Blood Pressure Regulation in Humans
Calculation of an “Error Signal” in Control of Sympathetic Nerve Activity

Erica A. Wehrwein, Michael J. Joyner, Emma C.J. Hart, B. Gunnar Wallin, Tomas Karlsson, Nisha Charkoudian

Abstract—Within an individual, diastolic blood pressure (DBP) is negatively related to sympathetic burst incidence, such that lower pressure is associated with high burst incidence. Our goal was to explore the use of a calculation of a DBP “error signal” in the control of muscle sympathetic nerve activity in men and women. Baseline muscle sympathetic nerve activity was measured in healthy young men (n=22) and women (n=28). Women had significantly lower muscle sympathetic nerve activity than men (29±3 versus 43±2 bursts per 100 heartbeats; P<0.05). For each individual, the DBP at which there is a 50% likelihood of a muscle sympathetic nerve activity burst, the “T50” value, was calculated. Mean DBP was subtracted from the T50 blood pressure as an approximate error signal for burst activation. Error signal was negative in both sexes, indicating that DBP in both sexes was higher than the DBP value associated with a 50% burst likelihood. However, average error signal was significantly larger in women (−4±2 mm Hg; P<0.05 versus women). We conclude that women operate at a mean DBP greater than their T50 compared with men, and this may be a contributing factor to low basal muscle sympathetic nerve activity in women. The relationship between error signal and burst incidence may provide important insight into the control of muscle sympathetic nerve activity across sexes and in various populations. (Hypertension. 2010;55:00-00.)

Key Words: sympathetic ■ MSNA ■ threshold ■ baroreflex ■ sex

There is accumulating evidence that men and women have unique hemodynamic balances, which play a key role in the long-term control of sympathetic nerve activity and blood pressure.1,2 Sex differences in blood pressure regulation can be related to differences in resting muscle sympathetic nerve activity (MSNA) and the relationship of MSNA to other cardiovascular measures. MSNA represents sympathetic neural vasoconstrictor drive and is usually but not always lower in young women than in young men.3,4 As we increasingly recognize the complex integration of blood pressure control mechanisms and hemodynamic balances that differ between men and women, it remains unclear why women could have a lower MSNA than men.

Our goal in the present study was to better understand why resting vasoconstrictor nerve activity appears to be controlled differently between the sexes. Because of the strong baroreflex control of sympathetic vasoconstrictor nerve activity, sympathetic bursts are initiated during periods of low arterial pressure and are inhibited when pressure is higher.4 This phenomenon also accounts for the strong cardiac cycle dependence of MSNA bursts: each diastole has the potential to disinhibit MSNA, resulting in burst initiation, and the subsequent systole terminates the burst. Therefore, burst initiation can be viewed as a gating phenomenon on the basis of beat-to-beat diastolic blood pressures (DBPs), with the caveat that bursts are initiated before the end of the DBP period, suggesting that other factors, such as the rate of reduction of pressure, may actually be the primary factor. DBP is the pressure parameter that best correlates with burst occurrence but is not the only parameter that determines sympathetic outflow. Therefore, there is not a fixed DBP value that causes burst initiation, but rather the blood pressure contributes to an integrated system determining burst initiation. In other words, there is a variable blood pressure “threshold” for burst initiation over a range of diastolic pressures depending on other integrated inputs. Again, because of the strong baroreflex influence, lower pressures are more likely to be associated with a burst and higher pressures are less likely to have a burst, and this occurs over a variable range of pressure values.

We aimed to examine the use of a novel calculation of a blood pressure error signal in understanding MSNA burst occurrence in men and women. We calculated a blood pressure error signal by subtracting average DBP during...
baseline from the pressure at which there was a 50% likelihood of burst initiation to assess how similar prevailing pressure was to the threshold for burst initiation in men and women. In this context, we used the error signal calculation to explore regulation of sympathetic nerve firing and blood pressure under well-defined resting conditions in healthy humans. We addressed the following main questions. First, is the blood pressure error signal different between men and women? Second, are the differences observed in resting MSNA between men and women related to sex differences in error signal? Using the approach of Kienbaum et al., we calculated a blood pressure threshold diagram for sympathetic bursts in healthy young men and women. A “T50” value, the DBP value at which 50% of cardiac cycles were associated with sympathetic bursts, was calculated. We evaluated the normal operating range of DBP in relation to this T50 value to determine the error signal.

