Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging

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Seals, Douglas R., and Frank A. Dinenno. Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging. Am J Physiol Heart Circ Physiol 287: H1895–H1905, 2004; doi:10.1152/ajpheart.00486.2004.—Adult aging in humans is associated with marked and sustained increases in sympathetic nervous system (SNS) activity to several peripheral tissues, including the heart, the gut-liver circulation, and skeletal muscle. This chronic activation of the peripheral SNS likely is, at least in part, a primary response of the central nervous system to stimulate thermogenesis to prevent further fat storage in the face of increasing adiposity with aging. However, as has been proposed in obesity hypertension, this tonic activation of the peripheral SNS has a number of adverse secondary cardiovascular consequences. These include chronic reductions in leg blood flow and vascular conductance, increased tonic support of arterial blood pressure, reduced limb and systemic α-adrenergic vasoconstrictor responsiveness, impaired baroreflex buffering, large conduit artery hypertrophy, and decreased vascular and cardiac responsiveness to β-adrenergic stimulation. These effects of chronic age-associated SNS activation on the structure and function of the cardiovascular system, in turn, may have important implications for the maintenance of physiological function and homeostasis, as well as the risk of developing clinical cardiovascular and metabolic diseases in middle-aged and older adults.

The sympathetic nervous system (SNS) is a key neuromodulator of cardiovascular, metabolic, and other physiological functions in the human. As such, it represents an important tool that the central nervous system uses to maintain homeostasis in the face of both acute and chronic changes in the physiological state, as well as in response to the development of pathophysiological conditions. For more than a decade we have been investigating the effects of primary human aging (i.e., aging in the absence of chronic clinical disease) on the SNS and its regulation of cardiovascular and metabolic function. This work has three main areas of interest.

Our initial efforts (11, 12, 23–25, 48–50, 65, 66) sought to build on earlier studies (3, 27, 31, 43, 52, 56, 62, 70, 77, 78) aimed at determining the effects of aging on SNS behavior under tonic (resting) conditions and in response to acute physical and mental-emotional stress. The earlier investigations had established that net whole body SNS activity, as estimated from total plasma norepinephrine spillover, was greater in older healthy adults compared with young controls (31, 43, 56, 70). As summarized in a previous review (59), we extended these observations by demonstrating that this increase in net systemic SNS activity with advancing age is the result of increases in SNS outflow to several peripheral tissues, including the heart, the liver-gut circulation, and skeletal muscle. In contrast, we showed that the whole body and regional SNS responses to acute stress generally were either similar or attenuated in healthy older adults compared with young adults but certainly not augmented as had been widely believed and promoted in the literature. Collectively, this work established that the primary influence of aging on the human SNS was an elevation in tonic activity rather than responsiveness to stress.

Given this, we next attempted to determine the key mechanisms underlying this increase in tonic SNS activity with aging (13, 14, 22, 34, 35, 45, 64). To date, we have identified at least two potentially linked mechanisms that are associated with the age-related increase in SNS outflow to peripheral tissues: 1) increases in total and abdominal adiposity and circulating adipose-sensitive signals (e.g., leptin) (34, 35, 45); and 2) increased subcortical suprabulbar brain noradrenergic activity, as estimated from measurements of norepinephrine turnover from the cerebrovascular circulation (22). From these observations, we (58) recently advanced an integrative working hypothesis that attempts to explain the increase in tonic SNS activity with aging as an adaptive response (i.e., stimulation of β-adrenergic thermogenesis) to increasing accumulation of peripheral body fat. Our findings indicate that the increase in SNS activity associated with this adaptive response is not effective in achieving a state of augmented thermogenesis in older adults (5, 58).

In settings of clinical disease such as congestive heart failure and essential hypertension, chronic SNS activation has deleterious effects on the cardiovascular system. In particular, it has been postulated that the hypertension commonly observed with human obesity may be a secondary cardiovascular consequence of SNS activation intended to stimulate thermogenesis and augment energy expenditure (40). Given this previously

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established link between tonically elevated peripheral SNS activity and adverse cardiovascular consequences in clinical disease states, we have performed a series of investigations aimed at determining the potential cardiovascular effects of the chronic SNS activation observed with primary human aging.

Accordingly, the purpose of this review is to discuss the key findings from this latter body of work, integrating complementary observations from earlier investigations where appropriate. We focus primarily on the effects of age-associated SNS activation on the function and structure of the vasculature in healthy adult humans, commenting only briefly on potentially adverse cardiac effects.

