The autonomic nervous system and its sympathetic arm play important roles in the regulation of blood pressure. Their role in the short-term regulation of blood pressure, especially in responses to transient changes in arterial pressure, via baroreflex mechanisms is well known. However, the role of the sympathetic branch in longer-term (days, months, and years) blood pressure regulation has been a focus of debate since at least the 1970s. Our goal in this Hypertension Highlights is to summarize and integrate our ideas on the role of the sympathetic nervous system in long-term blood pressure regulation in humans. We will focus primarily on information from studies conducted in humans and use data from animal studies to emphasize key points. In this context, we want to address 4 key questions. The first 3 focus on our recent work. The final issue is an emerging one and more speculative. First, what is the role of the sympathetic nervous system in long-term blood pressure regulation in young (18- to 40-year-old) normotensive men? Second, does the role of the sympathetic nervous system in long-term blood pressure regulation change as a function of age in men? Third, does sex influence the role of the sympathetic nervous system in long-term blood pressure regulation, and are sex differences modified by aging? Fourth, are we entering an era of sympathetically driven hypertension? Before we address these questions, we share a few thoughts about how to assess the overall activity of sympathetic nerves in humans.

Assessment of Sympathetic Activity in Humans

Various approaches used to assess sympathetic activity in humans have been reviewed recently by Grassi. We focus primarily on studies that use direct measurements of muscle sympathetic nerve activity (MSNA) as an overall marker of sympathetic outflow in humans and, to a lesser extent, on studies that use whole body and regional norepinephrine (NE) spillover and also plasma NE. There are advantages and disadvantages with each of these approaches that have been reviewed in detail.

In resting humans these 3 approaches are typically well correlated, and conclusions made with 1 technique are generally supported by studies using 1 of the other 2 approaches. There are 2 major caveats to this point. First, the correlations between MSNA and other indices of sympathetic activity have been most clearly demonstrated in young healthy men. Second, during nonresting conditions (eg, exercise and mental stress), there can be highly specific changes in sympathetic activity to selected tissues with no changes in other tissues. For example, MSNA after arousal stimuli (eg, startling the subject with a loud noise) either does not change or falls for a few bursts in some subjects, and MSNA can fall during mental stress. However, skin sympathetic activity increases during both arousal and mental stress. Skin sympathetic activity also increases at the onset of static exercise before any rise in MSNA.

MSNA as an Index of Overall Sympathetic Activity in Resting Young Men Has a Number of Attractive Features

Most of the studies from our laboratories and those of many colleagues have used MSNA as the primary index of sympathetic activity in humans. MSNA is a direct measure of vasoconstrictor neural activity to skeletal muscle, a vascular bed of which the sheer size makes it central to hemodynamic control both at rest and during daily activities. MSNA is also reproducible in a given subject over time. However, MSNA increases with age, such that measurements in a given individual increase after a period of several years. As noted above, MSNA also correlates well with other markers of sympathetic neural activity at rest, at least in young men. Most importantly from our perspective, measurements of MSNA can be combined with other hemodynamic measurements to paint an overall picture of the relationship between sympathetic neural activity and blood pressure regulation. In addition, because it has both rapid time resolution and is also stable within a given subject from day to day, MSNA can be used to address questions about both short- and long-term blood pressure regulation.

What Is the Role of the Sympathetic Nervous System in Long-Term Blood Pressure Regulation in Young Normotensive Men?

In normotensive young men, MSNA measured during rest can vary 5- to 10-fold, and there is substantial overlap in the
Our main findings (summarized in Figure 1) are that, in young men, there is an inverse relationship between MSNA and CO in the subjects. This reciprocal relationship helps explain why blood pressure is not consistently higher in subjects with high levels of MSNA. (Adapted from Charkoudian et al.)

This means that subjects with high levels of MSNA have lower COs and vice versa. At first we were surprised by the range of COs that we observed, but review of the literature indicated that the values that we observed were similar to those found using invasive techniques by Julius and Conway in their classic article from 1968.26

Importantly we also found that, in young men, TPR is highly correlated with resting MSNA.5 This observation is also consistent with studies in men showing that fall in blood pressure seen during ganglionic blockade with trimethaphan (so-called autonomic support of blood pressure) is proportional to resting MSNA and plasma NE concentrations (Figure 2).14

Next we demonstrated that the impact of high levels of MSNA on blood pressure in young men is blunted by reduced vasoconstrictor responsiveness to NE.7 Whether the inverse relationship between baseline MSNA and adrenergic sensitivity reflects receptor downregulation in response to high MSNA or whether high levels of MSNA are a compensatory response to low number or responsiveness of postjunctional receptors is not known. If the former were responsible for the inverse relationship between MSNA and adrenergic sensitivity, this would suggest that baroreflex control of MSNA might be blunted in subjects with high levels of MSNA. In the latter case, it would suggest that the high levels of MSNA were an appropriate baroreflex-mediated response to an inherently lower level of adrenergic receptors.

