Am J Physiol Heart Circ Physiol 321: H798–H806, 2021.
First published September 10, 2021; doi:10.1152/ajpheart.00422.2021

american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
HEART AND CIRCULATORY PHYSIOLOGY

RAPID REPORT

Cardiovascular Neurohormonal Regulation

Blood pressure oscillations impact signal-averaged sympathetic transduction of blood pressure: implications for the association with resting sympathetic outflow

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Abstract

Signal-averaged sympathetic transduction of blood pressure (BP) is inversely related to resting muscle sympathetic nerve activity (MSNA) burst frequency in healthy cohorts. Whether this represents a physiological compensatory adaptation or a methodological limitation, remains unclear. The current analysis aimed to determine the contribution of methodological limitations by evaluating the dependency of MSNA transduction at different levels of absolute BP. Thirty-six healthy participants (27 ± 7 yr, 9 females) underwent resting measures of beat-to-beat heart rate, BP, and muscle sympathetic nerve activity (MSNA). Tertiles of mean arterial pressure (MAP) were computed for each participant to identify cardiac cycles occurring below, around, and above the MAP operating pressure (OP). Changes in hemodynamic variables were computed across 15 cardiac cycles within each MAP tertile to quantify sympathetic transduction. MAP increased irrespective of sympathetic activity when initiated below the OP, but with MSNA bursts provoking larger rises (3.0 ± 0.9 vs. 2.1 ± 0.7 mmHg; $P < 0.01$). MAP decreased irrespective of sympathetic activity when initiated above the OP, but with MSNA bursts attenuating the drop (−1.3 ± 1.1 vs. −3.1 ± 1.2 mmHg; $P < 0.01$). In participants with low versus high resting MSNA (12 ± 4 vs. 32 ± 10 bursts/min), sympathetic transduction of MAP was not different when initiated by bursts below (3.2 ± 1.0 vs. 2.8 ± 0.9 mmHg; $P = 0.26$) and above the OP (−1.0 ± 1.3 vs. −1.6 ± 0.8 mmHg; $P = 0.08$); however, low resting MSNA was associated with a smaller proportion of MSNA bursts firing above the OP (15 ± 5 vs. 22 ± 5%; $P < 0.01$). The present analyses demonstrate that the signal-averaging technique for calculating sympathetic transduction of BP is influenced by the timing of an MSNA burst relative to cyclic oscillations in BP.

NEW & NOTEWORTHY The current signal-averaging technique for calculating sympathetic transduction of blood pressure does not consider the arterial pressure at which each muscle sympathetic burst occurs. A burst firing when mean arterial pressure is above the operating pressure was associated with a decrease in blood pressure. Thus, individuals with higher muscle sympathetic nerve activity demonstrate a reduced sympathetic transduction owing to the weighted contribution of more sympathetic bursts at higher levels of arterial pressure.

blood pressure; muscle sympathetic nerve activity; sympathetic transduction

INTRODUCTION

Microneurographic recordings of postganglionic efferent muscle sympathetic nerve activity (MSNA) have provided valuable insight toward our understanding of the neural regulation of blood pressure (BP) in health and disease states (1). However, in healthy participants across the lifespan, resting MSNA is unrelated to BP (2). Such data highlight important knowledge gaps regarding our understanding of the translation of the efferent neural signal to the functional hemodynamic or vascular response (3), defined as sympathetic or sympathetic vascular transduction (4). The challenge of quantifying sympathetic transduction in humans arises from the inability to quantify accurately neurotransmitter (i.e., norepinephrine) kinetics with sufficient time resolution, and the complexity of integrating both neural and nonneural mechanisms responsible for BP control. A common approach used to quantify sympathetic transduction involves studying the

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Submitted 4 August 2021 / Revised 27 August 2021 / Accepted 8 September 2021

effects of each MSNA burst on hemodynamic variables for 10–15 cardiac cycles through signal averaging (5–7). This method was validated pharmacologically by the abolishment of signal-averaged sympathetic transduction of brachial vascular conductance using α-adrenergic blockade (7).

One common observation among healthy human participants has been that sympathetic transduction of BP is inversely related to resting MSNA burst frequency, wherein individuals with high MSNA having lower sympathetic transduction (5, 8, 9). These results have been hypothesized to be caused by compensatory changes in adrenergic sensitivity (10, 11), which would reduce the hemodynamic consequences of elevated MSNA. Alternatively, we (8), and others (4, 9, 12), have raised concerns that these correlations may be the product of a methodological limitation in individuals with higher resting MSNA. For instance, the signal-averaging approach fails to consider cyclic BP oscillations that occur in resting humans. These low-frequency (~0.1 Hz) oscillations involve the complex interplay between neurogenic control of the vasculature and heart, respiration, arterial vasomotion, myogenic responses, and endothelial cells (13–15). The simple dichotomizing of cardiac cycles based on the presence of a MSNA burst may fail to account for parallel nonneural contributions. Cyclic BP oscillations are also particularly relevant in the context of interindividual differences in resting MSNA burst frequency. At lower resting MSNA burst frequencies, the occurrence of a MSNA burst primarily occurs at troughs within BP oscillations, due to input from the arterial baroreflex (16). At higher resting MSNA burst frequencies, a larger proportion of MSNA bursts occur when BP is above the mean resting value or operating pressure (OP) (16), and when BP is rising (17, 18). Thus, reduced sympathetic transduction in participants with high resting sympathetic activity may be secondary to a larger proportion of MSNA bursts occurring at a higher BP.