**Whole Limb Blood Flow and Vascular Conductance**

Barcroft and colleagues (2) first demonstrated in humans that under resting conditions the SNS exerts a tonic vasoconstrictor influence on limb blood flow. As such, we hypothesized that the tonically elevated SNS activity directed to skeletal muscle with primary human aging may act to suppress basal (resting) limb blood flow.

To determine this, femoral (whole leg) blood flow was measured originally in healthy young and older men using duplex ultrasound (17). We found that leg blood flow was ~25% lower in the older men (Fig. 1A). Follow-up cross-sectional investigations revealed that this decline in leg blood flow appears to be linear with adult aging (18), is independent of habitual physical activity status (18), is related to age-associated reductions in estimated leg oxygen consumption that are in part the result of reductions in leg fat-free mass (18), and also is observed with aging in healthy women (47). The decline in leg blood flow is not related to reductions in systemic arterial blood pressure or cardiac output but rather is mediated solely by a decrease in leg vascular conductance (increase in leg vascular resistance) (17, 18) (Fig. 1A). The reductions in leg blood flow and vascular conductance with aging in men were positively related to increases in directly recorded leg muscle sympathetic nerve activity (MSNA; peroneal microneurography) (17) (Fig. 1B). Indeed, correcting for leg MSNA abolished the age-associated differences in leg hemodynamics (17). These observations suggested that the increase in MSNA with aging in men might be responsible for the corresponding reductions in whole leg blood flow and vascular conductance. We also concluded that this reduction in whole limb flow with aging was likely mediated by reductions in blood flow and vascular conductance in skeletal muscle as opposed to skin (17).

To more definitively establish the cause and effect relation between age-associated increases in MSNA and changes in leg hemodynamics, in a follow-up study, Dinenno and colleagues (19) determined femoral blood flow and vascular conductance in young and older men under normal resting control conditions and during local (intrafemoral artery infusion) nonspecific α-adrenergic receptor blockade with phentolamine. Propranolol was preadministered locally to control for any β-adrenergic effects of phentolamine. Consistent with our original observations, whole leg blood flow and vascular conductance were ~30% lower in the older men under control conditions (Fig. 2). The acute increases in femoral blood flow and vascular conductance during phentolamine administration were much greater in the older men. Indeed, the age-associated differences in whole leg blood flow and vascular conductance observed in the normal resting state were abolished during phentolamine (Fig. 2). Taken together, the findings from this series of investigations demonstrate that the age-associated increase in leg MSNA in healthy men causes a chronically augmented α-adrenergic-mediated vasoconstrictor state as reflected by tonically reduced leg blood flow and vascular conductance.

It is important to note that this coupling between tonically elevated leg MSNA and reduced blood flow/vascular conduc-

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**Fig. 1. A:** whole leg blood flow and vascular conductance were lower in older men compared with young healthy men under resting (basal) conditions. **B:** these age-associated changes were strongly related to levels of leg (peroneal nerve) muscle sympathetic nerve activity (MSNA), suggesting that elevated sympathetic vasoconstrictor nerve activity is involved in the greater vasoconstrictor tone in older adults (Reproduced with permission from the Lippincott Williams & Wilkins; Dinenno et al. Limb blood flow and vascular conductance are reduced with age in healthy humans: relation to elevations in sympathetic nerve activity and declines in oxygen demand. *Circulation* 100: 164–170, 1999.).
suggested greater sympathetic outflow to the upper limb with age. Therefore, the findings of similar (32) or less (15) tonic sympathetic vasoconstriction in the forearm with age (compared with an augmented sympathetic vasoconstrictor tone in the leg) could be explained by: 1) less of an increase in MSNA; 2) less norepinephrine release per increase in sympathetic nerve discharge; and/or 3) a greater reduction in postjunctional α-adrenergic responsiveness (see Limb Vasoconstrictor Responsiveness) with age in the arm compared with the leg. Whatever the case, it should be noted that because a greater percentage of cardiac output at rest is directed to the legs (i.e., a much larger tissue mass than the arms), the augmented sympathetic vasoconstrictor tone in the legs of older adults would have a greater impact on systemic hemodynamic function.

**Tonic Support of Arterial Blood Pressure**

Given that the activation of the SNS with aging produces a chronic peripheral vasoconstriction, we postulated that this would result in an increase in tonic autonomic nervous system support of arterial blood pressure. Results of an earlier investigation were consistent with this possibility (73).