Methods

Subjects
In a retrospective analysis, we studied normotensive (systolic blood pressure: <130 mm Hg; DBP: <90 mm Hg) healthy young men (n = 22; 25.4 ± 1.0 years; body mass index: 24.4 ± 0.69) and women (n = 27, 25.2 ± 0.69 years, body mass index: 23 ± 0.51). All of the women were studied in the early follicular phase of the menstrual cycle or in the low hormone phase of oral contraceptive use. The subjects were nonobese (body mass index: <30), nonsmokers, nondiabetic, normally active (neither sedentary nor highly exercise trained), and not currently taking antihypertensive or other medications, except for oral contraceptives. Candidates were considered ineligible if they had any acute or chronic disorders associated with alterations in cardiovascular structure or function. Women of childbearing age had a negative pregnancy test within 48 hours of being studied.

Subject Monitoring
Arterial pressure was measured continuously using a 20-gauge, 5-cm catheter placed in the brachial artery of the nondominant arm under aseptic conditions and using ultrasound guidance, after local anesthesia (2% lidocaine). The catheter was then connected to a pressure transducer and continuously flushed at 3 mL/h with heparinized saline. Heart rate was measured with a 3-lead ECG. Baseline MSNA was assessed as described below over a 4-minute period.

Microneurographic Recordings of MSNA
Subjects underwent MSNA recording from the peroneal nerve during a supine rest. Multunit postganglionic MSNA was recorded from the peroneal nerve posterior to the fibular head with a tungsten microelectrode. The recorded signal was amplified 80,000-fold, bandpass filtered (700 to 2000 Hz), rectified, and integrated (resistance-capacitance integrator circuit; time constant: 0.1 seconds) by a nerve-traffic analyzer.

Data Acquisition
Data were digitized at 240 Hz² and stored for offline analysis with signal-processing software (WinDaq, DATAQ Instruments). Heart rate was derived from the ECG (3-lead ECG), and DBP was derived from the arterial pressure waveform. Sympathetic bursts were assessed in the integrated neurogram and were identified by a custom-manufactured automated analysis program; burst identification was then corrected by visual inspection by a single investigator. This program compensates for baroreflex latency and associates each sympathetic burst with the appropriate cardiac cycle.

Figure 1. Representative example of a threshold curve in an individual. In an individual there is a relationship between DBP and the percentage likelihood of burst occurrence. Lower DBP is associated with a high likelihood of sympathetic burst occurrence. For each individual, we determined the pressure at which there was a 50% likelihood of burst occurrence and refer to this value as T50. In this case, the T50 pressure is 66.5 mm Hg. Figure is modified from Charkoudian et al.³

Data Analysis

Blood Pressure Threshold Diagrams
We calculated blood pressure threshold diagrams for each subject on the basis of the approach of Kienbaum et al.⁴ and Sundlöf and Wallin.⁴ We obtained continuous recordings for arterial blood pressure and MSNA in all of the subjects over a 4-minute baseline recording. For each subject, we examined DBP with every cardiac cycle and determined whether there was a burst of MSNA for that pressure. In this way, we calculated a percentage likelihood of burst occurrence for each diastolic pressure. Specifically, the DBPs were separated into 1-mm Hg blood pressure bins. For each of these 1-mm Hg bins, the percentage of heartbeats associated with a sympathetic burst was plotted against the mean of the pressure in that bin. This is shown in Figure 1, which shows a typical threshold diagram for an individual subject from the present study.

