Hypovolemia and MSNA discharge patterns: assessing and interpreting sympathetic responses

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Kimmerly, D. S. and J. K. Shoemaker. Hypovolemia and MSNA discharge patterns: assessing and interpreting sympathetic responses. Am J Physiol Heart Circ Physiol 284: H1198–H1204, 2003. First published December 19, 2002; 10.1152/ajpheart.00229.2002.—We previously demonstrated that diuretic-induced hypovolemia resulted in an enhanced baroreflex-mediated increase in integrated muscle sympathetic nerve activity (MSNA) and vasomotor tone during lower body negative pressure (LBNP) (Am J Physiol Heart Circ Physiol 282: H645–H655, 2002). The purpose of this study was to perform a retrospective analysis of these data and examine the ability of relative MSNA burst amplitude distributions to highlight differences in baseline sympathetic nerve discharge patterns. An additional purpose was to determine whether differential responses in MSNA burst frequency and burst amplitude affect conclusions regarding sympathetic reflex control. MSNA, stroke volume (SV, Doppler), and estimated central venous pressure (CVP, dependent arm technique) were measured during LBNP within the placebo (Normo) and diuretic (Hypo; 100 mg/day spironolactone for 3 days) conditions (n = 8). Compared with Normo, MSNA burst frequency at rest was elevated, and there was a rightward shift in the median of the relative burst amplitude distribution (P < 0.05) in Hypo. During LBNP, the larger rise in total MSNA during Hypo versus Normo was due to greater increases in relative burst amplitude with no difference in the burst frequency response. The MSNA burst frequency response to LRNP was shifted to a higher position on the same MSNA-CVP curve during Hypo compared with Normo. In contrast, the Hypo burst amplitude response was shifted to a new curve with a slope that was similar to the Normo relationship. These data support the use of probability distribution analysis to examine intraindividual differences in baseline and reflex-mediated increases in MSNA burst amplitude. Furthermore, the differential effect of hypovolemia on the responses of burst frequency and amplitude during graded LBNP suggests that burst frequency data alone may not adequately represent reflex control of sympathetic outflow.

HAGBARTH AND VALLBO (7) first demonstrated the methods to directly record sympathetic nerve activity aimed at resistance vessels within human skeletal muscle. From these and other reports (23, 30), it is established that the multiunit discharge of postganglionic muscle sympathetic nerve fibers occurs as bursts of activity synchronized with the cardiac cycle (5) that continuously varies in frequency and amplitude (12). Thus, in humans, muscle sympathetic nerve activity (MSNA) is traditionally measured according to the number of bursts per minute (burst frequency) (8, 27) or per hundred heartbeats (burst incidence) (16, 30) or to relative changes in total integrated MSNA activity. One difficulty with this latter approach is that the percent change in total MSNA may be severely affected by differing baseline levels rather than the autonomic response per se. Also, there may be important information about central recruitment strategies contained within the relationship between burst frequency and amplitude (15) that is lost if only changes in the burst frequency response are considered. Specifically, changes in burst frequency are thought to represent the rate of neuronal firing (13), whereas the amplitude of sympathetic nerve bursts is related to the number of recruited neurons (23) with possible contributions of multiple firing of the same neuron (14, 18). Therefore, the MSNA response may be more correctly characterized by a dynamic variation in frequency and amplitude reflecting moment-by-moment modulation of efferent sympathetic discharge by central neural mechanisms.

Because absolute sympathetic burst amplitude is a function of electrode proximity to active nerve fibers and on signal amplification, it is not possible to use this variable to discern interindividual differences or to discriminate between repeated tests with new electrode positions. As a consequence, attention to this detail of the neural signal is often ignored. However, probability analysis of relative burst amplitude distributions may overcome this methodological constraint. Support for this methodological approach comes from evidence of similar relative amplitude distributions obtained from simultaneous peroneal nerve recordings in the same patient (24). In addition, separate observations that relative burst amplitudes (31) and norepinephrine spillover (9) were greater in the arm than the leg with no difference in burst frequency (31) strengthens the use of relative burst amplitudes as a distin-
guishable quantitative descriptor of MSNA. With the use of this approach, differential patterns in renal sympathetic nerve activity were quantified during baroreceptor loading (13) and chemoreceptor stimulation (14), providing evidence that probability distribution analysis may be a sensitive method to detect differences in sympathetic neural recruitment strategies. Similar analysis methods have been applied to human MSNA. Recent work by Sverrisdottir et al. (24, 25) demonstrated that the median value of the relative amplitude distribution can be used to characterize differences in baseline sympathetic outflow between groups. They also concluded that relative burst amplitude distribution was a more sensitive indicator of altered baseline MSNA than traditional measures of burst frequency.

