Sympathetic Neural Regulation of Blood Pressure: Influences of Sex and Aging

Sex and age have important influences on sympathetic neural control of blood pressure in humans. Young women are relatively protected against risk of hypertension due to greater peripheral vasodilator influences compared with young men and older people. This protective effect is lost at menopause. Older men and women have higher sympathetic nerve activity and tighter coupling between SNA and blood pressure, contributing to the increased risk of hypertension with aging.

It is well recognized that young women tend to have lower blood pressure, and less risk of hypertension, compared with men of similar age. As people age, both blood pressure and risk of hypertension tend to increase, and this trend is particularly marked in women around the time of menopause. Less well understood are the mechanisms contributing to these differences and to the changes that occur with aging that may be different between the sexes. Over the past decade, evidence has been accumulating that, to understand integrative mechanisms of blood pressure control, it is important to understand interindividual differences in these mechanisms and how those variables relate to each other in the integrated physiological system.

The goal of the present discussion is to review recent evidence for differences between men and women in mechanisms controlling blood pressure via the autonomic nervous system. In particular, we will focus on evidence regarding interindividual variability in sympathetic neural and hemodynamic variables in men and women, and how these variables form an integrated balance that represents the evolving framework for blood pressure regulation over the lifespan.

Autonomic Control of Blood Pressure: Short-Term Transients

In terms of cardiovascular control, the autonomic nervous system is best known for its control of blood pressure on a beat-to-beat basis and over seconds to minutes. The arterial baroreflex responds to rapid changes in stretch of mechanosensitive afferents in key areas of the circulation (carotid sinus, aortic arch, pulmonary great vessels, and atria/ventricles). These stretch-sensitive baroreceptors send afferent information to central nuclei involved in efferent control of sympathetic and parasympathetic (vagal) neural output. Transient changes in blood pressure, therefore, result in reciprocal changes in sympathetic and vagal activity to “buffer” (minimize) the potential changes in arterial pressure that might occur. A common physiological example is orthostasis (upright posture). In humans, standing up from a supine or sitting posture increases the hydrostatic column of blood between the head and the feet, thereby increasing the influence of gravity to decrease venous return. The baroreflex senses decreases in arterial pressure or pulse pressure at the level of the heart and responds by withdrawing vagal activity (increasing heart rate) and increasing the activity of cardiac and vascular sympathetic nerves (leading to further increases in heart rate as well as stroke volume and vasoconstriction to increase peripheral vascular resistance). These adjustments serve to maintain arterial pressure in the face of the decreases in venous return caused by gravity. With no reflex adjustments, standing up would decrease arterial blood pressure. Indeed, in patients without functioning baroreflexes (such as in certain forms of autonomic dysfunction), it is impossible for them to stand without fainting due to excessive drops in arterial pressure.

In addition to the baroreflex, other acute reflex adjustments in response to exercise and environmental stressors are essential to the normal maintenance of arterial pressure and to the successful performance of activities of daily living. The chemoreflex, mechanoreflex, and metaboreflex are important modulators of autonomic tone and blood pressure in response to exercise and environmental stressors such as hypoxia/hypercapnia (25, 26, 36). Without appropriate changes in autonomic tone and blood pressure in response to these stressors, humans would not be able to function in their day to day lives.

Long-Term Role of Sympathetic Neural Mechanisms in Blood Pressure Regulation and Importance of Interindividual Variability

Whether the sympathetic nervous system is involved in long-term blood pressure control has been a matter of debate for many years (see Ref. 43 for a thorough review). Early studies that focused on
sino-aortic denervation in animals demonstrated that the long-term level of blood pressure was not altered (10). Furthermore, when the procedure was performed in hypertensive animals, blood pressure was not reduced (42).

However, more recent data suggest that there is an important role for autonomic control in long-term blood pressure regulation. In humans with baroreflex failure (due to carotid denervation or central nervous system degenerative disorders), long-term resting blood pressure becomes quite labile, and these patients tend to become hypertensive in the long term (23). These patients also have elevated resting sympathetic nerve activity and almost no vagal control of heart rate. Data such as these suggest that autonomic neural mechanisms are important in the control of resting blood pressure in humans. Additionally, it has been suggested that central neuronal plasticity associated with the original sino-aortic denervation studies may have confounded some of the original conclusions regarding the autonomic nervous system (42).