As in previous work,⁴,⁵ we calculated a midpoint, or T50 value (in millimeters of mercury), for each subject’s curve, representing the diastolic pressure at which there was a 50% likelihood of a burst occurring. This value can be viewed as a “midpoint” value for MSNA burst occurrence. The slope of this threshold diagram represents the variability in the threshold value that initiates a burst of MSNA. The threshold for occurrence of a burst is not constant but varies over a range of blood pressures. Because of the strong baroreflex control of MSNA, lower diastolic pressures have a higher likelihood of burst occurrence, whereas higher diastolic pressures are less likely to be associated with bursts. We also measured the within-individual variability in DBP by calculating the SD in the DBP over the 4-minute resting period.

When calculating threshold slopes, it is important to be mindful of a technical caveat. When subjects have very low nerve activity, the threshold curve is based on fewer total bursts. The calculated slope becomes more uncertain because of the scatter at the lower burst incidence. In addition, the threshold line is really a sigmoid curve. Therefore, a true threshold line can be calculated only in the middle portion. To avoid the error introduced by the sigmoid shape, we used specialized probit analysis for subjects with very low burst incidence. Sigmoidal relationships can be linearized using probit transformation. The concept of probit analysis was described by Finney.¹¹

Determination of Blood Pressure Error Signal
Because the T50 value offers an indication of how often burst will occur, it is of interest to determine how often DBP in an individual crosses this T50 pressure. Therefore, we calculated a blood pressure threshold curve is based on fewer total bursts.
error signal by subtracting average DBP during baseline from the T50 pressure value in each individual (individual midpoint for burst initiation). This difference can yield a positive or negative value depending whether the average resting DBP is higher or lower than T50. A negative error signal means that average DBP is higher than T50 and a sympathetic burst is less likely to occur. A positive error signal means that average DBP is lower than T50 and a burst is more likely to occur. If the error signal was 0 (DBP=T50) for a given subject, this individual would have, on average, 50 bursts per 100 heartbeats at his or her prevailing DBP. However, a negative error signal would be consistent with a lower burst incidence. By determining this error signal, we can assess whether the mean DBP exists on a portion of the threshold curve that is associated with a high or low likelihood of burst initiation.

**Statistical Analyses**

The relationships of error signals to MSNA were measured using linear regression analysis and the Pearson correlation coefficient. In a secondary analysis, women were split into subgroups of low (burst incidence: <25; n=12) and high (burst incidence: ≥25; n=15) MSNA, and regression analysis was performed separately on each group. The intraindividual SD in arterial pressure over the 4-minute resting period was used as an index of blood pressure variability in each individual subject. Test statistics with an associated probability (P) to be higher in men despite having a lower error signal (within-subject SD of blood pressure) was not different between men and women, but DBP tended to be higher in men despite having a lower error signal (P=0.061). The calculated error signal was negative in both sexes (ie, mean DBPs were higher than T50 pressure). Furthermore, the average error signal was significantly greater in women (P<0.05). As a secondary analysis, when women were split into subgroups of low and high burst incidence, the high subgroup had an average error signal of −1±0.3 that was similar to that in men and the low subgroup had a lower error signal −6±2. The threshold slope was not different between sexes.

**Baseline Characteristics**

Group average data indicate that women had significantly lower DBP, lower midpoint (T50) pressure for burst initiation, and lower MSNA (P<0.05; Table). Average blood pressure variability (within-subject SD of blood pressure) was not different between men and women, but DBP tended to be higher in men despite having a lower error signal (P=0.061). The calculated error signal was negative in both sexes (ie, mean DBPs were higher than T50 pressure). Furthermore, the average error signal was significantly greater in women (P<0.05). As a secondary analysis, when women were split into subgroups of low and high burst incidence, the high subgroup had an average error signal of −1±0.3 that was similar to that in men and the low subgroup had a lower error signal −6±2. The threshold slope was not different between sexes.

