

## MECHANISMS OF HYPERTENSION

# Evaluation of Sympathetic Activity in Hypertension

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## ABSTRACT

The sympathetic nervous system (SNS) plays a major role in the pathogenesis of hypertension and contributes to hypertensive target organ complications. Advances in technology over the last three decades have improved the ability to measure sympathetic nerve activity (SNA), thus enabling investigators to probe the role of SNS in the development of cardiovascular diseases. The most direct method of measuring SNA employs the technique of microneurography, which involves recording of postganglionic sympathetic action potential using a subcutaneous electrode inserted into the candidate nerve. This method allows assessment of sympathetic vasoconstrictor discharge to the peripheral circulation in hypertension and provides prognostic information in patients with cardiovascular diseases. However, application of microneurography and other methods of assessment of SNS activity, including norepinephrine spillover and imaging of SNS innervation, in routine clinical practice is limited by availability of the technique and lack of normal reference range established from large population-based data. Nevertheless, these measurements provide further insight into mechanisms of hypertension and effectiveness of various interventions in modifying sympathetic regulation of blood pressure.

**Keywords:** Hypertension, Microneurography, Muscle sympathetic nerve activity, Norepinephrine spillover, Renal denervation, Sympathetic nerve activity.

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## INTRODUCTION

The sympathetic branch of the autonomic nervous system plays an important role in regulating the function of different organs over a range of physiologic conditions.<sup>1</sup> The sympathetic nervous system (SNS) promotes hypertension

by inducing direct vasoconstriction and indirectly via activation of the renin–aldosterone–angiotensin system (RAAS).<sup>2</sup> In recent years, numerous device-based therapies have been developed to tackle SNS to reduce blood pressure (BP), particularly in patients with resistant hypertension. The effectiveness of these therapies is limited by lack of real-time assessment of sympathetic nerve activity (SNA) during the procedure to determine procedural success. This article provides a brief overview of the different modes of evaluating SNS activity that have been applied in the study of hypertension.

## OVERVIEW OF THE SYMPATHETIC PATHWAY

Afferent signals emanate from visceral organs via the afferent autonomic pathway to the central nervous system where signals are integrated and transmitted through the efferent pathway back to effector organs. Preganglionic efferent fibers have cell bodies in the brain and the intermediolateral horn of the spinal cord at the T1-L2 or L3 levels. The axon terminals of these neurons synapse in vertebral or paravertebral sympathetic ganglia with cell bodies of postganglionic neurons which project to effector organs. Synapses in the sympathetic ganglion use acetylcholine while synapses of postganglion neurons use norepinephrine (NE), with the exception of postsympathetic neurons to the sweat glands which use acetylcholine.

## MODES OF SYMPATHETIC NERVE ACTIVITY EVALUATION

### Microneurography

Microneurography was initially developed by Hagbarth and Vallbo in Upsala, Sweden around 1965 to 1966.<sup>3</sup> Since then, it has developed into a powerful investigational tool for examining the SNA to muscular and cutaneous vascular beds, both in healthy and diseased states. The technique involves externally mapping the course of a superficial nerve (e.g., peroneal, popliteal, radial, and median) by transcutaneous stimulation to evoke motor or sensory effects. In the case of the commonly used peroneal nerve, the nerve is accessed just under the fibular head with the subject in the supine or seated position. A 200 µm tungsten electrode is inserted subcutaneously into the peripheral nerve fascicle to directly record postganglionic efferent sympathetic nerve bursts to the skeletal muscle or skin with a reference electrode positioned within 2 to 3 cm.<sup>4</sup> The raw muscle