The current study aimed to establish the importance of time dependency of MSNA bursts on sympathetic transduction in humans by evaluating measures across different levels of absolute BP. We hypothesize that *1*) signal-averaged transduction of BP will be influenced by the prevailing BP level at which the MSNA burst occurs and *2*) the differences in the proportion of MSNA bursts firings above and below the OP will contribute to differences in sympathetic transduction of BP between participants with low versus high resting MSNA.

METHODS

Participants

The present data included 36 participants (27 men, 9 women) from a previous study evaluating resting signal-averaged sympathetic transduction (19). Participants were unmedicated young to middle-aged healthy adults (18–51 yr) with a resting BP < 140/90 mmHg. All female participants were tested during the early follicular phase (*days 0–5*) or placebo week of their natural or controlled menstrual cycle, respectively. All research protocols were approved by the research ethics boards of the University of Guelph and the University of Brasilia, and all participants completed written informed consent before testing.

Experimental Protocol

Participants completed a baseline recording (average baseline: 7.6 ± 2.11 min) in the supine position while resting heart rate, BP, and MSNA were collected. Heart rate was collected by single-lead electrocardiography (ADInstruments, Australia or DX2022, Dixtal, Manaus, Brazil), whereas blood pressure was collected by finger photoplethymography (Finometer MIDI, Finapres, The Netherlands or Human NIBP Controller, ADInstruments, NSW, Australia). Efferent postganglionic multiunit MSNA was quantified using microneurography, as described (20). A high-impedance tungsten microelectrode was inserted into the common peroneal nerve and adjusted until spontaneous bursts of sympathetic activity were observed from the MSNA neurogram. Activation to an end-expiratory apnea and a lack of responsiveness to skin stroking or an auditory perturbation were used to confirm MSNA bursts (21). The raw MSNA neurogram was then amplified (75,000×), band-pass filtered (0.7–2.0 or 0.3–2.0 kHz), rectified, and integrated using a 0.1 or 0.2-s time constant to generate the integrated MSNA neurogram (Nerve Traffic Analyzer, Model 662 C-4; University of Iowa, Iowa City, IA or NeuroAmpEX; ADInstruments, Sydney, Australia).

Data Analysis

All data were digitized and stored using LabChart (v. 8; PowerLab, ADInstruments, New South Wales, Australia) at a sampling frequency was 1 kHz. The raw MSNA neurogram was sampled at ≥10 kHz. All MSNA neurograms were analyzed using a semiautomated custom LabVIEW program (National Instruments, Austin, TX). Determination of a sympathetic burst was based on a 3:1 signal:noise ratio and alignment with the time-shifted cardiac cycle (21). From the integrated neurogram, MSNA burst frequency (bursts/minute) and burst incidence (bursts/100 heartbeats) were computed. Beat-to-beat cardiac output (CO) was calculated noninvasively using the Windkessel model (noninvasive cardiac output extension, ADInstruments, New South Wales, Australia), whereas beat-to-beat total vascular conductance (TVC) was subsequently calculated [TVC = CO/mean arterial pressure (MAP)].

Resting sympathetic transduction was first quantified using the burst-triggering signal-averaging technique, described previously (6, 9, 19). Serial changes in MAP, CO, and TVC across 15 cardiac cycles were determined for each heartbeat associated with and without a sympathetic burst and subsequently averaged across each serial time point. With these computed averages, the peak MAP and CO, and nadir TVC were used to quantify resting sympathetic transduction, whereas the hemodynamic responses to sympathetic quiescence were quantified using the nadir MAP and CO, and peak TVC. MAP was used as the primary outcome variable for measures of sympathetic transduction instead of diastolic BP for ease of translation with sympathetic transduction of CO and TVC. Sympathetic transduction of diastolic BP is presented as supplemental data. The influence of MSNA burst amplitude tertiles on sympathetic transduction of BP was also calculated. Tertiles were used to maximize the number of bursts incorporated into signal averaging at each BP level. Because of the lower occurrence of MSNA bursts around and above the OP, a minimum of five

bursts were required for inclusion into the burst amplitude analysis. Based on this criteria, 0, 2, and 13 participants were excluded from analyses of MSNA burst firing below, around, and above the OP, respectively.

Time dependency of MSNA bursts on signal-averaged sympathetic transduction was then evaluated across different BP levels. With the use of all cardiac cycles within the baseline recording, tertiles of resting MAP were computed for each participant. The low, middle, and high MAP tertile represented cardiac cycles occurring below, around, and above the MAP OP, respectively (Fig. 1*A*). The OP was defined as the mean MAP of the baseline recording and is incorporated within the middle tertile. Cardiac cycles were grouped accordingly and sorted based on the presence or absence of an MSNA burst. Signal averaging was then conducted as described above for each MAP tertile for both bursts and nonburst cardiac cycles. As the prevailing MAP level influenced the directionality of sympathetic transduction and, in some scenarios, resulted in biphasic transduction responses (Fig. 1, *B* and *C*), we computed the average (opposed to the peak or nadir) sympathetic transduction across all 15 cardiac cycles. We also calculated the difference between sympathetic transduction to MSNA bursts and nonbursts as an additional metric of sympathetic transduction of BP. The proportion of MSNA bursts firing when BP was below, around, and above OP was quantified as the number of MSNA bursts within a given BP tertile divided by the total number of MSNA bursts within the baseline recording.

Lastly, we evaluated the influence of resting MSNA burst frequency on sympathetic transduction of all MSNA bursts (conventional approach) and sympathetic transduction when BP was below, around, and above the OP. Individuals were separated into two groups: *1*) low resting MSNA and *2*) high resting MSNA, which was determined based on a median split of MSNA burst frequency within the cohort.