Other recent studies have provided additional mechanistic insight into the potential long-term role of the autonomic nervous system in blood pressure regulation. In dogs, carotid baroreflex stimulation causes sustained decreases in systemic blood pressure (30, 31). Data from human subjects provide very strong translational evidence that afferent carotid baroreceptor stimulation (via a device implanted at the carotid sinus) causes sustained decreases in blood pressure in people with chronic idiopathic hypertension. Concomitant to a reduction in blood pressure, carotid baroreceptor stimulation also decreased central sympathetic outflow and increased parasympathetic tone (22), demonstrating an important link between basal autonomic tone and long-term blood pressure control.

Further evidence for the importance of resting sympathetic outflow in long-term blood pressure determination comes from early studies investigating whether sympathectomy improved blood pressure in hypertensive patients. Surgical interruption of spinal sympathetic outflow effectively decreased blood pressure in hypertensive patients (39). However, this treatment had predictable deleterious side effects, including severe orthostatic hypotension. Along these lines, other treatments that interrupt the outflow of sympathetic nerve activity also affect long-term blood pressure in humans. For example, pharmacological inhibition of brain nuclei, which control sympathetic neural function, results in reduced SNA and decreases in blood pressure in hypertensive men and women (57).

Although both sympathetic and parasympathetic nervous systems have important roles in blood pressure control, in this review, we focus primarily on the role of the sympathetic system in human blood pressure regulation. Sympathetic nerve activity can be measured directly in humans via microneurography. Developed in the 1960s in Uppsala, Sweden, this technique allows for direct measurement of electrical activity in postganglionic sympathetic nerves using a minimally invasive, percutaneous approach (49, 52).

For cardiovascular physiologists, the most common measurements are of muscle sympathetic nerve activity (MSNA), which provides important information regarding blood pressure control for several reasons. First, sympathetic nerves innervating skeletal muscle are vasoconstrictor in nature, and therefore increases and decreases in their activity can be related to changes in vasoconstriction and peripheral vascular resistance. Second, since skeletal muscle blood flow represents such a large percentage of cardiac output in resting humans, the sympathetic innervation of this circulation is highly relevant to overall blood pressure regulation. Third, in resting humans, MSNA is representative of the activity of sympathetic nerves innervating other important vascular beds, including the heart and the kidney (55, 56), as measured by the more invasive norepinephrine spillover technique, and to whole body norepinephrine spillover (representing whole body sympathetic nerve activity). Finally, MSNA is very reproducible in a given subject over time (with the caveat that MSNA increases with age (13, 38, 40)).

Although MSNA has proven to be a strong technique for mechanistic assessment of sympathetic neural mechanisms in humans, a challenge to clinical interpretation has been that resting values for MSNA exhibit a wide interindividual variability among healthy normotensive humans. MSNA can vary as much as 5- to 10-fold in a given group of young healthy subjects (8, 20, 50). Surprisingly, this variability is not correlated with arterial blood pressure in young people. Thus, although MSNA is vasoconstrictor in nature and stimuli that increase SNA will acutely increase blood pressure, in terms of long-term, resting values, people with higher MSNA do not necessarily have higher blood pressure than people with lower MSNA. Over the past decade, the study of this apparent paradox has provided important insight into mechanisms of blood pressure regulation in young and older humans, and into differences between the sexes in these mechanisms (8, 9, 18–21, 38).

**Sympathetic Neural-Hemodynamic Balance in Young Men**

As mentioned above, several studies have shown variability of 5- to 10-fold in MSNA among groups of otherwise healthy, similar, and normotensive...
young men (8, 9, 46, 50). In these groups, MSNA is directly related to total peripheral vascular resistance (TPR), supporting the idea that MSNA is a good index (in young men) of total body “net” sympathetic vasoconstrictor tone (8, 20). The question of “why” MSNA is therefore not related to blood pressure in young men was answered by application of the hydraulic/cardiovascular equivalent of Ohm’s law (MAP = cardiac output × TPR). We found that MSNA is inversely related to cardiac output in resting, healthy young men (8, 20). Therefore, the pressor effect of higher MSNA in this group is offset by the depressor effects of a lower cardiac output. Additional central hemodynamic factors are also important in this relationship. For example, indexes of aortic wave reflection, including aortic augmentation index, are positively related to resting MSNA in young men (7).

A further aspect of this neural-hemodynamic balance is the interaction between sympathetic neural activity and vasoconstriction at the level of the peripheral vasculature (9). In subjects with higher MSNA, peripheral vascular responsiveness to norepinephrine was decreased compared with people with lower MSNA. This phenomenon likely also contributes to the balance of factors that maintain normal blood pressure across young men with a range of values for resting sympathetic nerve activity.

