phenylephrine. Indices of spontaneous baroreflex function were calculated using four methods. The sequence method was calculated in the time-domain, by using sequences of three or more consecutive beats where both SAP and R-R interval either increased or decreased. The baroreflex sensitivity between the SAP and R-R interval was computed as the average slope of consecutive beat sequences using a least squares fit for each sequence (26).

Discrete Fourier transform of R-R interval and SAP used a Hanning windowed fast Fourier transfer algorithm. For analysis, SAP and
R-R interval data were converted into a beat sequence. Autospectral and cross-spectral estimators were computed by the Blackman-Tukey method, using an eight-point Gaussian window for smoothing in the frequency domain (39). Band average baroreflex sensitivities (transfer function gains) were computed as the average value of transfer function modulus for frequencies between 0.01 and 0.04 Hz, (very low frequency), from 0.04 to 0.15 Hz (low frequency, LF), and from 0.15 to 0.4 Hz (high frequency) with coherence >.5. LF gain and total Fourier index (average gain from 0.01 to 0.40 Hz) were also calculated. Power spectra were also obtained for SAP and R-R interval. The alpha index was calculated as the square root of the ratio of LF R-R interval power to LF SAP power.

Statistical Analysis

Measurements made in the supine and HUT positions were compared using paired $t$-tests for repeated measures and using ANOVA for comparisons of the modified Oxford method analyses. Linear regression analyses of the percent change in slope from supine to upright were conducted. When appropriate, post hoc comparisons were performed using Tukey’s test. To relate the spontaneous vs. modified Oxford method analyses, linear regression analyses of the percent change in slope from supine to upright were conducted. Differences were considered significant when $P < 0.05$. All values are reported as means ± SD. Results were calculated using SPSS (Statistical Package for the Social Sciences) software version 11.0.

RESULTS

Effect of HUT on hemodynamics. Results obtained during supine and HUT pre-Oxford baseline periods are presented in Fig. 2 and Table 1. SAP (122 ± 5 vs. 121 ± 5 mmHg), DAP (62 ± 3 vs. 66 ± 3 mmHg), and MAP (82 ± 5 mmHg supine vs. 83 ± 4 mmHg) were not significantly different ($P > 0.05$) following HUT. However, R-R interval was expectedly lower during HUT compared with supine (993 ± 63 vs. 719 ± 42 ms; $P < 0.05$).

Effect of the modified Oxford method on hemodynamics. The modified Oxford maneuver resulted in a decrease in SAP (122 ± 5 to 98 ± 7 mmHg; $P < 0.05$) below baseline following SNP and an increase (122 ± 5 to 137 ± 5 mmHg; $P < 0.05$) above baseline after phenylephrine. The magnitude of the changes in SAP were similar when measured when subjects were supine or during HUT. The decrease blood pressure was associated with a decrease in R-R interval (993 ± 63 to 643 ± 27 ms; $P < 0.05$) during SNP and an increase (993 ± 63 to 1,249 ± 70 ms; $P < 0.05$) during phenylephrine.

Cardiovagal baroreflex determined by the modified Oxford method. A sigmoid fit of supine and upright cardiovagal baroreflex curves to data from a representative subject is shown in Table 2. Supine and upright curves are of similar shape, but the baroreflex curve was reset downward and to the right of the supine curve. The maximum slope, $G_{\text{max}}$, of the upright baroreflex curve was slightly greater than supine $G_{\text{max}}$, but did not reach significance ($P = 0.07$) (Table 2). The operating point shifted to a lower portion of the curve with a lower slope during HUT. As shown in Table 2 there were significant differences in the thresholds, saturations, and operating points of the curves with posture, but there were no differences in response range. The shift in the operating point was consequent to decreased R-R interval (increased HR) during HUT with a small but not significant increase in SAP. When subjects were supine, the average slope of the sigmoid curve at the operating point was only 20% less than that of the maximum slope because of its proximity to the centering point. When subjects were upright, the average slope at the operating point was 70% smaller than the $G_{\text{max}}$ (Table 2) because it was displaced farther from the centering point of the reset curve. The percent change in operating point slope from supine to upright was significantly reduced compared with the percent change in the

Table 1. Pre-Oxford hemodynamic measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Supine</th>
<th>HUT</th>
</tr>
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<tbody>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>13.6 ± 1.1</td>
<td>13.3 ± 1.6</td>
</tr>
<tr>
<td>ETCO$_2$, Torr</td>
<td>43 ± 1</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>4.8 ± 0.3</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>TPR, mmHg l$^{-1}$ min</td>
<td>17 ± 2</td>
<td>22 ± 2*</td>
</tr>
</tbody>
</table>

Values are means ± SD. HUT, head up tilt; ETCO$_2$, end-tidal carbon dioxide; CO, cardiac output; TPR, total peripheral resistance. *$P < 0.05$ compared with the supine position.
slopes at the centering point (Δ −60 ± 14% vs. Δ +10 ± 17%, respectively; Fig. 4).