Statistical Analysis

A two-way repeated-measures ANOVA was used to evaluate the effect of an MSNA burst and cardiac cycles on the sympathetic transduction of MAP, CO, and TVC. A one-way repeated-measures ANOVA was used to compare the

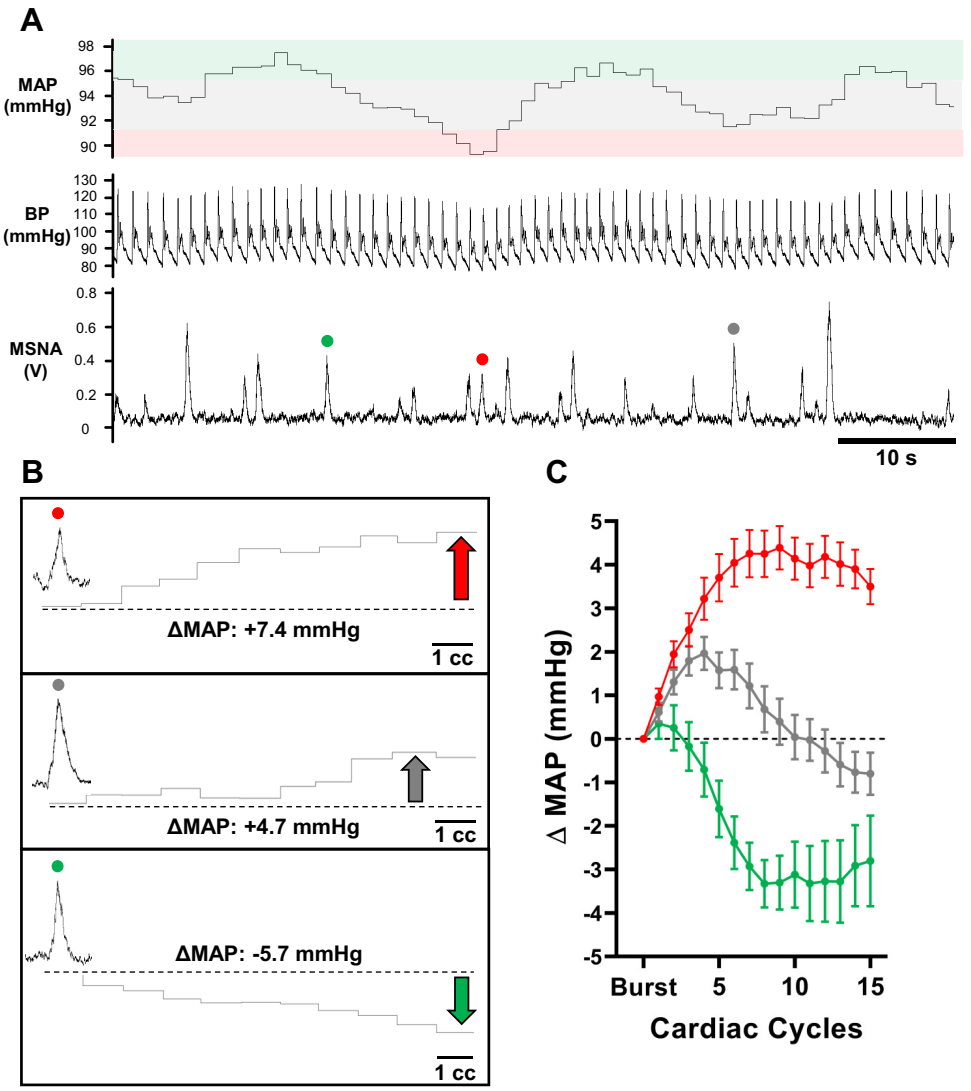


Figure 1. *A*: representative 1-min recording of beat-to-beat mean arterial pressure (MAP), blood pressure (BP), and muscle sympathetic nerve activity (MSNA). Green, gray, and red areas represent tertiles of MAP defined as being above, around, or below the operating pressure (OP), respectively. Green, gray, and red dots within MSNA channel represent representative sympathetic bursts occurring within the respective areas described above. *B*: corresponding MAP transduction to individual MSNA bursts identified in *A* when MAP was above, around, or below the OP. *C*: sympathetic transduction of MAP for all MSNA bursts occurring when MAP was above (green), around (gray), or below (red) the OP for one participant.