To more definitively test this hypothesis, we directly measured arterial blood pressure (intrabrachial artery catheter) in groups of young and older healthy men under normal (supine resting) control conditions and during ganglionic blockade achieved by intravenous administration of trimethaphan (36). Trimethaphan abolishes postganglionic SNS activity and, therefore, its tonic vasoconstrictor effects, resulting in acute vasodilation in regional circulations and reductions in systemic vascular resistance and arterial blood pressure. Arterial blood pressure did not differ in these young and older normotensive men at baseline but decreased almost twice as much in the older men in response to trimethaphan (Fig. 3A). Importantly, the magnitude of the acute reduction in arterial blood pressure with trimethaphan was directly related to the baseline levels of plasma norepinephrine and MSNA (Fig. 3B). These findings are consistent with the idea that the increase in SNS activity with aging contributes to the greater tonic autonomic support of arterial blood pressure observed in older adults.

**Peripheral Vasoconstrictor Responsiveness**

In general, physiological or pathophysiological states associated with tonic activation of the SNS and release of norepinephrine produce an agonist-promoted desensitization of α-adrenergic signaling. As such, we reasoned that the chronic SNS activation associated with primary human aging would result in impaired α-adrenergic vasoconstrictor responsiveness in both the limb circulation and systemically. Earlier studies (20, 29, 32, 51) in experimental animals and humans suggested that this might be the case. We performed a systematic series of investigations to comprehensively test this hypothesis.

**Limb Vasoconstrictor Responsiveness**

To gain initial insight into the possible effects of age-associated chronic SNS activation on limb vasoconstrictor...
responsiveness, Davy et al. (13) determined MSNA, forearm blood flow, and vascular resistance in groups of healthy young and older men under supine resting control conditions and during graded lower body negative pressure. The latter produces progressive reductions in cardiac filling pressure, thus unloading the baroreceptors causing incremental reflex increases in MSNA and consequent forearm vasoconstriction. Dose-response ($\Delta$MSNA vs. $\Delta$forearm blood flow or vascular resistance) curves can be constructed to examine peripheral vasoconstrictor responsiveness to acute endogenous SNS activation. Baseline MSNA was greater in the older men and was associated with a forearm vasoconstrictor response to graded lower body negative pressure that was only one-third of that observed in the young men. The increase in plasma norepinephrine concentration per unit increase in MSNA during lower body negative pressure did not differ with age, indicating that the attenuated forearm vasoconstrictor response in the older men was not the result of an inability to release norepinephrine in response to an increase in sympathetic nerve discharge. These results were consistent with our subsequent observation of a smaller leg vasoconstrictor response to another acute SNS stimulus, immersion of a hand in ice water (cold pressor test), in older compared with young men (19), as well as with other reports in the literature (63). Collectively, these findings established that primary human aging is associated with impaired limb vasoconstrictor responsiveness to SNS stimulation.

We next sought to establish the mechanism underlying this age-associated impairment in SNS-mediated limb vasoconstriction with aging. Hogikyan and Supiano (32) had reported earlier that older subjects demonstrated a smaller reduction in forearm blood flow in response to intra-arterial administration of norepinephrine, an agonist for all $\alpha$-adrenergic receptor subtypes (as well as for $\beta$-adrenergic receptors). We attempted to extend this observation by determining whether: 1) the forearm vasoconstrictor response to endogenous norepinephrine release also was impaired in older adults; and 2) impaired postjunctional $\alpha_1$- and/or $\alpha_2$-adrenergic receptor signaling is involved (15). All vasoconstrictor responses to $\alpha$-adrenergic stimulation were determined during local $\beta$-adrenergic blockade to control for any age-related differences in $\beta$-adrenergic vasodilation (see $\beta$-Adrenergic Modulation of Cardiovascular Function). We found that the forearm vasoconstrictor response to intrabrachial artery infusion of tyramine, which causes endogenous release of norepinephrine from postganglionic sympathetic nerve endings, was blunted in older subjects (Fig. 4A). This was associated with an attenuated forearm vasoconstrictor response to phenylephrine, a selective $\alpha_1$-adrenergic receptor agonist (Fig. 4B), but a preserved response to clonidine, an $\alpha_2$-adrenergic receptor agonist (Fig. 4C). These observations were consistent with previous findings of an age-related decline in $\alpha$-adrenergic vasoconstrictor responsiveness in human subcutaneous arteries studied in vitro (51). Together, these data indicate that the age-related decline in limb vasoconstrictor responsiveness might be selective for postjunctional $\alpha_1$-adrenergic receptors.