Another aspect of our original hypothesis regarding interindividual variability in MSNA was that the absence of a relationship between MSNA and blood pressure in young men was because of tonic NO release from the vascular endothelium. The idea was that NO release (and subsequent vasodilation) proportional to the level of sympathetic activity offsets the vasoconstriction caused by the MSNA. The best evidence for this came from studies showing that plasma nitrate levels are correlated with baseline MSNA.27 To test this hypothesis, we performed systemic dose-response studies with the NO synthase inhibitor N\textsuperscript{G}-monomethyl-L-arginine in normotensive volunteers. We found that the rise in BP was greater in subjects with high levels of baseline MSNA.7 This was especially marked with the lower doses of NG-monomethyl-L-arginine.

Interestingly, the hemodynamic mechanisms for the greater increase in blood pressure in the high-MSNA group were related to CO because TPR responses to NO synthase inhibition were similar between high- and low-MSNA groups. The high-MSNA group had a lower CO to begin with and showed a smaller decline in CO during NO synthase inhibition. In this context, these data suggest that humans with high levels of baseline MSNA are at higher risk for the development of hypertension if they experience an even modest reduction in endothelial function. A major limitation to this interpretation is that systemic administration of N\textsuperscript{G}-monomethyl-L-arginine causes a potentially confounding increase in blood pressure and a baroreflex-mediated inhibition of MSNA.

An important final point is that the sources or cause of the interindividual variability in MSNA are unknown. Identical twins demonstrate similar values, suggesting a strong genetic component, but neither the physiological nor potential genetic mechanisms responsible for the interindividual variability in MSNA have been identified.28
Does the Role of the Sympathetic Nervous System in Long-Term Blood Pressure Regulation Change in Aging Men in the Absence of Diseases and Conditions Known to Affect Blood Pressure?

Whole body sympathetic neural activity increases with aging. This is reflected by increases in MSNA, whole body NE spillover, and increases in plasma NE levels. In addition, indices of sympathetic activity, especially MSNA, become more linked to blood pressure as a person ages. In general, MSNA increases by 1 burst per minute per year, starting around age 30 years (Figure 3). This means that MSNA in 60- to 70-year-old subjects is roughly twice as high as it is in 20- to 30-year-old subjects, but a wide range of MSNA is still seen in older subjects.

In healthy older subjects free of coexisting disease, there are several possible explanations for the rise in sympathetic activity with aging. First, there might be a loss of central inhibitory pathways in the brain stem. Central sympathetic disinhibition is clearly seen in animal models of diseases like congestive heart failure, but it is unclear whether this occurs with healthy older humans without overt cardiovascular disease. However, there is evidence for increased central NE spillover in aging humans. Second, the large blood vessels become less distensible with aging, and this might cause a given level of blood pressure to evoke fewer baroreflex-mediated afferent signals and less reflex inhibition of sympathetic outflow. Third, aging (even in the absence of weight gain), is associated with increases in body fatness, and there is evidence that visceral adiposity is associated with increased levels of sympathetic activity. This might be because of inflammatory mediators or substances released by visceral fat cells that stimulate sympathetic outflow at the level of the central nervous system. However, all of these potential mechanisms are speculative, and there is at least some evidence for all of them in humans and animal models.

In spite of the increased sympathetic activity with aging, the relationship between MSNA and blood pressure remains modest in older men. One factor that limits the impact of the increased levels of sympathetic activity on blood pressure is age-related blunting of adrenergic sensitivity. In older men, there is clear evidence in the forearm and leg that vasoconstrictor responsiveness (sensitivity) to adrenergic stimulation is reduced, and postjunctional α-2 sensitivity appears reduced more than α-1 sensitivity. In addition, infusions of phenylephrine after ganglionic blockade (to block baroreflex buffering of blood pressure) cause blood pressure to rise 50% less in older versus younger men.