Cardiovagal baroreflex determined by spontaneous fluctuation indices. As shown in Table 3, spontaneous indices yielded slopes (gains) when subjects were supine that were smaller than Gmax determined by the modified Oxford method. Spontaneous slopes were, however, similar to calculated operating point slopes for individual sigmoidal modified Oxford method fits. During HUT, all spontaneous methods yielded slopes that were greatly reduced compared with the supine position, and were greatly reduced compared with Gmax from the modified Oxford method. However, spontaneous slopes were not different from modified Oxford slopes calculated at the operating point of the upright curve for every subject. Fig. 5 shows the percent changes in operating point slopes from supine to upright that were not significantly different between spontaneous indices (α index, Δ −52 ± 8%; sequential slope, Δ −58 ± 7%; total Fourier index, Δ −69 ± 3%; low-frequency transfer, Δ −61 ± 5%) vs. the modified Oxford method (Δ −60 ± 14%). Linear regression statistics are reported in Table 4. Spontaneous indices were correlated each other and with the modified Oxford method.

DISCUSSION

Our main finding indicates that measurements of spontaneous indices of cardiovagal baroreflex function accurately measure the gain (slope) at the operating point on the full baroreflex curve. A similar decrease in local operating point gain is obtained from spontaneous fluctuation measures and from the modified Oxford method during both supine and HUT positions. However, because the operating point is displaced from the centering point, particularly during tilt, a lower gain is obtained at that point. In addition, Gmax was shifted to higher SAP and lower R-R interval when subjects were upright compared with supine. This resetting of the cardiovagal baroreflex curve may be a driving force the shift of the operating point to a more physiological advantageous position to counter gravity. This novel finding rationalizes the use of spontaneous fluctuation estimates of local operating point gain, and accounts for the orthostatic reduction of local gain on the basis of resetting of the baroreflex and a change of operating point.

It is known that spontaneous fluctuations in SAP drive small fluctuations in R-R interval around an operating point, and local slopes can be calculated at these operating points. With the use of open loop methods, slopes can be calculated for a wide range of points on the generated baroreflex curves. In particular, the slope can be generated for both an operating point and the maximum slope, Gmax, which occurs at the maximum point gain (Gmax) from supine to upright positions. Operating point gain significantly decreased during HUT, but the Gmax was not significantly different. *Significantly different from supine baseline (P < 0.05). †Significantly different from Gmax (P < 0.05).

Table 2. Calculated sigmoid parameters using the modified Oxford method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supine</th>
<th>HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gmax, ms/mmHg</td>
<td>26.1 ± 2.2</td>
<td>28.3 ± 3.4</td>
</tr>
<tr>
<td>SAP at maximum gain, mmHg</td>
<td>124 ± 5</td>
<td>129 ± 5</td>
</tr>
<tr>
<td>R-R interval at maximum gain, ms</td>
<td>898 ± 56</td>
<td>778 ± 41†</td>
</tr>
<tr>
<td>Threshold, ms</td>
<td>689 ± 35</td>
<td>547 ± 34†</td>
</tr>
<tr>
<td>Saturation, ms</td>
<td>1,104 ± 77</td>
<td>1,010 ± 66†</td>
</tr>
<tr>
<td>Response range, ms</td>
<td>415 ± 90</td>
<td>463 ± 63</td>
</tr>
<tr>
<td>At operating point*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>122 ± 5</td>
<td>121 ± 5</td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>865 ± 48†</td>
<td>657 ± 31‡‡</td>
</tr>
<tr>
<td>Slope (operating point) ms/mmHg</td>
<td>21.2 ± 3.4†</td>
<td>8.6 ± 3.7‡‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. Gmax, maximum slope; SAP, systolic arterial pressure. *Operating points were assessed as the average baseline values in both supine and HUT positions before vasoactive drug administration. †P < 0.05 compared with corresponding value at maximum gain. ‡P < 0.05 compared with the supine position.

