Alpha males: muscle sympathetic discharge on beat-to-beat forearm vascular conductance

Philip J. Millar¹ and Emma O’Donnell²
¹University Health Network and Mount Sinai Hospital, Division of Cardiology, Toronto, Ontario, Canada
²Cardiovascular Research Laboratory, Department of Exercise Sciences, University of Toronto, Toronto, Ontario, Canada

Email: pmillar@uhnresearch.ca

The sympathetic nervous system is an important regulator of arterial pressure due to its dynamic effects on vascular tone and cardiac output. With respect to the former, postganglionic sympathetic neurons innervate the adventitial–medial borders of most blood vessels and when stimulated release noradrenaline (norepinephrine; along with other co-transmitters) which bind to postsynaptic α-adrenergic receptors to produce contraction of vascular smooth muscle. While this general action has long been appreciated, the beat-to-beat sympathetic modulation of vascular and haemodynamic outputs has not been studied. Understanding the actions of the sympathetic nervous system remains an important area of study, not only to determine its specific role in cardiovascular regulation but because excessive sympathetic activity is implicated in the pathophysiology of many cardiovascular diseases, including hypertension and heart failure (Floras, 2009).

In a recent issue of The Journal of Physiology, Fairfax et al. (2013a) investigated the effects of spontaneous sympathetic outflow on beat-to-beat forearm vascular conductance (FVC) in 19 healthy young men. In the supine rested state, simultaneous recordings of multi-unit muscle sympathetic nerve activity (MSNA) using microneurography and brachial artery diameter and blood velocity using duplex Doppler ultrasound, were acquired continuously for 20–35 min. Spike-triggered averaging was employed to determine beat-to-beat changes in FVC and central cardiovascular variables (total vascular conductance, cardiac output, mean arterial pressure) over the subsequent 15 cardiac cycles following each identified event (i.e. each cardiac cycle with a MSNA burst or without). Briefly, they reported that FVC exhibited a biphasic response following a MSNA burst, characterized by a modest increase during the first two cardiac cycles (peak + 3.3 ± 0.3%; Mean ± SEM) and a more robust decrease during beats 5–15 (nadir −5.8 ± 1.6%). During this time, mean arterial pressure was increased (peak + 3.1 ± 0.4%) as a result of early increases in cardiac output (beats 1–2) and subsequent reductions in total vascular conductance (beats 3–15). In comparison, following cardiac cycles without a MSNA burst, FVC was increased during beats 6–15 (peak + 1.8 ± 0.4%), highlighting the role of spontaneous sympathetic activity in maintaining vascular tone. Mean arterial pressure decreased also following non-burst cardiac cycles. The study also included a random sampling of cardiac cycles to serve as a control, which did not detect any significant beat-to-beat changes in FVC or central cardiovascular variables.

Recognizing the diverse firing characteristics of efferent sympathetic outflow the authors further probed the effect of differing MSNA burst patterns on the vasoconstrictor response. In general, FVC demonstrated a graded response to the number of consecutive MSNA bursts and the combination of burst number and size (amplitude); this relationship was less consistent with burst size alone. This graded response would be anticipated since increased postganglionic sympathetic discharge (burst number or size) should be associated with greater noradrenaline release. The detailed examination of MSNA burst pattern highlights an important methodological consideration that may limit interpretation. In this study, MSNA was measured from the peroneal nerve in the lower leg (calf) while vascular conductance was assessed in the brachial artery. Although previous research has reported a comparable mean MSNA burst frequency (and heart rate-corrected incidence) between simultaneous measurements in the arm and leg and a ‘high degree of similarity’ of integrated neurograms (Rea & Wallin, 1989), the potential for non-synchronous sympathetic outflow directed towards the upper and lower limbs should be acknowledged. It is plausible that even if multi-unit MSNA bursts are synchronous between vascular beds, the burst size may still be different. This could explain why MSNA burst size did not produce a strong graded effect on FVC, as the authors reported previously in a similar assessment of leg vascular conductance (Fairfax et al. 2013b). Alternatively, the observation that a MSNA burst produced less vasoconstriction in the forearm compared to previous reports in the leg (Fairfax et al. 2013b) may suggest a lower α-adrenoceptor sensitivity in the forearm (Pawelczyk & Levine, 2002). It would be an important consideration for future research to simultaneously measure MSNA in the upper and lower limbs, such as from the radial or median nerve.