In their earlier study, Hogikyan and Supiano (32) demonstrated that compared with baseline responsiveness, short-term (3 wk) suppression of SNS activity and norepinephrine release (via oral guanadrel) in older adults augmented their vasoconstrictor response to local brachial artery infusion of norepinephrine (Fig. 5) without affecting the response to angiotensin II (nonadrenergic control). Overall, these results support the concept that primary human aging results in a reduced ability to evoke vasoconstriction in the limbs in response to acute activation of the SNS and release of norepinephrine as a consequence of chronic agonist (i.e., tonically elevated SNS...
activity)-mediated desensitization of the $\alpha_1$-adrenergic vascular signaling pathway.

**Systemic Vasoconstrictor Responsiveness**

Key cardiovascular functions that regulate arterial blood pressure and, therefore, vital organ perfusion such as cardiac output and peripheral vascular resistance obviously are influenced more by net systemic vascular responsiveness than by vascular responsiveness in a single regional circulation like the limb. As such, it was important to establish whether the attenuated limb $\alpha_1$-adrenergic vasoconstrictor responsiveness in older adults reflected a decrease in systemic $\alpha_1$-adrenergic responsiveness with aging.

To determine this we (36) compared the acute increase in arterial blood pressure (radial artery catheter) in response to systemic $\alpha_1$-adrenergic receptor stimulation (intravenous phenylephrine) during ganglionic blockade (intravenous trimethaphan) in groups of young and older healthy men. An earlier study (20) in which phenylephrine was infused intravenously in small groups of young and older healthy subjects reported that a greater dose was needed to produce a 20-mmHg increase in mean arterial blood pressure in the older group, suggesting an age-associated reduction in systemic $\alpha_1$-adrenergic responsiveness. However, because 1) baroreflexes modulate the arterial blood pressure response to systemic administration of vasoactive drugs, and 2) baroreflex responsiveness is altered with aging (33), systemic vascular responsiveness to adrenergic stimulation can only be determined during ganglionic blockade, which abolishes the counter-regulatory changes in autonomic activity evoked by baroreflexes.

During ganglionic blockade, we found that the increase in arterial blood pressure in response to phenylephrine was markedly impaired in the older men (Fig. 6A). Importantly, among the individual young and older men (i.e., in the pooled sample), the increase in arterial blood pressure with phenylephrine was inversely related to baseline levels of MSNA (Fig. 6B). Together, these observations provide novel experimental evidence for the concept that the chronic elevation in SNS activity and norepinephrine release with primary human aging causes impaired systemic $\alpha_1$-adrenergic vasoconstrctor responsiveness.

![Figure 4](image-url)

**Fig. 4.** A: forearm vasoconstrictor responses to increases in endogenous norepinephrine (NE) release (evoked via intra-arterial tyramine) were significantly reduced in older compared with young healthy men. B: forearm vasoconstrictor responses to phenylephrine (PE) (selective $\alpha_1$-agonist) also were reduced with age. C: responses to $\alpha_2$-receptor stimulation (clonidine) were similar in young and older men. These data suggest that the age-related impairment in limb $\alpha$-adrenergic responsiveness to acute sympathetic stimulation is specific for postjunctional $\alpha_1$-adrenergic receptors (Reproduced with permission from the Lippincott Williams & Wilkins; Dinenno et al. Aging and forearm postjunctional $\alpha$-adrenergic vasoconstriction in healthy men. Circulation 106: 1349–1354, 2002.).

![Figure 5](image-url)

**Fig. 5.** Suppression of sympathetic nervous system activity for 21 days (via oral guanadrel) in older adults augments the forearm vasoconstrctor responses to intra-arterial infusions of NE. These data indicate that the chronic elevation in sympathetic nervous system activity with human aging leads to reduced limb vasoconstrctor responsiveness via desensitization of adrenergic signaling [from Hogikyan and Supiano (32)]. FAV, forearm volume.
Baroreflex Buffering

Baroreflexes are powerful cardiovascular reflexes that regulate intravascular pressure and cardiac filling volume with the goal of maintaining circulatory homeostasis. They consist of afferent, central nervous system integration and efferent response elements. The final step in the SNS efferent arm of the reflex is vascular coupling, which involves changes (decreases or increases) in SNS activity, the release of norepinephrine, and the consequent vascular smooth muscle response (i.e., relaxation and vasodilation or contraction and vasoconstriction).