**Results**

**Table. Group Mean Data for Men and Women**

<table>
<thead>
<tr>
<th>Physiological Variable</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>61±2</td>
<td>58±1</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>125±2</td>
<td>138±2*</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>68±1</td>
<td>73±1*</td>
</tr>
<tr>
<td>Mean SD in DBP, mm Hg</td>
<td>3±0.2</td>
<td>7±1</td>
</tr>
<tr>
<td>Burst frequency, burst per min</td>
<td>18±2</td>
<td>24±1*</td>
</tr>
<tr>
<td>Burst incidence, burst per 100 heartbeats</td>
<td>29±3</td>
<td>41±2*</td>
</tr>
<tr>
<td>Mean T50, mm Hg</td>
<td>64±1</td>
<td>72±1*</td>
</tr>
<tr>
<td>Error signal, T50 minus DBP, mm Hg</td>
<td>−4±0.7</td>
<td>−1±0.4*</td>
</tr>
<tr>
<td>Threshold slope</td>
<td>−8.5±0.6</td>
<td>−8.1±0.6</td>
</tr>
</tbody>
</table>

*P<0.05.

**Error Signal and Sympathetic Nerve Activity**

**Figure 2.** Error signal in blood pressure is positively related to burst incidence in men and women. Young men (○) and young women (●) are shown. The error signal (x axis) is the difference between T50 pressure and mean DBP. When mean DBP is equal to T50, the error signal is 0, as noted on the graph with a thin solid vertical line. Young women (dashed vertical line) have a more negative mean error signal than men (thick solid vertical line). However, the slope of this relationship is the same in men and women. *Average error signal is significantly greater in women vs men (P<0.001).

**Error Signal Relates to Burst Incidence**

We plotted the error signal (T50 pressure minus mean DBP) for each subject versus their individual burst incidence then compared all of the women and all of the men to determine the slope of this relationship for each sex (Figure 2). We found a positive relationship between error signal and MSNA (burst incidence) in both men (slope: 5.05; r²=0.907; P<0.001) and women (slope: 4.58; r²=0.843; P<0.001). When women were split into low and high subgroups of MSNA, regressions were as follows. For burst incidence <25, slope is 1.58, r²=0.57, and P<0.003. For burst incidence ≥25, slope is 4.56, r²=0.804, and P<0.001.

In addition, women had a more negative error signal than men. Women operate at a mean diastolic pressure that was much higher than their T50 as compared with men (Figure 2). As reported in the Table, the error signal between men and women was significantly different (P<0.05). The average slope of the threshold relationship was the same in men and women. All of the largest error signals occurred in women, and in some cases the mean DBP was ≈9 mm Hg higher than T50.

**Theoretical Threshold Slope Comparison**

The group mean threshold slopes and T50 values for men and women were used to construct Figure 3. The T50 for men and women occurred at different DBP values: average T50 in women was significantly lower, but average threshold slopes were similar between sexes. The shaded areas show that the error signal was larger in women than in men (ie, the mean DBP was further away from T50 in women). This plot shows that women were operating at a mean DBP (right side of shaded area) that was much higher that their T50 (left side of shaded area, crossing 50% on the y axis), whereas the mean DBP in men was much closer to their T50 value.
previous work, we calculated a midpoint, or T50 value (in millimeters of mercury), for each subject’s curve, representing the diastolic pressure at which there was a 50% likelihood of a burst occurring. In this study, the T50 was calculated under well-defined resting conditions and does not encompass the entire possible range of blood pressure, as would be achieved with challenge. Therefore, our conclusions are applicable to the control of burst initiation at rest only.

The slope of this threshold diagram represents the variability in the threshold blood pressure value, which initiates a burst of MSNA. For example, if the slope was infinite (a straight vertical line), there would be no variability in burst initiation, because every diastolic pressure below a certain threshold level at the location of the hypothetical vertical line would be associated with a burst, whereas every diastolic pressure above that level would never have a burst. It follows then that a steeper slope is associated with smaller threshold variability, and a less steep slope means more a variable threshold for the occurrence of MSNA bursts. As discussed in previous work, the threshold for occurrence of a burst is not constant but varies over a range of blood pressures. Because of the strong baroreflex control of MSNA, lower diastolic pressures have a higher likelihood of burst occurrence, whereas higher diastolic pressures are less likely to be associated with bursts.