Additionally, it is also worthwhile to consider what multi-unit MSNA burst size represents: the summation of all discharging action potentials in proximity to the recording electrode. However, a distinction readily appreciable from single-unit MSNA techniques (Macefield et al. 1994) is that a multi-unit burst can be composed of individual neurons firing once per cardiac cycle or fewer fibres with multiple firing characteristics. This difference in sympathetic discharge may be functionally important as a high incidence of irregular multiple spike firing has been associated with greater cardiac noradrenaline spillover (Lambert et al. 2011). Further determination of sympathetic vascular transduction should consider employing single-unit MSNA techniques to provide greater clarity on the effects of discharge patterns.

Fairfax et al. (2013a) also completed a follow-up study aimed at determining the contribution of α-adrenergic receptor-mediated vasoconstriction to the observed FVC responses. In seven healthy males, MSNA and FVC were recorded similarly during infusion with phenolamine, a reversible non-selective α-adrenoceptor antagonist. Inhibition of α-adrenergically mediated vasoconstriction would be expected to, and did, increase forearm blood flow, thus altering potentially the concentrations of shear stress-stimulated vasodilators known to moderate sympathetic vasoconstriction (e.g. nitric oxide). To control for this, angiotensin II was co-infused to ensure brachial blood flow was similar to a saline control condition.
Interestingly, while the observed reductions in FVC following a MSNA burst were abolished by phenolamine, the initial vasodilator response was not impacted, suggesting an alternative mechanism of action. If this observation is physiological, and not an artifact of non-synchronous limb differences in MSNA outflow, the dilator response may represent a local myogenic response, acting to increase blood flow in the face of decreasing diastolic blood pressure (the arterial baroreflex-mediated stimulus for the MSNA burst). In contrast, the authors did not observe this early dilator response in the common femoral artery (Fairfax et al. 2013b), perhaps because the largest myogenic response is thought to occur in vessels of intermediate diameter (Schubert & Mulvany, 1999). Of interest would be to examine the early vasodilator response in the forearm following a pre-mature ventricular contraction, an event known to prolong diastole and stimulate an exaggerated MSNA burst. Further work is required to confirm this observation and to determine the physiological impact and mechanism(s) responsible.

The observation that phenolamine completely abolished the beat-to-beat vasoconstrictor actions of a MSNA burst identifies a key role for $\alpha$-adrenergic receptors in resting sympathetic neurovascular transduction in young men. This finding raises important questions regarding sex-specific differences in mechanisms of blood pressure control. For example, in young men, resting MSNA is considered to be a good indicator of vascular tone, owing to its positive association with total peripheral resistance (Hart et al. 2012). In contrast, this relationship is absent in young women, suggesting that sympathetic neurovascular transduction is offset or blunted in females. Mechanisms responsible for this disparity are thought to include lower $\alpha$-adrenergic receptor sensitivity and greater $\beta$-adrenergic vasodilatation, the effects of which may be enhanced by the sex hormones, particularly oestriol (Hart et al. 2012). These effects are thought to contribute to the lower resting arterial blood pressure and greater likelihood of developing hypertensive disorders, such as orthostatic intolerance, in young women (Fu et al. 2004; Hart et al. 2012). Thus, a crucial extension of the work by Fairfax et al. (2013a) would be to repeat this study in young women. In light of the opposing sympathoexcitatory effects of oestriol and progesterone, it would be of particular interest to examine responses across the menstrual cycle. These results would add important information relevant for the delineation of sex-specific differences in sympathetic vascular control and systemic haemodynamics.

Similarly, it will be important to extend this novel analysis to patients with elevated MSNA, such as those with hypertension or heart failure. In severe cardiovascular disease MSNA burst incidence can exceed 70% (as compared to 30% found in young men; Fairfax et al. 2013a) and impairments in sympathetic vascular transduction have been reported previously (Negrão et al. 2001).

In closing, Fairfax et al. (2013a) provide important information on the temporal and graded transduction of sympathetically mediated vasoconstriction. Their novel methods to probe the beat-to-beat relationships between sympathetic outflow to skeletal muscle and local and systemic vascular and haemodynamic variables enhances our understanding of how spontaneous sympathetic activity modulates vascular tone and mean arterial pressure. Future investigations designed to examine the effects of sex, ageing, and disease will advance our knowledge of sympathetic vascular transduction, as will studies performed during acute interventions where the balance between vasoconstrictor and vasodilator influences are altered, such as exercise.

### References


### Additional information

#### Competing interests

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