Sympathetic burst patterns likely reflect important information on central nervous system control over efferent neural recruitment. In addition, altered sympathetic discharge patterns may be functionally important in terms of vasomotor control (12). This aspect of MSNA outflow was demonstrated previously where diuretic-induced hypovolemia enhanced baseline MSNA burst frequency, augmented the "integrated" (i.e., combined cardiopulmonary and arterial) baroreflex-mediated increase in total sympathetic outflow (percent change in total MSNA), and heightened neurovascular control during lower body negative pressure (LBNP) (10). It is possible that the enhanced vascular response to LBNP in this earlier study was associated with a different pattern of MSNA outflow.

An additional concern with differentiated MSNA outflow is that the choice of output variable may affect the conclusions that pertain to reflex cardiovascular control. For example, a greater sympathetic response to upright tilt has been observed in males than females (22). Embedded within these previous data was the concept that if only the burst frequency response was used, then no differences between the gender groups would have been observed.

Therefore, the purpose of this study was to examine the hypothesis that relative MSNA burst amplitude distributions could highlight intradividual differences in sympathetic nerve discharge patterns. For this, a retrospective analysis of earlier MSNA data obtained before and after acute hypovolemia (10) was performed. In addition, we examined how the reporting of MSNA data affects conclusions about sympathetic neurovascular control.

**METHODS**

**Participants.** Eight healthy normotensive males, who were 21–25 yr of age, 165–180 cm in height, and 75–96 kg in weight, participated as volunteers for this study. Each person provided signed consent to the experimental procedures, which were approved by the University of Western Ontario Review Board for Health Science Research Involving Human Subjects.

**General procedures.** All participants refrained from nicotine and caffeinated and alcoholic beverages for a minimum of 24 h, and no physical exercise was performed at least 12 h before testing. They were instructed to maintain their normal food and fluid intake between each test session. Everyone arrived to the laboratory after a 12-h fast, was given a standardized carbohydrate snack and beverage, and asked to void their bladder before the instrumentation.

**Experimental design.** Specific details regarding the experimental setup have been described previously (10). In brief, each participant underwent two separate test sessions at the same time of day, separated by a minimum of 1 wk. One session occurred after the oral administration (100 mg/day, 3 days) of the aldosterone antagonist spironolactone (Aldactone) and the other after placebo administration. The order of diuretic (Hypo) versus placebo (Normo) testing was randomly assigned to each participant.

**Data collection.** Heart rate (HR) was determined by standard three-lead electrocardiogram (ECG) techniques. Continuous measures of tonometric radial arterial blood pressure (ABP) were also collected (Pilot, Colin Medical Instruments; San Antonio, TX) (32) and reported earlier (10). An estimate of central venous pressure (CVP) was determined from antecubital venous pressure in the dependent arm referenced to the aortic root. Alterations in plasma volume (PV) between the two experimental sessions were estimated from changes in venous hematocrit (26). Stroke volume velocity in the ascending aorta was obtained from the suprasternal notch by using a hand-held 2.0-MHz pulsed wave probe (model CFM750, Vingmed). Combined with diameter measurements of the aortic root (2.5-MHz transducer, parasternal long-axis view, GE/Vingmed-System Five) and accounting for changes in cardiac period, an estimate of stroke volume was calculated.

Multiunit recordings of MSNA were obtained from the common peroneal nerve using microneurographic techniques (5, 6) as described in our earlier study (10). A MSNA site was confirmed by observation of a characteristic pulse-synchronous burst pattern that increased in frequency during a voluntary apnea but did not change in response to arousal or produced skin paresthesias (6). Once a sympathetic fascicle was found, the microelectrode was further manipulated to maximize the signal-to-noise aspect.