Importantly, the T50 pressure for burst initiation may or may not relate to the prevailing mean blood pressure in an individual. For example, if an individual normally has blood pressures that vary around a mean value that is below the T50 pressure, they would have a higher likelihood of burst occurrence (and a burst incidence >50 bursts per 100 heartbeats), whereas if an individual has pressures far above the T50, there is a decrease in the likelihood of a burst occurrence for that individual. The blood pressure error signal (the difference between the T50 pressure and the mean DBP) could offer insight into the difference in burst occurrence in individuals, as well as across sexes. Those individuals that have mean diastolic pressures far above the T50 would be likely to have low nerve activity.

**A Blood Pressure Error Signal Exists in Men and Women**

There is accumulating evidence that men and women have distinct hemodynamic balances contributing to the long-term control of sympathetic nerve activity and blood pressure. Importantly, women tend to have a lower level of sympathetic activity and lower mean arterial pressure than men. The integrative mechanisms of sex differences in autonomic control of systemic hemodynamics remain incompletely understood. In the present study, we evaluated blood pressure thresholds for MSNA burst occurrence by plotting the DBP associated with each cardiac cycle for an individual versus the percentage of those cardiac cycles that were associated with a burst of sympathetic activity (threshold diagram).

The DBP at which there was a 50% likelihood of a burst occurring was called T50. The T50 for each individual was based on his or her individual threshold diagram constructed from data collected during supine rest. However, the threshold diagram does not offer information on the frequency at which these pressures are observed (eg, how often does the beat-to-beat DBP reach the T50?). We, therefore, assessed mean DBP in each individual in reference to that individual’s T50 pressure. This assessment offers insight into gating for sympathetic bursts. If the mean DBP was equivalent to the T50 pressure, then, on average, there would be a 50%
likelihood of burst initiation during resting conditions. However, if the mean DBP was very low compared with the T50, then the individual would be operating in a range on the threshold curve that has a much higher likelihood of burst occurrence. This would be in contrast to individuals who have a mean DBP that is much higher than their T50 value; these individuals are operating on the part of the relationship associated with low MSNA. Therefore, the difference between mean DBP and T50 pressure (error signal) could be a useful tool in understanding the interindividual variability in resting MSNA among individuals, as well as in understanding sex differences in MSNA and its relationship to arterial pressure.

In the present study we found that, on average, both men and women have a higher mean diastolic pressure than their T50 pressure (a negative error signal), meaning that they are operating on a part of the threshold curve associated with <50% likelihood of burst occurrence. We then sought to determine whether the error signal was related to average resting MSNA in men and women.

**Does the Blood Pressure Error Signal Relate to Burst Incidence?**

Both men and women had a mean negative error signal, yet mean burst incidence was significantly different between the sexes (Table). Consistent with Sundlöf and Wallin,4 in all of the individual threshold diagrams in the present study, higher diastolic pressures were associated with lower burst incidence. Similarly, individuals with the most negative error signal (diastolic pressure much higher than T50) had the lowest average MSNA in both men and women. The higher the mean DBP is relative to the T50 in an individual, the lower the mean resting burst incidence.

**Is the Relationship of Error Signal Versus Burst Incidence Different in Men and Women?**

The women in our study demonstrated a significantly greater mean error signal (difference between T50 and mean diastolic pressure). This meant that their resting DBP values, although lower than the DBP in the men, were much higher than their T50 and that this difference was greater than the difference (error signal) that we observed in men. Because a higher DBP relative to T50 would be associated with suppressed burst initiation, the larger error signal in women could help explain why women tend to have lower resting MSNA than men despite an overall lower mean DBP. It is important to point out that, as expected, there were many individual women with very low nerve activity and larger error signal that made the overall mean error signal for women large. It was not the case that all of the women had a large error signal; in fact, when the women with low nerve activity were analyzed separately, the remaining women had an error signal similar to the men.