Because the ability to produce changes in α1-adrenergic-mediated vascular tone in response to acute changes in SNS activity is an important determinant of baroreflex function, we hypothesized that the blunted systemic α1-adrenergic responsiveness observed with aging would be associated with impaired baroreflex buffering of acute changes in arterial blood pressure in older adults. To test this, Jones et al. (33) measured baroreflex buffering in groups of healthy young and older men. Baseline MSNA and plasma norepinephrine concentrations were greater, whereas baroreflex buffering was markedly reduced in the older men (Fig. 7A). Moreover, the age-associated reduction in baroreflex buffering was related to both the increase in baseline SNS activity (Fig. 7B) and the decrease in α1-adrenergic vascular responsiveness (Fig. 7C) with aging. These findings support the idea that the chronic activation of the SNS associated with primary human aging causes impaired baroreflex buffering, at least in part, via reduced α1-adrenergic vascular responsiveness.

Vascular Hypertrophy

Adult aging is associated with an increase in the wall thickness of conduit arteries as a result of smooth muscle hypertrophy and a consequent thickening of the intima-media layer. This is observed in the absence of clinical atherosclerosis.

Fig. 6. A: systemic α1-adrenergic responsiveness, measured as the increase in systolic blood pressure (SBP) per unit increase in plasma concentration of the α1-agonist PE during ganglionic blockade (GB), was significantly blunted in older compared with young healthy men. B: systemic α1-adrenergic vasoconstrictor responsiveness was inversely related to basal muscle sympathetic nerve activity, supporting the concept that chronic elevations in sympathetic stimulation contribute to α-adrenergic desensitization with age (Reproduced with permission from the Lippincott Williams & Wilkins; Jones et al. Baroreflex buffering is reduced with age in healthy men. Circulation 107: 1770–1774, 2003).

Fig. 7. A: baroreflex buffering (BRB), measured as the change in blood pressure (BP) in response to acute intravenous administration of vasoactive drugs before versus during GB, was markedly reduced in older compared with young healthy men. BRB was inversely related to basal MSNA (B) and positively related to systemic α1-adrenergic vasoconstrictor responsiveness (C). Taken together, these data suggest that chronic increases in sympathetic nervous system activity result in reductions in α1-adrenergic vasoconstrictor responsiveness, which subsequently impairs baroreflex buffering of BP in older adults (Reproduced with permission from the Lippincott Williams & Wilkins; Jones et al. Baroreflex buffering is reduced with age in healthy men. Circulation 107: 1770–1774, 2003).
and hypertension, but the exact mechanisms involved are unknown. In experimental animals, sustained SNS-adrenergic stimulation causes vascular smooth muscle hypertrophy and arterial wall thickening (10, 54, 75).

Accordingly, we sought to determine whether the chronic SNS activation that occurs with aging in humans is associated with conduit artery hypertrophy. Dinenno et al. (16) measured tonic leg MSNA and the intima-media thickness (IMT via high resolution ultrasonography) of the femoral artery in groups of healthy young and older men. Baseline MSNA was 70% higher in the older men, and this was associated with an ~75% greater femoral IMT and femoral IMT-to-lumen ratio (Fig. 8A). Most importantly, femoral IMT and the femoral IMT-to-lumen ratio were strongly and positively related to MSNA in the pooled group (r = 0.82–0.85) (Fig. 8B). Indeed, the age-group differences in femoral IMT and the femoral IMT-to-lumen ratio were abolished when the influence of leg MSNA was removed. Significant positive relations between MSNA and femoral wall thickness also were observed within the young and older groups, indicating that the overall relation was not simply colinear with increasing age (16). No factor other than baseline leg MSNA was independently related to femoral IMT. These observations are consistent with the postulate that the chronic elevation in leg MSNA with advancing age plays an important mechanistic role in the development of femoral artery hypertrophy in healthy adults.