**Sympathetic Neural-Hemodynamic Balance in Young Women**

Before menopause, women tend to have lower blood pressure and less risk of hypertension compared with men. Indeed, the entire continuum of blood pressure regulation appears to be “shifted” to lower values in women, and the prevalence of hypotensive disorders (such as orthostatic intolerance and orthostatic hypotension) are greater in young women than in young men (44).

Several studies suggest important differences between young men and women in acute/transient responses, which might contribute to some of the overall differences in blood pressure regulation between the sexes. For example, Carter and colleagues reported differences between men and women in terms of acute responses to sympathoexcitatory challenges including orthostasis and mental stress (4, 58, 59). Sympathetic neural responses to tilt, and their relationships to blood pressure, were different between men and women, including lower coherence between MSNA and diastolic pressure during orthostatic stress in women (58). However, other studies have not found differences between men and women in terms of sympathetic neural responses to orthostasis (16). Although evidence suggests influences of female reproductive hormones on sensitivity of baroreflex control of sympathetic activity (33, 34), there does not appear to be a consistent sex difference in this variable in young adults (51).

During mental stress, MSNA responses were similar between men and women, but the resulting vascular effects are often different, with women tending to have more vasodilation and/or smaller pressor effects compared with men (4, 59). This suggests altered neurovascular transduction, which may be similar in mechanism to the sex differences in long-term blood pressure regulation, as described below. Additionally, resting MSNA changes over the course of the menstrual cycle and with oral contraceptive hormones (3, 33, 34). This phenomenon appears to be related primarily to changes in circulating estradiol and the ratio of estradiol to progesterone (3), although the dynamic interactions among estradiol, progesterone, and MSNA remain to be completely understood.

In terms of neural and hemodynamic factors contributing to long-term blood pressure regulation, we originally hypothesized that the balance of factors seen in young men (e.g., MSNA-cardiac output relationship) would be shifted to lower absolute values in women but would otherwise, qualitatively, be similar to those seen in men. We were therefore surprised to observe a complete lack of relationship between MSNA and cardiac output (and similarly no relationship between MSNA and TPR) in a group of healthy young women (20). As with previous studies in young men, women showed no relationship between MSNA and arterial pressure, such that women with higher MSNA had similar blood pressures to women with very low MSNA.

Previous evidence suggested that the transduction of sympathetic nerve activity into vascular resistance (that is, the physiological “translation” of the norepinephrine signal into vasoconstriction) might be different between men and women due to different subpopulations of adrenergic receptors on the vascular smooth muscle (28). Specifically, Kneale and colleagues demonstrated that women showed greater β-adrenergic vasodilation compared with men. More importantly (with regard to the potential for hypertension), the extent of vasoconstriction for a given amount of norepinephrine was less in women than in men. When a β-adrenergic antagonist was administered, the vasoconstrictor response to norepinephrine became similar to that seen in men. The authors therefore concluded that β-adrenergic vasodilation was an important factor offsetting sympathetic vasoconstriction in women and possibly a contributing factor to the lower blood pressures seen in women (28).
We subsequently evaluated whether β-adrenergic receptors were important at the systemic level in explaining the relationships among sympathetic nerve activity, arterial pressure, cardiac output, and vascular resistance in young women (19, 20). We measured MSNA, cardiac output, and arterial pressure in young men and young women before and after β-adrenergic blockade with systemic propranolol. Before β blockade, young women showed no relationship between MSNA and TPR (19, 20). During β blockade, the MSNA-TPR relationship became significant and positive.

These data indicated that, in women, β receptors are important on a systemic scale in offsetting the relationship between sympathetic nerve activity and peripheral vasoconstriction. Interestingly, β blockade had no effect on the MSNA-TPR relationship in young men, suggesting that there are not enough vasodilating β receptors in young men to substantially affect this relationship (19).

As summarized in FIGURE 1, these data strongly suggest that β-adrenergic receptors are important in modulating the transduction of sympathetic nerve activity into peripheral vascular resistance in young women. These influences may represent important mechanisms in the maintenance of normal blood pressures in healthy young women and may contribute to the lower incidence of hypertension compared with other groups.

In addition to sex differences in peripheral vascular mechanisms, recent data indicate important influences on central aortic pressure dynamics (6, 7, 18). In contrast to young men, young women exhibit inverse relationships between resting MSNA and indexes of aortic wave reflection (7). For example, women with higher MSNA tended to have lower aortic augmentation index. These factors potentially contribute to the balance that keeps arterial pressure constant in women across a range of MSNA values and that may keep women relatively protected from hypertension before menopause. In this context, systemic β-adrenergic blockade increased aortic wave reflection indexes in both men and women, but the effect was more pronounced in women, suggesting a greater contribution of β-mediated vasodilation to resting aortic wave reflection characteristics in the women (6).