**LBNP protocol.** After a 10-min supine rest period, with the subjects legs and hips sealed in the LBNP chamber, 5-min applications of randomly assigned negative pressures at −5, −10, −15, and −20 mmHg were performed. A 5-min rest period without suction was situated between each of these levels of LBNP. The same order of negative pressures was applied to each individual in the two experiments. After the final LBNP level, chamber pressure was immediately reduced to −40 mmHg for an additional 5-min period.

**Data analysis.** Analog signals for ABP, CVP, stroke volume velocity, and MSNA were sampled at 200 and 400 Hz for ECGs and collected with an on-line data acquisition and analysis system (PowerLab, ADInstruments; Castle Hill, New South Wales, Australia). Data were obtained from minute 3 to 5 of each level of LBNP and the intervening baseline periods.

**Traditional MSNA analysis.** Only pulse-synchronous bursts of MSNA activity with characteristic rising and falling slopes and amplitudes that were at least twice that of the interburst baseline fluctuations (2:1 signal/noise) were included in the analysis. MSNA activity was measured for amplitude per burst, interburst interval, and frequency per minute during each baseline period and LBNP level. Total MSNA activity was calculated as the sum of analog burst amplitudes per minute.

**Probability distribution analysis of MSNA.** A major objective in the current analysis was to determine the independent effect of hypovolemia on sympathetic discharge patterns
while diminishing the impact of electrode reposition. Therefore, sympathetic bursts were normalized in proportion to the largest burst in each of the baseline and LBNP segments of both the Normo and Hypo conditions. Subsequently, probability distribution analysis was performed on both relative burst amplitude (24, 25) and interburst interval data (13, 14). Individual relative amplitudes were placed into 1 of 20 equally sized bins. Probability data were determined as the number of bursts within a given bin relative to the total number of bursts used in the analysis. Distribution curves of interburst interval data were also performed by using bins of 1- to 20-s durations. From the relative burst amplitude and interburst interval distributions, a median value was extracted and used for statistical comparisons (24, 25).

Further analysis of integrated baroreflex MSNA control was also performed. Here, stimulus-response curves between changes in CVP and percent changes in MSNA burst frequency, amplitude, and total MSNA were evaluated. Individual slope and y-intercepts were determined for each subject in each condition. Mean curves were then generated from the individual slope and y-intercept values. A change in the slope of these curves would indicate a change in the sensitivity of integrated baroreflex function, whereas differences in the y-intercept value would represent a vertical shift in the relationship.

Statistical analysis. The effects of LBNP and PV on hemodynamic and MSNA variables were analyzed by using a repeated-measures two-way ANOVA and Tukey’s post hoc analysis to estimate significant differences among means. Probability levels during multiple point-wise comparisons were corrected by using Bonferroni’s approach. Changes in the slopes and y-intercepts between Hypo and Normo for all stimulus-response relationships were determined using two-tailed paired t-tests. Statistical significance in all comparisons was set at \( P < 0.05 \). Values are presented as means ± SE.

RESULTS

Technical limitations prevented collection of complete data from all study segments in all subjects. Condition- and time-specific information on the number of participants in which successful CVP and MSNA data were collected are represented in Table 1. Direct statistical comparisons at each level of LBNP were only performed on those individuals who had complete data \( (n = 6–8) \) during both Normo and Hypo conditions.

Baseline responses. As previously reported (10), the 15.5 ± 1.7% reduction in resting PV (range = 8–20%) in Hypo versus Normo conditions was associated with a 6 ± 1 bursts/min increase in baseline MSNA (22 ± 2 bursts/min, Normo vs. 28 ± 2 bursts/min, Hypo), a 1.8 ± 1 mmHg reduction in CVP, and a 14 ± 2 ml drop in stroke volume (all \( P < 0.05 \)).

<table>
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<tr>
<th>Variable</th>
<th>Normo</th>
<th>Hypo</th>
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<td>LBNP</td>
<td>-5</td>
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<td>MSNA</td>
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LBNP, lower body negative pressure; CVP, central venous pressure; MSNA, muscle sympathetic nerve activity (microneurography); Normo, placebo; Hypo, diuretic administered.