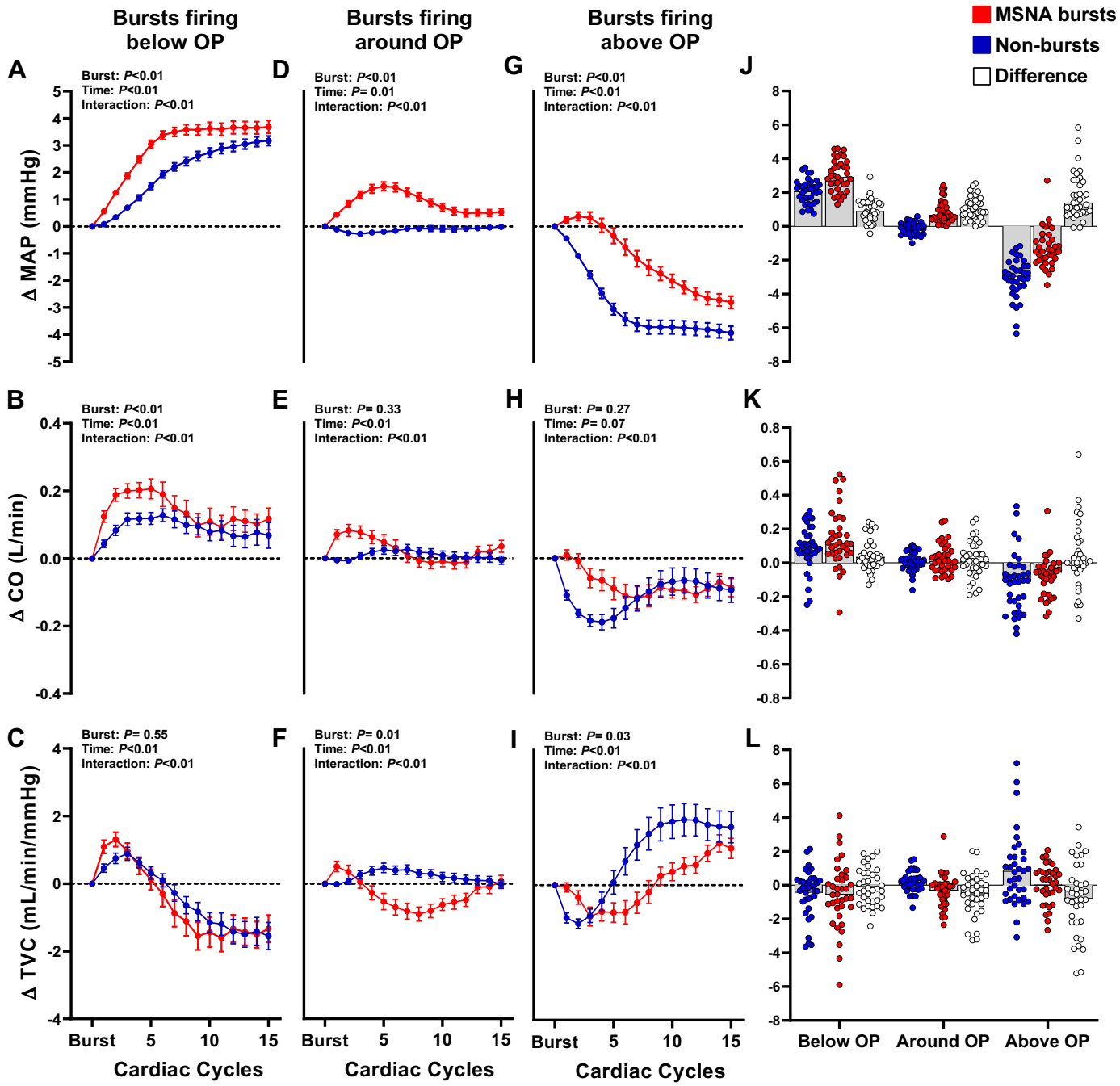


Figure 2. Signal-averaged sympathetic transduction of mean arterial pressure (MAP; *top horizontal*), cardiac output (CO; *middle horizontal*), and total vascular conductance (TVC; *bottom horizontal*). From *left* to *right*, column panels represent cardiac cycles when MAP was *1*) below the operating pressure (OP; *A–C*), *2*) around the OP (*D–F*), *3*) above the OP (*G–I*), and *4*) mean responses (*J–L*) for each participant. Red lines represent cardiac cycles associated with a muscle sympathetic nerve activity (MSNA) bursts; blue lines represent cardiac cycles associated with no MSNA burst. All analyses were conducted using a two-way repeated-measures ANOVA to evaluate the effect of MSNA bursts and time on the sympathetic transduction in 36 participants. All data presented as means ± SE.

proportion of MSNA bursts firing below, around, and above OP. Significant interactions were followed with post hoc analyses using a Bonferroni adjustment. The relationships between *1*) MSNA burst frequency and the proportion of MSNA bursts firing below the OP and *2*) the proportion of MSNA bursts firing below the OP and sympathetic transduction of MAP were evaluated using Pearson's bivariate correlations. Last, sympathetic transduction and the proportion of MSNA firing at different prevailing BP levels were compared between participants with low versus high resting MSNA burst frequency using independent sample *t* tests and ANCOVA analyses. All statistical analyses were performed with IBM SPSS Statistics 23 (Armonk, NY). Data are presented as means ± SD unless otherwise specified. Significance was defined as $P < 0.05$.

RESULTS

The mean age and body mass index were 27 ± 7 yr and 26 ± 4 kg/m^2. Resting systolic BP, diastolic BP, and heart rate were 115 ± 13 mmHg, 65 ± 10 mmHg, and 63 ± 10 beats/min, respectively. Resting MSNA burst frequency, burst incidence, and normalized burst area were 22 ± 13 bursts/min, 36 ± 20 bursts/100 heartbeats, and 36 ± 10%, respectively. Full baseline characteristics are available in Supplemental Table S1 (https://doi.org/10.6084/m9.figshare.16413096.v2). Resting sympathetic transduction of ΔMAP, ΔCO, and ΔTVC was 2.1 ± 1.1 mmHg, 0.2 ± 0.1 L/min, and −1.2 ± 1.4 mL/min/mmHg, respectively. The ΔMAP, ΔCO, and ΔTVC to cardiac cycles not associated with a sympathetic burst was −1.3 ± 1.1 mmHg, −0.1 ± 0.1 L/min, and 1.0 ± 1.4 mL/min/mmHg, respectively.