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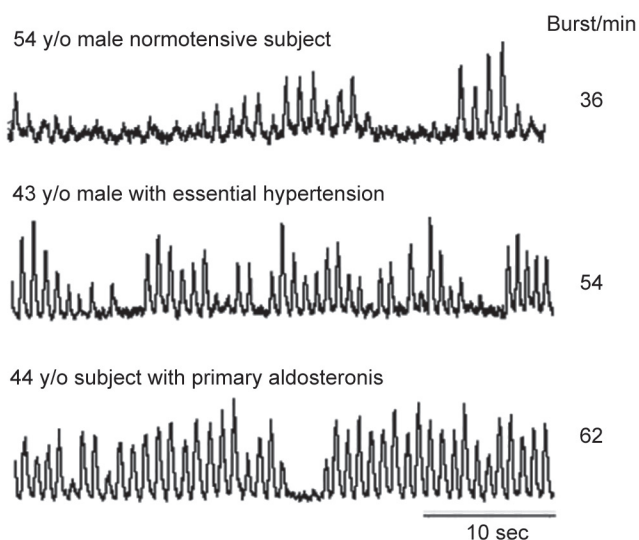


Fig. 1: Representative neurogram

sympathetic nerve activity (MSNA) signal is amplified, filtered, rectified, and integrated to produce a neurogram, as shown in Figure 1.

Microneurography provides direct and beat-to-beat measurement of central sympathetic outflow to skeletal muscle or cutaneous circulation. Muscle sympathetic nerve activity recordings have a reliable intra-individual reproducibility over time, and nerve activity and pattern obtained from different sites in the same individual are very similar.<sup>5,6</sup> The ability to quantitate muscle or skin nerve activity is also valuable.

However, microneurography only provides information regarding central sympathetic discharge to the regional vasculature innervated by the superficial nerve studied, but not to other regional vascular beds, such as renal or splanchnic circulation. This limits generalizability of SNA to the whole body due to regional variation in the control of SNA.<sup>1</sup> Despite this major limitation, total body, cardiac, and renal norepinephrine spillover positively correlates with MSNA.<sup>7</sup> Another limitation of microneurography is that burst amplitude is highly dependent on the position of the recording electrode relative to the active nerve fibers, making comparison of burst amplitude between different individuals problematic.<sup>5</sup> Microneurography also provides information on the muscle or skin nerve activity under laboratory conditions with no information on ambulatory conditions. However, microneurography can be performed repeatedly in the same human subjects over long-term duration of months or years, which allows assessment of pharmacologic or non-pharmacologic intervention of the SNS.

### Plasma Norepinephrine Measurement

Norepinephrine is the sympathetic postganglionic neurotransmitter, and measurement of this hormone has

been used as a surrogate for SNA. Plasma NE is easy to obtain but has significant limitations.

Plasma NE concentration depends on the rate of release of the neurotransmitter from sympathetic nerves as well as mechanisms related to neurotransmitter clearance from plasma.<sup>8</sup> Plasma NE concentration may be elevated in the conditions associated with decreased NE reuptake in the postsynaptic sympathetic nerve terminals, such as the use of cocaine or tricyclic antidepressants, or reduced renal clearance in the presence of renal failure, which is independent of central sympathetic outflow.<sup>9-11</sup> Thus, without accounting for these factors, plasma NE serves as a poor marker for SNA. Furthermore, plasma NE represents a small fraction of the total NE released from neurotransmitter terminals and does not take into account the regional variation of SNS regulation.<sup>1</sup> Finally, plasma NE concentration demonstrates suboptimal reproducibility, though this can be improved by obtaining the average of multiple repeated measurements in the supine position through a venous catheter that has been placed for at least 30 minutes.<sup>5</sup>

### Norepinephrine Spillover

Steady-state infusion of small amounts of tritiated NE permits the calculation of NE plasma clearance and NE spillover rate. This method addresses some of the limitations of plasma NE concentration because it accounts for NE clearance and has the ability to measure total body and organ-specific NE spillover using the following equations;

$$\text{Organ NE spillover rate} = [(NE_{\text{venous}} - NE_{\text{arterial}}) + (NE_{\text{arterial}} * T-NE_{\text{extraction}})] \times PF$$

$$\text{Total body NE spillover} = \frac{\text{Infusion rate of T-NE (dpm)}}{\text{Plasma NE specific activity (dpm/pg)}}$$

$$\text{Total body NE clearance} = \frac{\text{Infusion rate of T-NE}}{\text{Plasma T-NE concentration}}$$

where  $NE_{\text{venous}}$  and  $NE_{\text{arterial}}$  are plasma venous and arterial norepinephrine concentrations respectively,  $T-NE_{\text{extraction}}$  is the fractional extraction of tritiated norepinephrine across the organ, PF is organ plasma flow, dpm is disintegrations per minute of T-NE, and pg is picograms.<sup>12</sup>