MSNA responses during LBNP. Compared with baseline, absolute burst amplitudes increased \( (P > 0.05) \) during -40 mmHg LBNP in both Normo (0.22 ± 0.06 to 0.40 ± 0.11 arbitrary units) and Hypo (0.35 ± 0.11 to 0.44 ± 0.12 arbitrary units) conditions. Percent changes from baseline in MSNA mean burst amplitude (%ΔAMP), burst frequency (%ΔFreq), and total activity (%ΔMSNA_TOT) are shown in Figs. 1, A–C. Compared with Normo, the %ΔAMP and %ΔMSNA_TOT activity were augmented in Hypo (main effect of spironolactone, \( P < 0.05 \)). Specifically, the %ΔAMP from -5 to
−40 mmHg LBNP increased by 29 ± 6% during Normo and by 45 ± 9% in Hypo. Over the same time period, %ΔMSNA_TOT increased by 127 ± 12% during Normo and by 137 ± 15% in Hypo. Absolute burst frequency was greater (P < 0.05) at −40 mmHg LBNP in Hypo (48.7 ± 4 bursts/min) than Normo (41.6 ± 4 bursts/min). However, the %ΔFreq response was not different between Normo and Hypo conditions (P = 0.65).

Probability distribution analysis. At rest, there was a significant (P < 0.05) rightward shift in the median relative amplitude during Hypo versus Normo (Fig. 2A). The median relative amplitude (percentage of largest burst amplitude) at baseline increased from 37 ± 2% in Normo to 46 ± 1% in Hypo (P < 0.05). In addition, there was a significant leftward shift toward a lower median interburst interval (2.3 ± 0.4 → 1.4 ± 0.3 s; P < 0.05) during Hypo versus Normo, respectively (Fig. 2B). The median shift in the interburst interval was due to an increase in the percentage of bursts within the 1-s bin during Hypo (30 ± 7%) versus Normo (18 ± 5%) (P < 0.05).

In Normo, the median burst amplitude increased from 37 ± 2% at rest to 43 ± 3%, and the median interburst interval shortened from 2.3 ± 0.4 to 1.3 ± 0.3 s during −40 mmHg LBNP (both, P < 0.05). Similar shifts also occurred during LBNP in Hypo (from 46 ± 1 to 53 ± 1% and from 1.5 ± 0.3 to 0.9 ± 0.1 s for relative median burst amplitude and median interburst interval, respectively; both P < 0.05). Furthermore, the median burst amplitude at −40 mmHg LBNP in Hypo (53 ± 1%) was larger than the corresponding amplitude during Normo (43 ± 3%) (P < 0.05; Fig. 2C). Unlike the baseline histograms of burst periodicity (Fig. 2B), there was no difference in the median interburst interval between Normo and Hypo at −40 mmHg LBNP (P = 0.2; Fig. 2D).

Integrated baroreflex control of MSNA. The %ΔMSNA-ΔCVP stimulus-response relationship slopes were not affected by Hypo (Fig. 3, A–C). However, the y-intercept increased from 101 ± 3 arbitrary units in Normo to 116 ± 4 arbitrary units in Hypo (P < 0.05) for %ΔAMP (Fig. 3A) and from 72 ± 4 to 122 ± 4 arbitrary units (P < 0.05) for %ΔMSNA_TOT (Normo vs. Hypo, respectively) (Fig. 3C). In contrast, Hypo did not affect the y-intercept values between conditions (P = 0.41) for the %ΔFreq-ΔCVP relationships (Fig. 3B).

To further examine the limitations of interpreting integrated baroreflex control of sympathetic outflow, the absolute MSNA burst frequency versus CVP relationship was evaluated (Fig. 4) for post hoc comparison against Figs. 1 and 3. Hypo did not affect the y-intercept or slope of the relationship but shifted the LBNP response to a higher portion of the same MSNA-CVP curve.