**Sympathetic Neural-Hemodynamic Balance in Older Men**

Resting blood pressure tends to increase with age, and there appear to be significant contributions of sympathetic neural mechanisms to this increase. Aging has two important effects in terms of the relationship between MSNA and blood pressure. First, MSNA increases with age. In general, MSNA is considered to increase at the rate of ~1 burst·min⁻¹·yr⁻¹ (13), although a range of age-related increases have been reported (38, 40), consistent with the interindividually variability inherent in resting MSNA. Second, the lack of relationship between MSNA and arterial pressure that is seen in younger humans is transformed into a significant positive relationship starting approximately in the fifth decade of life (38). That is, SNA contributes more to blood pressure such that older people with higher MSNA tend to have higher blood pressure compared with people with lower MSNA.

Why does sympathetically mediated vasoconstriction become a more important contributor to blood pressure in older men? It appears that there is a lack of balance between neural and hemodynamic factors, which leads to a stronger link between sympathetically mediated vasoconstriction and resting blood pressure (21, 24, 38). However, the mechanisms involved are complex, and some aspects of the sympathetic-vascular relationship are somewhat counterintuitive in this regard. For example, vascular α-adrenergic responsiveness is decreased in older men (12, 47), and the level of resting MSNA is not related to TPR (or to cardiac output) (21).

Furthermore, older men do not demonstrate the inverse relationship between MSNA and vascular...
adrenergic responsiveness that was observed in younger groups (21). It is possible that circulating hormones such as vasopressin, angiotensin, and more locally acting substances such as endothelin may play a more prominent role in maintaining basal vascular tone in older men.

Despite the fact that MSNA is not related to peripheral vascular tone (TPR), tonic levels of sympathetic activity are related to resting blood pressure in older men (21, 38). Specific mechanisms for this link remain unclear, but ganglionic blockade studies have shown a stronger reliance on autonomic support of blood pressure in older compared with younger men (24). Also, Vianna and colleagues (53) showed that the average change in blood pressure following an individual burst of MSNA was smaller in older men (and women) compared with younger people. However, the drop in pressure following a cardiac cycle without a burst was greatest in the older men, showing a stronger dependence on SNA for maintenance of pressure in that group (53).

Since MSNA is a good index of sympathetic activity to other organ systems, including the kidney (56), one possibility is that increased renal sympathetic activity may result in increased blood pressure due to renal mechanisms and increased circulating levels of vasoconstrictor hormones that result from renal sympathoexcitation. Other possible mechanisms include increased local vasoconstrictor substances such as endothelin that might be indirectly linked to the prevailing level of sympathetic nerve activity. However, further work is clearly required to provide greater mechanistic insight into why aging increases the risk of developing hypertension and other cardiovascular diseases in men.

**Sympathetic Neural-Hemodynamic Balance in Postmenopausal Women**

As in men, aging is associated with higher MSNA and a stronger link between sympathetic nerve activity and blood pressure in women, a phenomenon that is particularly marked after menopause (38). Narkiewicz and colleagues concluded that MSNA increases at a faster rate in women than in men with age (38), although this is not a universal finding (40). It is, however, a consistent finding that older age is associated with higher MSNA in both men and women. However, in older women, the direct relationship between sympathetic outflow and blood pressure appears to be mediated via different mechanisms compared with that in older men. For example, unlike in older men, MSNA was directly related to TPR in postmenopausal women (19). However, there was no relationship between MSNA and cardiac output in this cohort of women (19). Consequently, a combination of high tonic vasoconstrictor drive and the lack of ability to counterbalance this vasoconstrictor drive via changes in cardiac output results in blood pressure becoming directly related to SNA. It is unclear why cardiac output does not balance the vasoconstrictor effect of MSNA (as it does in young men). One possibility is that this might be related to reductions in left ventricular compliance and thus stroke volume, which occurs with age and sedentary lifestyle (17, 45).

Why does MSNA become directly related to blood pressure in older women? It appears that a change in the role of β-adrenergic receptors in maintaining vascular tone is an important factor. In this context, the ability of the β-adrenergic receptors to offset norepinephrine-mediated vasoconstriction that is seen in younger women (19, 28) disappears in postmenopausal women (19). In postmenopausal women, MSNA was directly related to TPR both before and during β-blockade, suggesting that the ability (in young women) of the β-adrenergic receptors to buffer the transduction of MSNA into vasoconstrictor tone at rest is lost at menopause (19). Whether this change in the role of the β-adrenergic receptors is related to a decrease in circulating female sex hormones or to some other age-related process is unclear. However, the fact that the β-receptor modulation occurs in young women (and not young men) and disappears around menopause points to an important role for the female reproductive hormones in this process.