Norepinephrine spillover does not directly measure NE release; thus it does not directly measure SNA. The rate of NE spillover is dependent on factors, such as reuptake at nerve terminals and into non-neural cells, o-methylation after reuptake into non-neural cells, and diffusion into plasma. Changes in these factors may affect conclusions drawn from this NE spillover test. Measurement of organ NE spillover requires simultaneous arterial

and venous cannulation and infusion of radiolabeled NE. Thus, it is used mainly in the research setting and not applicable in clinical practice. Alteration in NE spillover in each organ may vary depending on the condition studied. For example, renal NE spillover is elevated in obese when compared to lean individuals. In contrast, cardiac NE spillover is paradoxically suppressed in obese when compared to lean individuals while the splanchnic NE spillover was comparable in lean and obese subjects. Thus, the regional NE spillover in one organ cannot be extrapolated to other organs or to the whole body response.<sup>13</sup>

### Neuroimaging

Sympathetic activity has been investigated by neuroimaging techniques that use radiolabeled sympathetic amines (e.g., [<sup>123</sup>I] metaiodobenzylguanidine/<sup>123</sup>I-MIBG, 6 [<sup>18</sup>F] fluorodopamine, [<sup>11</sup>C]-hydroxyephedrine) to image sympathetic innervation of an organ. The heart has been the most studied organ using sympathetic imaging and <sup>123</sup>I-MIBG is the most utilized tracer. Washout of the injected <sup>123</sup>I-MIBG or heart:mediastinum ratio of MIBG radioactivity are used as a surrogate for cardiac sympathetic activity.<sup>5,14</sup> Imaging techniques are limited by the costs and limited availability. Furthermore, certain drugs including cocaine, antidepressants, some antipsychotic drugs, and reserpine were shown to interfere with MIBG uptake, thereby limiting its sensitivity and specificity.<sup>15</sup>

### Heart Rate and Heart Rate Spectral Analysis

Elevation in heart rate could be the consequence of sympathetic activation or vagal withdrawal.<sup>16</sup> Power spectral analysis of heart rate variability was thought to provide more specific information regarding vagal *vs* sympathetic control of the heart rate. A power spectrum of very low (~0.03 Hz), low (~0.05–0.15 Hz), and high (~0.3–0.4 Hz) frequency oscillations is constructed by Fourier transformation of instantaneous heart rate (converted from ECG-derived RR intervals).<sup>17</sup> The area under the low-frequency (LF) oscillation was thought to represent cardiac sympathetic activity while the area under the high-frequency (HF) oscillation represents parasympathetic activity. However, this dichotomy has been called into question<sup>18</sup> as autonomic blocking studies showed that the HF power was also increased by beta adrenergic receptor (AR) blocker propranolol and reduced by intranasal cocaine, which was not shown to have an impact on the vagal tone in humans.<sup>19,20</sup> Furthermore, results from multiple studies have shown that LF spectral oscillations were not a measure of cardiac sympathetic activity, but rather a measure of baroreflex function.<sup>18</sup>