We used individual relationships (threshold diagrams) to calculate average regression equations for men and women. Figure 3 shows these averaged relationships, as well as the average error signal, for each group. Interestingly, the mean slopes of the individual threshold diagrams (DBP versus percentage of burst occurrence) were identical for men and women.

A key difference was that, relative to their T50, women were operating at a larger delta pressure (error signal) than were the men (ie, on average, women had a DBP that was substantially higher than their T50 and, therefore, showed greater relative suppression of MSNA than men). Despite having a lower absolute value for mean DBP, DBP in women was actually much higher than their T50 midpoint for nerve activation. The relatively higher DBP actually results in a central suppression of MSNA and a lower nerve activity. Consistent with this idea, our subgroup analysis of women with lower and higher MSNA showed that the women with lower MSNA values had the largest negative error signal.

**Potential Implications for Sex Difference in Central Sympathetic Drive**

The error signal calculation represents more than a novel calculation to assess control of MSNA in men and women. The findings can be interpreted more broadly in support of less central sympathetic drive in women than in men. First, Sundlöf and Wallin4 reported that bursts occur more frequently during a period of lower DBP in an individual resulting in a tight negative correlation between DBP and burst incidence. Given this relationship in an individual, it is tempting to speculate that the lower average DBP in women would be associated with women having high MSNA. However, although the mean diastolic pressure is generally lower in women than men, our study and others have shown that MSNA tends to be lower in women despite lower pressure.1,3

Second, young women have less autonomic support of their blood pressure than young men, as demonstrated by a lesser drop in pressure during ganglionic blockade.2 Consistent with these findings, we report that women not only had lower MSNA than men but that they were also operating in a mean range of pressures that was associated with suppression of bursts on the basis of their T50. Men, on the other hand, have more autonomic support of blood pressure (ie, a larger reduction in blood pressure to ganglionic blockade).2 In our present study, because mean blood pressure in men was closer to their T50 values, there was relatively less suppression of bursts in men. This is consistent with the observation that men generally have higher MSNA and greater autonomic support of blood pressure. Our data are consistent with the idea that premenopausal women have less autonomic support of blood pressure and are supportive of a different central integration and a reduced central sympathetic drive compared with men.

Finally, we present evidence that error signal may be an explanation for lower nerve activity in women than in men. We do not suggest that women with high error signal have a lesser quality of blood pressure regulation. In the present study, intraindividual blood pressure variability (assessed as SD of DBP over the 4-minute resting period) was not different between men and women. In fact, it tended toward being larger in men (who have a smaller error signal).

**Perspectives**

Control of arterial pressure is multifactorial and is broadly determined by 2 categories of influences: sympathetic neural mechanisms and central and peripheral nonneural factors,
including vasoactive substances and hormones. Sympathetic activity is regulated by both the arterial baroreflex and by baroreflex-independent factors in the central nervous system. Osborn and colleagues\(^{14,15}\) proposed a central neural set point for long-term control of sympathetic nerve activity that was modulated by multiple nonneuronal inputs. There is also a central effect of estrogen in regulation autonomic tone.\(^{16}\) We presume that the T50 value is set by these and other factors, but we have not yet directly tested this idea.

The interindividual variability in our calculated error signal likely stems from variability in interactions between neural and nonneuronal factors controlling sympathetic nerve activity. One interpretation is that the neuronal baroreflex influence is not always enough to move pressure closer to T50 in the context of other central and peripheral factors. Thus, T50 minus DBP may be viewed as a measure of the influence of nonneuronal factors in setting sympathetic nerve activity. In some individuals, particularly young women, the influence of the nonneural factors may be unusually large or the T50 may be extreme, resulting in large error signals. This could indicate that nonneuronal influences are greater in women and that women have less central sympathetic outflow. A better understanding of the underlying mechanisms that influence T50 and testing these concepts over a wider range of blood pressures are goals for future work.

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**Disclosures**

None.

**References**

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