Table 3. Baroreflex sensitivity using spontaneous fluctuation indices

<table>
<thead>
<tr>
<th>Spontaneous Index</th>
<th>Supine</th>
<th>HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>α index</td>
<td>18.5 ± 3.0</td>
<td>7.6 ± 1.0*</td>
</tr>
<tr>
<td>Sequential slope</td>
<td>23.6 ± 4.0</td>
<td>9.0 ± 1.6*</td>
</tr>
<tr>
<td>Total Fourier index</td>
<td>24.5 ± 4.7</td>
<td>6.8 ± 0.9*</td>
</tr>
<tr>
<td>Low-frequency transfer gain</td>
<td>19.5 ± 3.4</td>
<td>6.7 ± 0.6*</td>
</tr>
<tr>
<td>Modified Oxford slope</td>
<td>21.2 ± 3.4</td>
<td>8.6 ± 3.7*</td>
</tr>
</tbody>
</table>

Values are means ± SD. Comparable modified Oxford values are abstracted from Table 2 to facilitate comparisons. Slopes are measured in ms/mmHg. *P < 0.05 compared with supine.
Baroreflex properties change during orthostasis. Once hemodynamic equilibrium is reached, healthy subjects experience baroreflex-mediated tachycardia and vasoconstriction despite either unchanged or even increased AP compared with the supine position (15). While changes in blood pressure pulsatility may play a role in maintaining systolic and diastolic pressure (4), if the arterial baroreflex is intact, a resetting of the relationship between SAP and R-R interval occurs. Resetting of the cardiovagal baroreflex has been previously observed using NS/NP during 40° upright tilt (25). Akimoto et al. (2) found an increase in \( G_{\text{max}} \) and a shift in the sigmoidal functional relationship between the estimated carotid SAP and HR. However, using the modified Oxford method to generate representative standard cardiovagal baroreflex curves for each subject we found, as did Ogoh et al. (25), that the open loop baroreflex measures were shifted to lower R-R intervals at similar upright and supine pressures, but there was no change in \( G_{\text{max}} \). Similarly, cardiovagal baroreflex resetting is known to occur during exercise (9), when it is essential to homeostasis. Resetting has recently been reported during orthostasis (2, 25, 35). It has been determined that baroreflex resetting is a consequence of interactions of the arterial baroreflex with central command, cardiopulmonary pressure reflexes and, in the case of exercise, the exercise pressor reflex (9). However, during orthostasis the carotid sinus is above the level of the heart, and thus is exposed to an arterial pressure that is reduced by hydrostatic effects compared with the pressure measured by the Finometer. If the effects of carotid baroreceptors predominate, then the hydrostatic pressure difference may account in part for the shift of the cardiovagal baroreflex response curve along the pressure axis.

We were unable to demonstrate a significant increase in \( G_{\text{max}} \) sensitivity, which may reflect a difference in techniques (NS/NP vs. modified Oxford) and in tilt angle (40° vs. 70°). The NS/NP method manipulates the carotid baroreceptors, whereas the modified Oxford method uses pharmacological agents to alter the aortic and the carotid baroreceptors. Currently, there are no other comparable studies using the modified Oxford method during upright tilt. Akimoto et al. (2) recently compared \( G_{\text{max}} \) and gains at low and high frequency bands generated by NS/NP with spontaneous indices of baroreflex function. These investigators found that slopes (gains) decreased with orthostasis, whereas NS/NP \( G_{\text{max}} \) increased. They concluded that spontaneous indices do not represent cardiovagal baroreflex characteristics during orthostatic stress. However, they did not compare full cardiovagal baroreflex curves, and open loop local slopes were not reported. We currently demonstrate that when taking the full baroreflex curve into account, spontaneous indices do in fact represent a part, the operating point, of the baroreflex curve, but cannot be used to infer full baroreflex function.

Comparisons of spontaneous indices and NS/NP measurements of cardiovagal baroreflex sensitivity have previously been made during exercise (11, 24). Fisher et al. (11) demonstrated that at rest spontaneous indices were correlated with baroreflex measurements using NS/NP in young but not older subjects. Using both spontaneous indices and the modified

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Model} & \alpha \text{ Index} & \text{Sequential Slope} & \text{Total Fourier Index} & \text{Low-Frequency Transfer} \\
\hline
\text{Modified Oxford} & r = 0.74 & r = 0.66 & r = 0.74 & r = 0.75 \\
& P < 0.005 & P < 0.005 & P < 0.005 & P < 0.005 \\
\alpha \text{ index} & r = 0.60 & r = 0.88 & r = 0.88 & r = 0.88 \\
& P < 0.01 & P < 0.005 & P < 0.001 & P < 0.001 \\
\text{Sequential slope} & r = 0.75 & r = 0.63 & r = 0.88 & r = 0.88 \\
& P < 0.005 & P < 0.01 & & \\
\text{Total Fourier index} & r = 0.88 & P < 0.001 & & \\
\hline
\end{array}
\]

Fig. 5. Percent changes in the operating point slope from supine to upright positions for all spontaneous indices and modified Oxford method. There were no significant differences between indices. *Significantly different from supine baseline (\( P < 0.05 \)).
Oxford method, we demonstrated a shift in the operating point to a lower portion of the full baroreflex curve. There must be a physiological advantage to such a shift of the operating point while upright. The cardiovagal baroreflex buffers arterial blood pressure by changing heart rate (1, 8, 20, 34). For a given baroreflex relationship, the buffering action depends on the position of the operating point along the sigmoid curve. Maximum bi-directional buffering occurs at the centering point where the slope, or sensitivity, is greatest. When displaced from the center the local slope at an operating point decreases with the displacement and the bi-directional buffering capacity of the reflex is reduced.