### SYMPATHETIC NERVE ACTIVITY AND HYPERTENSION

Using the technique of microneurography and other complementary techniques, researchers have observed sympathetic overactivity in pre-hypertensive individuals, suggesting the role of SNS in the pathogenesis of hypertension.<sup>21</sup> Individuals with essential hypertension display high sympathetic nerve traffic when compared to normal controls across young, middle, and elderly age groups.<sup>1</sup> Plasma NE, cardiac, and renal NE spillover were also shown to be elevated in hypertensive individuals compared to age-matched controls.<sup>1,10,22</sup> Sympathetic nerve activity as measured by microneurography is also increased in secondary forms of hypertension, including primary aldosteronism and renovascular hypertension, which was reversed after specific treatment to eliminate secondary causes (adrenalectomy for unilateral aldosterone producing adenoma and percutaneous renal intervention in renovascular hypertension).<sup>23,24</sup> Total body NE spillover was also increased in patients with renovascular hypertension compared to age-matched controls.<sup>25</sup> Sympathetic nerve activity and BP also increased in individuals with renal failure, which improved after renal transplantation, suggesting the role of renal disease in inducing sympathetic overactivation.<sup>26–28</sup> Sympathetic innervation to the kidneys is potentially more important than SNS influence to other organs in BP regulation via increasing renal sodium absorption in the renal tubules via alpha AR, renin release through beta AR, and renal vasoconstriction through alpha AR mechanism. As a result, renal sympathetic denervation has been developed to reduce BP in patients with resistant hypertension. The procedures were designed to ablate both efferent nerve terminals and afferent nerve ending, which may, in turn, reduce overall central sympathetic discharge to other organs. However, recent studies failed to show reduction in MSNA<sup>29,30</sup> as assessed by microneurography or cardiac sympathetic activity measured by <sup>123</sup>I-MIBG after renal denervation.<sup>31</sup>

In addition to renal disease, previous studies have demonstrated increased SNA in individuals with type 2 diabetes mellitus, related to the sympathoexcitatory effects of insulin. Diabetic patients with hypertension display higher MSNA compared with hypertensive patients without diabetes.<sup>32</sup> Similarly, higher levels of SNA have been observed in patients with both metabolic syndrome and hypertension when compared to patients with hypertension alone without metabolic syndrome.<sup>33</sup> Individuals with obstructive sleep apnea (OSA) exhibit increased SNA<sup>34</sup> related to chronic intermittent hypoxia causing activation of chemoreflex. Human studies have also demonstrated a strong association between OSA and hypertension, with a recent study showing a

direct correlation between OSA severity and increase in MSNA in normotensive individuals.<sup>35,36</sup> Functional brain imaging studies have shown that compared to controls, individuals with OSA have decreased signal intensity changes and increased gray matter concentration in brainstem regions important for SNA regulation, such as the rostral ventrolateral medulla, ventral mid-brain, dorsolateral pons, and medullary raphe. Furthermore, these changes were not only directly correlated with increase in MSNA but were reversed with chronic continuous positive airway pressure (CPAP) treatment with sustained improvement of mid-brain functional magnetic resonance imaging (fMRI) changes and SNA at 12 months.<sup>37</sup> Thus, chronic intermittent hypoxia in OSA may predispose to anatomic and functional changes resulting in increase in sympathetic outflow from the brainstem center which can be ameliorated with CPAP. This increase in SNA seen in OSA is likely to be important in the recognition of OSA as an important secondary cause of hypertension and an important cause of uncontrolled or resistant hypertension.<sup>38,39</sup>

Excessive activation of SNS is not only implicated in the pathogenesis of hypertension, but also in the pathogenesis of hypertensive target organ complications. Patients with left ventricular hypertrophy (LVH) possess higher levels of SNA compared to hypertensive patients without LVH.<sup>40,41</sup> Increased SNS activity has been linked to increased mortality in patients with congestive heart failure, renal failure, stroke, and chronic obstructive pulmonary disease,<sup>42-45</sup> which may explain increased cardiovascular events in hypertensive patients with LVH.

## CONCLUSION

Different methods used in evaluating SNA have shown that SNA is increased in various types of human hypertension. There is currently no ideal method for obtaining an instantaneous snapshot of the complex systemic regional regulation of SNA. Microneurography and NE spillover are the most direct methods for assessing SNA, though these methods are not used beyond the investigational setting or in highly specialized centers. Given the regional regulation of the SNS and the limitations of the different methods of evaluating SNA, the use of complimentary methods may provide a more comprehensive assessment of SNA in humans.

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