A rise in MAP was observed irrespective of the presence or absence of an MSNA burst when initiated below the OP; however, MSNA bursts resulted in larger rises in MAP (burst: 3.0 ± 0.9 vs. nonburst: 2.1 ± 0.7 mmHg; $P < 0.01$; Δ1.0 ± 0.7 mmHg; Fig. 2*A*). An MSNA burst resulted in larger increases in CO (burst: 0.14 ± 0.17 vs. nonbursts: 0.09 ± 0.13 L/min; $P < 0.01$; Δ0.05 ± 0.10 L/min; Fig. 2*B*), but not TVC (burst: −0.6 ± 2.0 vs. nonbursts: −0.5 ± 1.4 mL/min/mmHg; $P = 0.55$; Δ−0.1 ± 1.1 mL/min/mmHg; Fig. 2*C*), compared with nonbursts. A rise in MAP was also observed following MSNA bursts initiated around the OP but unchanged following nonburst cardiac cycles (burst: 0.9 ± 0.6 vs. nonburst: −0.1 ± 0.4 mmHg; $P < 0.01$; Δ1.0 ± 0.7 mmHg; Fig. 2*D*). There was no difference in ΔCO between cardiac cycles with and without an MSNA burst (bursts: 0.03 ± 0.09 vs. nonbursts: 0.01 ± 0.06 L/min; $P = 0.33$; Δ0.02 ± 0.11; Fig. 2*E*), but larger decreases in TVC following MSNA bursts (bursts: −0.3 ± 1.0 vs. nonbursts: 0.2 ± 0.6 mL/min/mmHg; $P = 0.01$; Δ−0.5 ± 1.3 mL/min/mmHg; Fig. 2*F*). A drop in MAP was observed irrespective of the presence or absence of an MSNA burst when initiated above the OP, with MSNA bursts attenuating the reduction in MAP (bursts: −1.3 ± 1.1 vs. nonbursts: −3.1 ± 1.2 mmHg; $P < 0.01$; Δ1.8 ± 1.4 mmHg; Fig. 2*G*). The decrease in CO was similar between cardiac cycles with and without an MSNA burst (bursts: −0.08 ± 0.12 vs. nonbursts: −0.12 ± 0.18 L/min; $P = 0.33$; Δ0.04 ± 0.2 L/min; Fig. 2*H*), whereas MSNA bursts attenuated the increases in TVC (bursts: 0.0 ± 1.1 vs. nonbursts: 0.9 ± 2.2 mL/min/mmHg; $P = 0.03$; Δ−0.8 ± 2.1 mL/min/mmHg; Fig. 2*I*). Results were similar when sympathetic transduction of diastolic BP was used as the outcome variable. (Supplemental Fig. S1; https://doi.org/10.6084/m9.figshare.16413174.v3).

The effects of MSNA burst amplitude on sympathetic transduction of MAP, CO, and TVC are displayed in Supplemental Fig. S2 (https://doi.org/10.6084/m9.figshare.16452195.v1). For MSNA bursts firing below the OP, a main effect of MSNA burst amplitude was observed for MAP (2.5 ± 0.9 vs. 3.0 ± 1.1 vs. 3.6 ± 1.1 mmHg; $P < 0.01$), and CO (0.11 ± 0.17 vs. 0.16 ± 0.19 vs. 0.16 ± 0.19 L/min; $P = 0.01$), but not TVC (−0.6 ± 2.0 vs. −0.4 ± 2.0 vs. −0.8 ± 2.2 mL/min/mmHg; $P = 0.13$). For MSNA bursts firing around OP, a main effect of MSNA burst amplitude was observed for MAP (0.7 ± 0.9 vs. 0.7 ± 0.6 vs. 1.2 ± 0.8 mmHg; $P < 0.01$) and TVC (0.0 ± 1.2 vs. −0.3 ± 1.0 vs. −0.9 ± 1.2 mL/min/mmHg; $P < 0.01$), but not CO (0.04 ± 0.12 vs. 0.02 ± 0.09 vs. 0.00 ± 0.12 L/min; $P = 0.45$). For MSNA bursts firing above OP, a main effect of MSNA burst amplitude was observed for MAP (−1.5 ± 1.4 vs. −1.3 ± 1.3 vs. −0.9 ± 1.1 mmHg; $P = 0.02$), but not CO (−0.10 ± 0.14 vs. −0.03 ± 0.11 vs. −0.06 ± 0.15 L/min; $P = 0.45$) or TVC (0.0 ± 1.4 vs. 0.6 ± 1.3 vs. −0.1 ± 1.4 mL/min/mmHg; $P = 0.06$). Results were similar when sympathetic transduction of diastolic BP was used as the outcome variable (Supplemental Fig. S3; https://doi.org/10.6084/m9.figshare.16413213).

As expected, the number of MSNA bursts firing when BP was below, around, or above the OP exhibited a stepwise decrease (48 ± 7% vs. 34 ± 4% vs. 19 ± 6%; $P < 0.01$). MSNA bursts firing below the OP had larger MSNA burst amplitudes compared to MSNA bursts firing when BP was at or above the OP (37 ± 11% vs. 35 ± 10% vs. 33 ± 12%; $P < 0.01$). A negative correlation was observed between resting MSNA burst frequency and the proportion of MSNA bursts firings below the OP ($r = −0.63$; $P < 0.01$, Fig. 3*A*). Further, a positive correlation was observed between the proportion of MSNA bursts firings below the OP and sympathetic transduction of MAP ($r = 0.67$; $P < 0.01$; Fig. 3*B*). Similar inverse relationships were found between resting MSNA and the proportion of MSNA bursts firing above the OP ($r = 0.61$; $P < 0.01$), and the proportion of MSNA bursts firings above the OP and sympathetic transduction of MAP ($r = −0.61$; $P < 0.01$).