Our data indicate that healthy young subjects operate close to the centering point when supine and more distantly when upright. Operating point sensitivity is greater when supine and smaller when upright near the relatively flat part of the sigmoid curve. However, in all of our subjects, the operating point shifts to the “knee” of the curve (i.e., the location on the sigmoidal curve where R-R interval begins to increase sharply with SAP). At this point if SAP decreases, the slope becomes nearly flat and R-R interval remains relatively unchanged. This is beneficial because whereas moderate tachycardia is physiologically advantageous, excessive tachycardia is not. Increased HR partially compensates for reduced stroke volume and cardiac output during orthostasis, though HR rarely exceeds 100–110 beats/min as the result of cardiovascular withdrawal alone (23). A much higher HR can impair blood pressure maintenance due to excessive decreases in cardiac filling time. Sympathetic baroreflex efferents are more effective than HR in maintaining blood pressure by increasing afterload and mobilizing venous blood (13, 31). Thus unrestrained sympathoexcitation, vasoconstriction, and hypertension would be buffered by an increase in R-R interval. Ultimately, the upright operating point may afford a desirable form of unidirectional blood pressure buffering.

Limitations. Analyses of threshold, saturation, and response range are model-dependent and obtained after fitting the data to a sigmoid curve. At times, only a few saturation points were acquired; however, we did capture the threshold and “most linear portion” of the curve (the center) in every subject as defined by Hunt and Farquhar (16). These investigators also determined that the sigmoid curve fit is superior to linear or piece-wise linear fits and superior to an extended five-parameter curvilinear fit.

The mean age of our study subjects was relatively young, and young adults are most often healthy. Age and infirmity have been shown to modify reflex function (10). While a younger age group may be ideal for investigating healthy physiological function, our findings may not be applicable to people outside of this age range.

The data from male and female subjects were pooled. Preliminary analyses showed no differences by sex. However, there were small numbers of subjects (6 men; 6 women), and differences in circulatory and autonomic function occur by gender (14). Nevertheless, baroreflex resetting was directionally similar in each subject regardless of sex.

Women were studied without regard to menstrual cycle. The phase of the menstrual cycle could alter baroreflex mechanisms. However, recent work suggests that neither the cardiovagal nor the sympathetic baroreflex are affected by the menstrual cycle (5, 12).

**Perspectives and Significance**

Using closed loop and open loop methods to assess the baroreflex function during orthostatic stress, we were able to demonstrate two important distinctions. First, using the modified Oxford method for comparison, we demonstrated that spontaneous indices are accurate for assessing baroreflex function at the operating point of the shifted baroreflex curve. Spontaneous indices measurements are commonly used to assess cardiovascular baroreflex function, but they are often reported as inadequate assessments during orthostatic stress. The distinction between the two methods lies in the interpretation of the baroreflex curve. Spontaneous indices can be used only to assess operating point slope and sensitivity, whereas the modified Oxford technique generates a full baroreflex curve allowing $G_{max}$ and local slopes to be assessed. Second, in agreement with others, we demonstrated a shift in the operating point to a lower portion of the cardiovagal baroreflex curve. This is an important distinction because it provides valuable insight into the physiological adaptations occurring during orthostatic stress that may help guard against orthostatic intolerance while upright. Together, these data put a better understanding on defining baroreflex function, and can be used to further explore hemodynamic changes occurring during orthostasis.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: C.E.S., M.S.M., and J.M.S. conception and design of research; C.E.S., M.S.M., Z.R.M., and J.M.S. performed experiments; C.E.S., M.S.M., Z.R.M., and J.M.S. provided data; C.E.S., M.S.M., Z.R.M., and J.M.S. interpreted results of experiments; C.E.S. and J.M.S. drafted manuscript; C.E.S., M.S.M., Z.R.M., and J.M.S. analyzed data; C.E.S., M.S.M., Z.R.M., and J.M.S. contributed new reagents/analytic tools; C.E.S., M.S.M., Z.R.M., and J.M.S. wrote the article; all authors approved the final version.

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