DISCUSSION

Previously, we reported that acute hypovolemia enhanced the integrated baroreflex sympathetic response to LBNP with corresponding improvements in vascular resistance and blood pressure (10). In the current retrospective analysis, we used this effect of hypovolemia to examine in greater detail methods of assessing MSNA discharge patterns and how these may affect interpretations of reflex cardiovascular control. Two of the main findings of this report were that 1) at rest, burst frequency and the probability that each burst was of greater relative amplitude was elevated in hypovolemia, whereas 2) during −40 mmHg of LBNP, hypovolemia augmented the relative burst amplitude without appreciable changes in the burst-frequency response. Therefore, probability analysis was able to detect differences in the baseline burst amplitude characteristics that would otherwise not be possible. Moreover, it was observed that interpretations about the effect of hypovolemia on the reflex control of sympa-

![Fig. 2. Probability distribution of relative burst amplitude (A and C) and interburst interval (B and D) during baseline (A and B) and −40 mmHg LBNP (C and D). Values are means ± SE for Normo and Hypo. Numbers and arrows above plots indicate the mean and direction of the median shift of either relative burst amplitude (A and C) or interburst interval (B and D) from Normo to Hypo. Max, maximum.](http://ajpheart.physiology.org/)
thetic outflow differed depending on whether MSNA burst frequency or the total response was used as the dependent variable. Therefore, the differential responses of frequency and amplitude factor importantly in forming conclusions regarding sympathetic recruitment and reflex circulatory control.

**Methodological considerations.** The total integrated sympathetic signal is composed of bursts that vary in both amplitude and frequency. Burst frequency is commonly used as an index of sympathetic outflow because it is quantifiable and reproducible (4) and not affected by electrode position in the sympathetic nerve fascicle. Evidence from single efferent C-fiber recordings suggests that, if a postganglionic neuron discharges, it will generally fire only once during a given cardiac cycle, with some exceptions (11). Whether or not different multunit bursts of similar amplitude are due to the recruitment of the same neuronal pool is not known.

In contrast, burst amplitude likely reflects the total number of neurons contributing to the integrated multiunit signal. Ninomiya et al. (18) demonstrated that the number of activated pre- and postganglionic fibers in anesthetized cats affected the amplitude of synchronized cardiac sympathetic nerve activity. From human investigations, Wallin and colleagues (28) have argued that the shorter burst latency in higher amplitude bursts represents the recruitment of faster conducting C-fibers because the reduced latency was related to a widening on the rising but not the trailing portion of the burst. Finally, the anecdotal observation that burst amplitude, but not frequency, is affected by electrode position also suggests that it is the number of neurons discharging in the recording field of the electrode that affects amplitude.

To circumvent the limitation that electrode position affects the ability to compare amplitude values across individuals and repeated studies, the neural signal may be normalized to the highest burst to facilitate the construction of probability distributions. This approach assumes that the burst of greatest amplitude reflects the maximal recruitment of sympathetic neurons at that recording site for that specific condition. In the current study, baseline burst amplitudes were normalized to the largest burst recorded during rest, and LBNP bursts were normalized to the largest obtained during ~40 mmHg LBNP. Because absolute burst amplitude increased with LBNP, it is likely that this approach underestimated the probability distribution shifts. To examine this issue, with the assumption that electrode position was maintained between baseline and LBNP, we repeated the distribution analysis by using the maximal absolute burst amplitude recorded during LBNP to normalize both baseline and LBNP data. Compared with the original values, this secondary analysis reduced the baseline median amplitude from 37 to 21 ± 3% in Normo and from 46 ± 1 to 39 ± 3% in Hypo groups. Subsequently, the rightward shift with LBNP was augmented by using this latter approach. Therefore, the combined results provide con-

**Fig. 3.** Percent change from the preceding baseline period (0 mmHg LBNP) in muscle sympathetic burst amplitude (A), frequency (B), and total activity (C) plotted as a function of absolute changes (from 0 mmHg LBNP) in central venous pressure (CVP). Values are means ± SE for both Normo and Hypo. Linear regression lines are included for Normo (dashed lines) and Hypo (solid lines), respectively. Int, intercept. *P < 0.05 vs. Normo.

**Fig. 4.** Relationship between absolute changes in CVP and MSNA burst frequency. Values are means ± SE for both Normo and Hypo. Linear regression lines are included for Normo (dashed line) and Hypo (solid line) respectively.
fidence in this analysis technique to detect changes in sympathetic discharge properties.