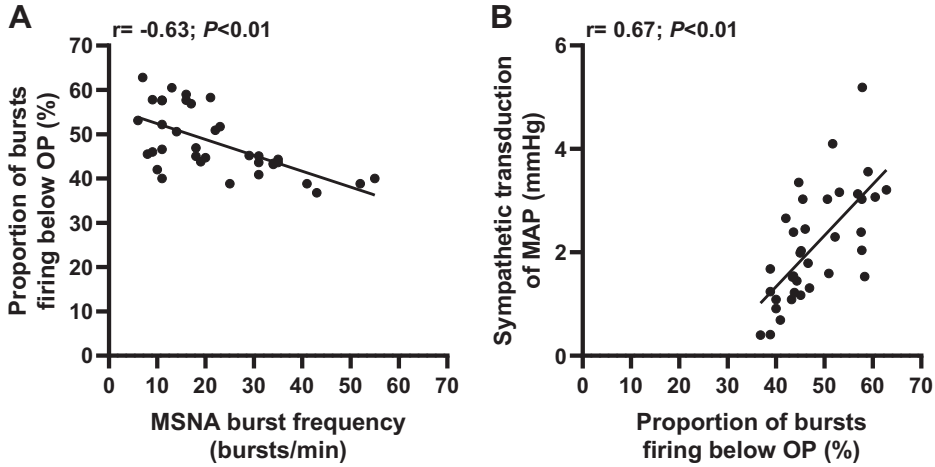
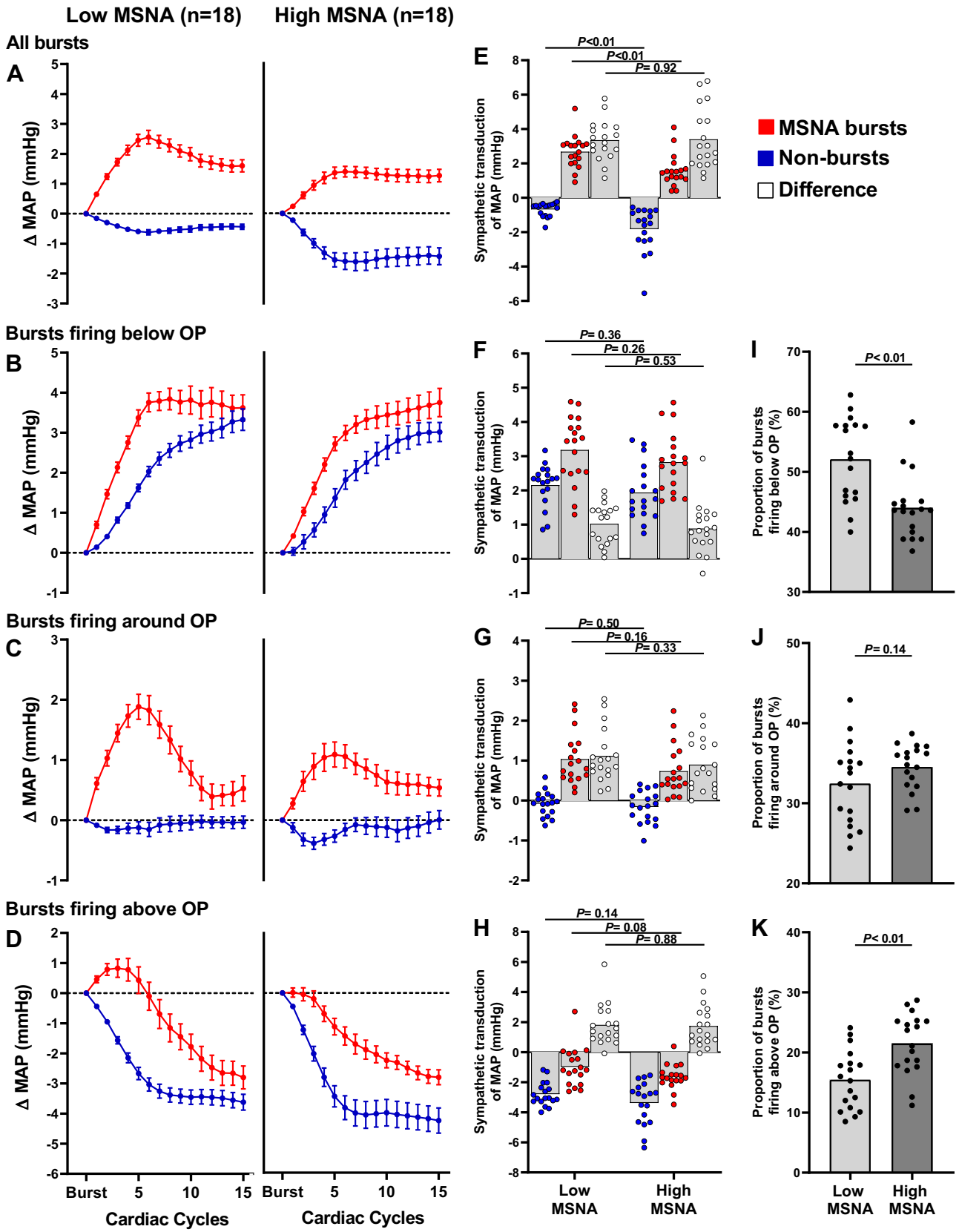


Figure 3. *A*: Pearson's bivariate correlation between resting MSNA burst frequency and the proportion of cardiac cycles with an MSNA burst when mean arterial pressure (MAP) was below the operating pressure (OP; $n = 36$). *B*: Pearson's bivariate correlation between the proportion of cardiac cycles with an MSNA burst when MAP was below OP and the overall signal-averaged sympathetic transduction of MAP ($n = 36$). MSNA, muscle sympathetic nerve activity.