We attempted to study the individual relationships among MSNA, CO, and TPR in healthy older men to determine whether the relationships that we saw in younger men were similar or altered in a systematic way with aging. In contrast to younger subjects, we could find no overall pattern of relationships among MSNA, CO, vascular resistance, and/or vascular adrenergic responsiveness in older men, indicating that the balances seen in younger men were absent in healthy men. However, it is interesting to note that autonomic support of blood pressure is greater in older men compared with younger men. Although some of this is because of a lower intrinsic heart rate in older men, it also suggests that the increase in sympathetic activity is not completely offset by age-related reductions in adrenergic sensitivity. Another possible factor is that healthy older men have reduced blood volume, which might lead to a larger fall in blood pressure after ganglionic blockade, and they can also have reduced endothelial function, which might further modify the relationships among MSNA, CO, and TPR. Taking into account all available information, we speculate that if aging affects different mechanisms in different subjects, systematic relationships between and among factors are more difficult to detect.

Does Sex Influence the Role of the Sympathetic Nervous System in Long-Term Blood Pressure Regulation and Are Any Sex Differences Modified by Aging?

With our observations in men as a background, an important question was whether the relationships (or lack thereof) among MSNA, CO, TPR, and adrenergic sensitivity are the same or different in women. When we studied young healthy women we again found a wide range of MSNA, but there was no relationship between MSNA and blood pressure. There was also no relationship between MSNA and CO and, most surprisingly, no relationship between MSNA and TPR (Figure 4). This suggests that the physiological “strategy” used to regulate blood pressure in young women is fundamentally different from that in young men.

In addition, the lack of relationship between MSNA and TPR in young women is consistent with observations suggesting that autonomic support of blood pressure is lower in...
young women than in young men. Unfortunately, there are no clear data on the relationship between MSNA and autonomic support of blood pressure in young women. However, based on the range of values typically seen in young women, and assuming a relatively normal distribution of MSNA, it is reasonable to speculate that the interindividual relationship between MSNA and autonomic support of blood pressure is blunted or absent in young women compared with young men.

What might explain the absence of a relationship between MSNA and TPR in young women? One explanation is that postjunctional β₂ receptors on the vascular smooth muscle and vascular endothelium in younger women are stimulated by NE and blunt the α-adrenergic vasoconstrictor effects of the sympathetic nerves. Indeed, Kneale et al showed that the vasoconstrictor responses to brachial artery infusions of NE are blunted in young women in comparison with young men. However, when NE dose-response curves were performed after β-adrenergic blockade with brachial artery administration of propranolol, vasoconstrictor responses to NE were augmented in the women and unchanged in the men. Thus, the forearm vasoconstrictor responses to NE were similar in men and women after propranolol. In this context, β₂ vasodilation in the forearm has both an endothelial and

**Figure 3.** Relationship between baseline MSNA and mean arterial pressure in a large group of young men, young women, older men, and older women. In both men and women <40 years of age, no relationship between MSNA and mean arterial pressure was seen. By contrast, in the older men there was a modest relationship between MSNA and blood pressure. This positive relationship was more pronounced in the older women. (Reprinted with permission from Narkiewicz et al.)

**Figure 4.** Relationship between MSNA and TPR in a group of normotensive young male subjects (left) and a group of normotensive young female subjects (right). The relationship between MSNA and TPR seen in the young men was absent in the young women. (Reprinted from Hart et al.)
nonendothelial component, and \(~30\%\) to \(40\%\) of the vasodilator effects are because of endothelial release of NO.\(^{45}\)

What is the situation in older women? As is the case for older men, MSNA rises with age, and the relationship between MSNA and blood pressure becomes stronger with aging.\(^{25}\) In addition, the strength of this relationship is greater in older women than in older men (Figure 4). However, there is little definitive data on why blood pressure is more strongly related to sympathetic activity in older women than men. This is important because it is well known that the incidence of hypertension rises after menopause in women.\(^{46}\) However, it is not known whether autonomic support of blood pressure is greater in older women than younger women or in their male counterparts. In addition, there are no data on adrenergic sensitivity in older women, and there are no comprehensive measurements of CO and MSNA in older women.

However, it is tempting to speculate that the loss of endothelial function seen postmenopause contributes to the more robust relationship between MSNA and blood pressure in older women.\(^{47}\) In addition, if aging is associated with a loss of \(\beta_2\)-mediated vasodilator function in women and these receptors normally blunt the relationship between MSNA and vascular resistance in young women, their loss could contribute to the positive relationship between MSNA and blood pressure in older women.

In summary, the relationship between MSNA and blood pressure differs in younger and older women and in comparison to their male counterparts. Understanding these differences may help explain why younger women are more prone to orthostatic intolerance and why older women are more subject to hypertension.