Previously, Sundlof and Wallin (23) determined that the proportion of high-amplitude bursts tended to increase with increasing burst incidence, suggesting that relative burst amplitude distribution may also be used as a quantitative descriptor of MSNA. In addition, the relative distribution of burst amplitude is argued to be a more sensitive indicator of changes in sympathetic outflow than counting neural bursts (24, 25). In the current analysis, this approach revealed that there was an increased tendency for each burst to be of greater amplitude both at rest (Fig. 2A) and during LBNP (Fig. 2C) in hypovolemia. The ability to detect differences in the baseline burst amplitude characteristics within the same individuals supports the value of this approach in the assessment of sympathetic neural recruitment.

In addition to its ability to discern differences in relative burst amplitude spectra, probability distribution analysis was capable of identifying changes in the interburst interval with LBNP, signifying an expected increase in burst frequency (3) as well as a shift toward higher baseline burst frequencies in Hyno versus Normo (10, 22) groups. However, this approach did not detect a difference in interburst interval when comparing LBNP values in Normo and Hyno groups, although absolute burst frequency was higher in Hypo. This discrepancy may be the result of inadequate statistical power, being ~46% with a calculated effect size of 0.8.

Integrative baroreflex control of MSNA burst frequency versus amplitude. Because burst frequency is quantifiable and reproducible, this feature of the MSNA signal is often used to describe changes in cardiovascular control in repeated tests. Across Figs. 1, 3, and 4, it is clear that, when absolute burst frequency was used as the dependent variable, hypovolemia elevated baseline MSNA and shifted the LBNP response to a higher portion of the same linear MSNA-CVP relationship. However, this conclusion must be modified when the changes in burst amplitude, or total MSNA, are used as the dependent variable, as shown in Figs. 3 and 4. In this latter case, hypovolemia did not affect the slope of the linear %ΔMSNA-ΔCVP relationship but did shift the response to a new curve, as indicated by the higher y-intercept values, producing greater sympathetic nerve activity for a given reduction in CVP (Figs. 3, A and C). Note that the higher total MSNA curves are due to different amplitude responses. Therefore, conclusions vary regarding the effect of hypovolemia on reflex sympathetic control depending on whether burst frequency is analyzed separately from the amplitude characteristic.

Hypovolemia, MSNA discharge patterns, and neurovascular control. Although other vasomotor control features, such as myogenic (21) or metabolic (19) responses, may interfere with interpretations regarding sympathetic vasomotor control, MSNA is largely regarded as a vasoconstrictor signal (1, 20, 29, 31). Despite recent data that the bursting pattern of MSNA is important for vascular control (2), it is not known to what extent the frequency versus amplitude relationships are important. Nonetheless, the functional impact of MSNA discharge patterns on vasomotor control may be gleaned from conditions where burst amplitude is affected differently from frequency. As such, the greater increases in vascular resistance and blood pressure during LBNP after diuretic-induced hypovolemia (10) were more closely related to the change in burst amplitude than to burst frequency (current analysis). In addition, changes in burst frequency alone could not account for the greater blood pressure responses to graded head-up tilt in males versus females (22). Therefore, it appears that vascular tissue integrates information about MSNA amplitude as well as frequency. It has been proposed that “(sympathetic) bursting behavior offers an extra dimension to sympathetic outflow (synchrony), which can extend the dynamic range of neuroeffector control” (17). From the above analysis, we further hypothesize that distinct neurovascular functions are accomplished by the differential pattern of sympathetic burst frequency and amplitude and that these two features of the integrated sympathetic signal serve different but complimentary roles in reflex cardiovascular control.

To summarize, a main finding of this report was that probability distribution analysis is a useful method to examine differences in the relative amplitude of MSNA bursts at rest and during reflex excitation. In addition, examinations of the Δ%MSNA-ΔCVP curves (i.e., stimulus-response relationships) indicated that conclusions about whether or not hypovolemia affected baroreflex sympathetic integration differed depending on whether burst amplitude (or total MSNA) or burst frequency were used as the dependent variable. Thus the current data indicate that care must be taken in drawing conclusions about sympathetic control based solely on burst frequency data. Moreover, the rhythmicity of the sympathetic discharge pattern, including detailed analysis of burst amplitude and frequency, appears to be a useful tool to examine the manner in which the central nervous system integrates reflex sympathetic information.

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Hypovolemia and sympathetic rhythmicity

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