Participants were separated into two groups based on a low (12 ± 4 bursts/min; n = 18) or high (32 ± 10 bursts/min; n = 18) resting MSNA burst frequency, determined by a median split. As seen in supplemental Table S1 (https://doi.org/10.6084/m9.figshare.16413096.v2), individuals with low resting MSNA were younger (24 ± 4 vs. 31 ± 8 yr), had lower resting MAP (79 ± 6 vs. 87 ± 8 mmHg), and smaller MSNA burst amplitudes (41 ± 8 vs. 30 ± 10%, all $P < 0.01$). Sympathetic transduction of MAP was higher in participants with lower resting MSNA burst frequencies (low MSNA: 2.7 ± 0.9 vs. high MSNA: 1.6 ± 0.9 mmHg; $P < 0.01$; Fig. 4*E*), which persisted after adjusting for age, sex, resting MAP, and resting MSNA burst amplitude (low MSNA: 2.7 ± 1.2 vs. high MSNA: 1.6 ± 1.2 mmHg; P = 0.02). However, sympathetic transduction of MAP was not different between participants with low versus high resting MSNA when assessed separately for BP levels below (low MSNA: 3.2 ± 1.0 vs. high MSNA: 2.8 ± 0.9 mmHg; P = 0.26; Fig. 4*F*), around (low MSNA: 1.0 ± 0.6 vs. high MSNA: 0.7 ± 0.6 mmHg; P = 0.16; Fig. 4*G*), or above the OP (low MSNA: −1.0 ± 1.3 vs. high MSNA: −1.6 ± 0.8 mmHg; P = 0.08; Fig. 4*H*). These observations were consistent when the difference between MSNA bursts and nonbursts was used as a measure of sympathetic transduction (Fig. 4, *F–H*). Lastly, participants with low resting MSNA had a larger proportion of MSNA bursts when BP was below the OP (52 ± 7 vs. 44 ± 5%; $P < 0.01$; Fig. 4*I*), similar proportion of MSNA bursts when BP was around the OP (33 ± 5 vs. 35 ± 3%; P = 0.14; Fig. 4*J*), and a smaller proportion of MSNA bursts when BP was above the OP (15 ± 5 vs. 22 ± 5%; $P < 0.01$; Fig. 4*K*).

DISCUSSION

A burst of MSNA represents the signal for norepinephrine release, which, in the periphery, will result primarily in α-adrenergic receptor mediated vasoconstriction (4). The present analyses demonstrate that the signal-averaging technique for calculating sympathetic transduction of BP is influenced by cyclic variations in BP. This is most clearly shown during MAP levels above the OP, where a burst of MSNA was associated with a decrease in MAP. Thus, individuals with higher MSNA had a reduced sympathetic transduction of BP, as a result of more bursts occurring at higher prevailing BP levels and thus a higher proportion of small MAP responses contributing to the overall average sympathetic transduction calculation. Finally, incorporating changes in BP following MSNA bursts versus nonburst cardiac cycles resulted in consistent sympathetic transduction responses that appeared unaffected by the prevailing BP. These results advance our understanding of the physiological relevance of signal-averaged methods for calculating sympathetic transduction of BP.

We recently demonstrated, in the largest sample of males and females to date, that sympathetic transduction of BP was inversely related to resting MSNA burst frequency (8), confirming prior work primarily in males (5, 9, 22). However, despite concerns that signal-averaging sympathetic transduction may not be suitable for individuals with high MSNA (4, 9, 12), a cut-off threshold or rationale explaining this association has not been investigated. The present analysis reveals for the first time that the timing of MSNA bursts relative to cyclic variations in BP represents the principle computational mechanism responsible for reducing sympathetic transduction of BP at high MSNA burst frequencies in young healthy participants. The occurrence of an MSNA burst, representing the triggering event initiating signal averaging, is strongly controlled by the arterial baroreflex (23). However, individuals with high resting MSNA have a larger proportion of bursts firing at a BP above the OP. As shown in Fig. 2*G*, a MSNA burst was associated with a reduction in MAP when occurring above the OP using conventional signal-averaging methods and would have a larger contribution to the overall average sympathetic transduction in those with higher MSNA burst frequency. In contrast, subtraction of transduction responses following MSNA bursts and nonbursts yielded similar magnitude increases in MAP (Fig. 4, *F–H*, white bars). Although previous studies have calculated the changes in BP following nonburst cardiac cycles, to our knowledge, none have integrated these results into the calculation of sympathetic transduction. Interestingly, the mechanisms responsible for the rise in MAP differed depending on the initial BP level, with bursts below the OP driven largely by increases in CO, whereas bursts at or above the OP being mediated by reductions in TVC. Collectively, these results add to our understanding of interpreting sympathetic transduction of BP measures, revealing that it is not MSNA burst frequency per se but the proportion of MSNA bursts firing at higher BP levels that can lead to the confounding interpretations of within- or between-group comparisons. Our prior work proposed a method to normalize sympathetic transduction of BP across different levels of resting MSNA (8). Given the strong correlation between MSNA burst frequency and the proportion of bursts firing below or above the OP, this method may be suitable for use in some situations, but we cannot exclude the possibility that in some cases, MSNA may differ but the proportion of bursts occurring at different BP levels is similar, and thus no correction or normalization would need to be applied. Alternatively, future work could seek to use the difference in MAP responses following MSNA burst versus nonburst cardiac cycles, which was unaffected by the prevailing BP level.