**Are We Entering an Era of Sympathetically Driven Clinical Hypertension?**

Obesity and weight gain are conditions associated with increased MSNA (Figure 5).\(^{36,48-50}\) Obesity is also a major risk factor for obstructive sleep apnea, and obstructive sleep apnea appears associated with increases in both blood pressure and MSNA.\(^{51-53}\) In addition, similar results are found when NE spillover techniques are used to assess sympathetic activity in these populations.\(^{54}\) These factors appear to add to and perhaps amplify any age-related increases in MSNA. They are also associated with increased vascular stiffness and reduced endothelial function, which would limit baroreflex buffering of MSNA and NO-mediated buffering of vasoconstriction mediated by MSNA.\(^{1,34,42}\) This constellation of conditions, which is increasing in both developed countries and countries with emerging economies, is also associated with physical inactivity and/or metabolic disorders, such as type 2 diabetes mellitus and changes in blood lipids. Importantly, these factors would tend to reinforce the changes in MSNA and vascular function highlighted above and lead to higher blood pressure.\(^1\) In addition, there is evidence suggesting that blood pressure reactivity and chronic mental or social stress are related to the long-term risk of hypertension in humans.\(^{55,56}\)

There is also emerging evidence that obese humans with mild hypertension have increased autonomic support of blood pressure.\(^{57-59}\) This general idea is also supported by the NE spillover data reviewed by Esler et al,\(^{54}\) showing that sympathetic outflow to skeletal muscle and kidney is increased 2- to 3-fold in obese subjects. It is also supported by data from overfeeding studies in dogs showing that suppression of sympathetic neural activity in obese hypertensive animals by prolonged baroreflex stimulation lowers blood pressure, and similar data are emerging in humans with so-called resistant hypertension.\(^{60,61}\)

There is also evidence that the increased sympathetic activity seen in resistant hypertension is related in part to the kidney because radiofrequency denervation of the kidney lowers blood pressure in patients with resistant hypertension.\(^{62}\) In this context, if MSNA reflects renal sympathetic nerve activity, then increases in the latter may play a causal role in promoting hypertension by increasing sodium retention by the kidneys. Although increases in renal sympathetic nerve activity would be expected to increase arterial pressure, this might not happen if there were reductions in renal adrenergic vascular responsiveness, increased renal NO production, or other offsetting mechanisms. However, the interactions between the sympathetic nervous system and kidney in the long-term regulation of blood pressure in both normotensive and hypertensive humans remain unclear.\(^{53-65}\)

Blood pressure increases with salt loading in rats are amplified by barodenervation arguing for a reinforcing interaction\(^{65}\) between increased sympathetic outflow and renal sodium retention. By contrast, renal denervation does not blunt the sustained reductions in arterial pressure caused by long-term activation of baroreflexes.\(^{63,64}\) Clearly, the interactions and cross-talk between multiple redundant regulatory responses make it especially challenging to design definitive
experiments on this topic in humans. It is also possible that vascular beds that are hard to study with current approaches contribute to the relationship between sympathetic neural outflow and blood pressure. For example, the splanchnic bed is a potential volume reservoir, and long-term changes in vascular tone in this region could influence blood pressure.

Summary and Future Directions
We have attempted to summarize and highlight key elements of our recent thinking on the role of the sympathetic nervous system in long-term blood pressure regulation in humans. Our goal has been to use the marked interindividual variability in MSNA seen in humans to begin to explore this topic. In normotensive young men, MSNA is proportional to TPR but the effects of this relationship on blood pressure are limited by a reciprocal relationship between MSNA and CO and the fact that adrenergic sensitivity is blunted in subjects with high levels of MSNA. In young women these relationships are absent, and there is some evidence that β2-adrenergic receptor-mediated vasodilation limits the relationship between sympathetic activity and vascular resistance.

In older men the average level of MSNA is increased and modestly related to blood pressure, but there is still wide interindividuation variability in MSNA and no clear relationships among MSNA, CO, and vascular resistance. In older women, the average level of MSNA is also increased and more strongly related to blood pressure. This suggests that any effect of reproductive hormones and β2-adrenergic receptor-mediated vasodilation limits the relationship between sympathetic activity and vascular resistance.

When we consider our findings and those of others in the context of emerging demographic trends for conditions like obesity, sleep apnea, physical inactivity, and perhaps “social stress,” we propose that an era of sympathetically driven hypertension exacerbated by the factors discussed above is here.

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References


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