In postmenopausal women receiving transdermal estrogen replacement therapy, a reduction in arterial pressure and MSNA has been observed (54). This may be related to the effects of estrogen on the vascular β-receptors and nitric oxide availability. Estrogen is known to upregulate nitric oxide-mediated vasodilation, in part via its action on the NOS enzyme (for detailed review, see Ref. 32). β-Adrenergic vasodilation is mediated in part by nitric oxide and also may be upregulated by estrogen (see above). Specific details of the links among these mechanisms remain to be investigated. Interestingly, some evidence indicates that vascular β-adrenergic receptor sensitivity is also attenuated in hypertensive individuals (48). Therefore, changes in the sensitivity of the β receptors to norepinephrine may explain why the incidence of hypertension increases in postmenopausal women and becomes similar to (or sometimes greater than) that in men of the same age (2, 27). In this context, the role of other sex steroid hormones such as progesterone and testosterone in modulating sympathetic and vascular interactions is unclear but should not be ignored. This is particularly true in older men where the gradual decline
in circulating levels of testosterone (37) could play a role in changes in sympathetic nerve activity and its end-organ effects over time.

Changes in β-adrenergic control of the circulation may also influence central aortic pressure dynamics in women after menopause. Indexes of aortic wave reflection are higher in postmenopausal women compared with younger women (18). Additionally, sympathetic activity was positively related to aortic augmentation index, augmented pressure, and wasted left ventricular energy in this group (18), in contrast to younger women in whom the relationships were exactly the opposite. Finally, aortic wave reflection indexes were substantially less affected by β-adrenergic blockade compared with younger women, suggesting a minimal role of β receptors in altering central hemodynamics in the postmenopausal group (5). Therefore, it appears that changes in central (aortic) hemodynamics also contribute importantly to the altered cardiovascular risk profile seen in older women. Recent data also suggest that central arterial stiffness is linked to decreased arterial baroreflex sensitivity in older men and women, thus providing another mechanism contributing to the potential for hypertension in older age groups (41).

Perspectives and Considerations for Future Research

In the present discussion, we have summarized influences of sex and age on mechanisms controlling sympathetic nerve activity and blood pressure in humans. Many of the specifics of these mechanisms remain to be studied and more clearly understood. From both clinical and basic science perspectives, it would be of interest to more clearly define the influences of testosterone on sympathetic activity and its interaction with central and peripheral vascular characteristics across the lifespan. This could provide further insight into the changes in integrative mechanisms of blood pressure control that occur with aging in both men and women. Additionally, it is important to note that the biological influences of sex and age on SNA and blood pressure do not occur in isolation. Multiple other factors, including increased body fatness, changes in glucose and lipid metabolism, and related hormonal changes that occur with age, also contribute to the age-related alterations in sympathetic control of blood pressure (1, 11, 14, 15, 29, 35). Mechanisms for these complex interactions are important areas of focus for future work as well.

Summary and Conclusions

There are striking differences in control of blood pressure between men and women, and across groups of different ages. FIGURE 1 summarizes some of the mechanisms contributing to these differences and the net effects of these mechanisms in the context of the balance of factors regulating blood pressure in young and older men and women. Young people (both men and women) are at much lower risk for hypertension compared with people over 50. Young women tend to have the lowest blood pressure and the lowest sympathetic nerve activity, although there is wide inter-individual variability in all groups. Importantly, young women have the vasodilator influence of augmented β-adrenergic activity, which appears to be minimal in young men. As people age, sympathetic nerve activity and blood pressure increase, and the balance between neural and hemodynamic factors that is seen in young people becomes weaker. In women at menopause, the specific influence of reproductive hormones (particularly estrogen) to augment vasodilation (via β receptors and nitric oxide) is lost, also contributing to the tighter coupling between SNA and blood pressure in the postmenopausal years. Thus the increasing sympathetic nerve activity becomes a greater contributing factor to the increasing potential for high blood pressure as people age.

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Author contributions: E.H. and N.C. conception and design of research; E.H. and N.C. performed experiments; E.H. and N.C. analyzed data; E.H. and N.C. interpreted results of experiments; E.H. and N.C. prepared figures; E.H. and N.C. drafted manuscript; E.H. and N.C. edited and revised manuscript; E.H. and N.C. approved final version of manuscript.

The authors gratefully acknowledge the artistic contributions of Elizabeth Caruso in the design of the summary figure.

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