The present results do not preclude the possibility that chronic sympathetic activity can influence adrenergic sensitivity or vasoconstrictor responses. For example, the disruption of ganglionic neurotransmission using spinal transection to the rat hindlimb artery can potentiate the vasoconstrictor response to electrical stimulation (24, 25), whereas high resting sympathetic activity in humans is negatively related to α-adrenergic sensitivity (10, 11). However, at minimum, the

Figure 4. Comparison of sympathetic transduction in participants with low vs. high muscle sympathetic nerve activity (MSNA). Left column (*A–D*) demonstrate the sympathetic transduction of mean arterial pressure (MAP) for all bursts and nonbursts (*first row*), when BP was below the operating pressure (OP; *second row*), around the OP (*third row*), and below the OP (*fourth row*). Data are presented as means ± SE. Middle column (*E–H*) demonstrate average MAP response during an MSNA burst (*red*), nonburst (*blue*), and the difference between bursts and nonbursts (*white*). Participants with low (n = 18) vs. high (n = 18) resting MSNA were compared using an independent sample t test. Right column (*I–K*) demonstrate proportion of MSNA bursts firing when BP was below, around, or above the OP. Participants with low vs. high resting MSNA were compared using an independent sample t test.

methodological limitations described above can overestimate the effects of MSNA burst frequency on sympathetic transduction of BP.

Limitations

First, MSNA bursts and nonbursts were grouped based on their occurrence below, around, or above the MAP operating pressure, which was determined using the MAP tertiles for each participant. Differences in beat-to-beat BP variability or the magnitude of BP oscillations likely contribute interindividual variability within each MAP tertile of sympathetic transduction. Future work could examine more detailed analyses of BP levels but would require a longer epoch of data collection to ensure a sufficient number of MSNA bursts were available for signal averaging at each level. Second, sympathetic transduction was calculated as a dichotomous variable (burst vs. no burst) and across tertiles of MSNA burst amplitudes. More advanced analyses incorporating burst firing pattern should be employed in the future. However, multiple MSNA bursts firing consecutively can coincide with different BP levels (i.e., below, around, and above the OP) adding complexity toward isolating the effect of MSNA firing pattern. Such analyses will require longer recordings to permit a larger number of burst firing pattern combinations across each BP level. Third, we studied only healthy participants and the results may not be generalizable to clinical populations with elevated resting MSNA. Fourth, the present analyses focused on sympathetic transduction of BP. Whether similar results are observed when examining regional vascular conductance requires future work.

Conclusions

The magnitude and direction of signal-averaged MAP responses are influenced by the prevailing BP at the time of each MSNA burst. Most notably, MSNA bursts firing above the OP were associated with a reduction in MAP. As participants with higher resting MSNA have a larger proportion of MSNA bursts firing above the OP, these reductions in MAP contribute to a lower overall sympathetic transduction of BP. Instead, incorporating the changes in MAP following nonburst cardiac cycles demonstrates consistent increases in MAP following a burst across all BP levels. These findings provide evidence that the relationship between sympathetic transduction of BP and resting MSNA burst frequency is the result of a computational limitation of the signal-averaging method, which may require, depending on the characteristics of the study cohort, the use of a normalization metric (8) or the refinement of the current signal-averaging method.

SUPPLEMENTAL DATA

Supplemental Table S1: https://doi.org/10.6084/m9.figshare.16413096.v2; Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.16413174.v3; Supplemental Fig. S2: https://doi.org/10.6084/m9.figshare.16452195.v1; Supplemental Fig. S3: https://doi.org/10.6084/m9.figshare.16413213.

ACKNOWLEDGMENTS

Because of space considerations, we were not able to cite all relevant work in this area.

GRANTS

This research was supported by Natural Science and Engineering Research Council of Canada (NSERC) Discovery Grant 06019 (to P.J.M.), Canada Foundation for Innovation Grant 34379 (to P.J.M.), Ontario Ministry of Research, Innovation and Science Grant 18-14-288 (to P.J.M.), and the American Physiological Society Arthur C. Guyton Award for Excellence in Integrative Physiology (to L.C.V. and P.J.M.). P.J.M. is a recipient of an Early Researcher Award by the Ontario Ministry of Economic Development, Job Creation and Trade. L.C.V. receives research support from National Council for Scientific and Technological Development Grants 307293/2019-0 and 431740/2018-6. M.N. was supported by the Canadian Institute of Health Research Frederick Banting and Charles Best Canada Graduate Scholarship. A.V.I. was supported by an NSERC Alexander Graham Bell Canada Graduate Scholarship and NSERC Michael Smith Foreign Study Supplement.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.N., L.C.V., and P.J.M. conceived and designed research; M.N., A.V.I., A.L.T., L.C.V., and P.J.M. performed experiments; M.N. and C.K. analyzed data; M.N., C.K., L.C.V., and P.J.M. interpreted results of experiments; M.N. prepared figures; M.N. and P.J.M. drafted manuscript; M.N., C.K., A.V.I., A.L.T., L.C.V., and P.J.M. edited and revised manuscript; M.N., C.K., A.V.I., A.L.T., L.C.V., and P.J.M. approved final version of manuscript.

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