The exact cellular and molecular mechanisms by which sustained SNS activation, release of norepinephrine, and stimulation of adrenergic signaling lead to vascular hypertrophy in humans are not known, but data obtained from other experimental models may provide some insight. For example, norepinephrine added to culture stimulates smooth muscle cell gene expression and protein content (10, 75). This is consistent with findings that SNS-adrenergic stimulation is associated with increased vascular smooth muscle cell size (hypertrophy) rather than increased cell number (hyperplasia) (10, 61). Recent evidence (7) indicates the possible involvement of α₁-adrenergic stimulation of NADPH oxidase-mediated increases in reactive oxygen species in this process because the effects of norepinephrine in stimulating protein synthesis in vascular smooth muscle cells are abolished by antioxidant treatment. It also appears that there is an increase in smooth muscle cell sensitivity to the effects of SNS stimulation on vascular hypertrophy with aging (28). This is consistent with reports of increased vascular oxidative stress with aging in both experimental animals (68) and healthy adult humans (21). Taken together, these observations suggest the possibility that chronic activation of the SNS and release of norepinephrine may stimulate the generation of reactive oxygen species in the vascular wall via an α₁-adrenergic-dependent mechanism, which, in turn, activates gene expression that results in increased smooth muscle cell protein content leading to arterial wall hypertrophy.

Finally, it has been proposed that the vascular hypertrophy that occurs with experimental, and, perhaps, human hypertension is associated with an augmented responsiveness to vasoconstrictor stimuli (26), i.e., the so-called “amplifier effect.” In contrast, the conduit artery hypertrophy that develops with primary human aging is associated with attenuated vascular responsiveness (see Peripheral Vasoconstrictor Responsiveness). The physiological basis for these differences is unknown. However, the fact that the vascular hypertrophy associated with the hypertensive state is mediated by marked and sustained increases in arterial (intravascular) pressure, whereas the conduit (e.g., femoral) artery hypertrophy observed with primary adult aging in humans occurs in the absence of elevated blood pressure (16, 46) may provide at least a partial explanation. Moreover, the findings of Dinenno et al. (16) indicate that the limb conduit artery hypertrophy with aging is linked to chronically increased MSNA. It is not clear whether the vascular hypertrophy-related augmented responsiveness

![Fig. 8. A: absolute femoral artery intima-media thickness (IMT) and the IMT-to-lumen ratio were significantly greater in older compared with young healthy men in the absence of any group differences in atherosclerotic risk factors. B: femoral artery hypertrophy was significantly and positively related to basal muscle sympathetic nerve activity. These findings suggest that age-related increases in sympathetic activity contribute to peripheral conduit artery hypertrophy via chronic stimulation of α-adrenergic signaling [from Dinenno et al. (16)].](http://ajpheart.physiology.org/)

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observed in certain hypertension models or states is associated with tonically elevated SNS activity.

**β-Adrenergic Modulation of Cardiovascular Function**

In addition to adverse changes in α-adrenergic-mediated vascular function and structure, the chronic elevation in SNS activity with aging also appears to have important effects on β-adrenergic-modulated cardiovascular function. β-Adrenergic-mediated vasodilation and stimulation of heart rate and left ventricular contractility generally decrease with advancing age in both experimental animals and humans (1, 55, 57, 67, 73, 74). The mechanisms involved in this reduced responsiveness with aging are believed to involve both receptor and postreceptor elements of the β-adrenergic signaling pathway (57, 74).

It has been suggested that the decrease in tissue responsiveness to β-adrenergic stimulation with aging is the result of receptor downregulation produced by the tonic age-associated increase in SNS activity and release of norepinephrine (1, 74). Evidence supporting this notion comes from studies in both humans and animal models. In humans, the attenuated increase in heart rate in response to isoproterenol, a nonselective β-adrenergic agonist, with age is related to the corresponding increase in baseline norepinephrine concentrations (6). Although this observation is confounded by the presence of intact cardiovascular reflexes, we recently confirmed these findings. Specifically, we measured the heart rate response to isoproterenol in groups of healthy young and older men during ganglionic blockade. We found that the increase in heart rate in response to β-adrenergic stimulation was much smaller in the older men (Fig. 9A). Most importantly, the heart rate response to isoproterenol during ganglionic blockade was inversely related to baseline levels of both plasma norepinephrine and MSNA (Fig. 9B). These observations are consistent with the fact that: 1) we (25) have previously shown that tonic norepinephrine spillover in the heart is approximately twice as great in older compared with young healthy men, indicating a marked increase in chronic cardiac SNS activity and norepinephrine release with primary aging in humans; and 2) chronically increased exposure to norepinephrine causes a desensitization in cardiac β-adrenergic signaling in experimental animals (53, 69).

When considered together, the available evidence supports the view that the tonic increase in SNS activity with aging causes agonist-promoted downregulation of β-adrenergic receptors, desensitization of the β-adrenergic signaling pathway, and reduced vascular and cardiac tissue responsiveness to acute β-adrenergic stimulation.

**Physiological and Clinical Implications**

The adrenergic-cardiovascular effects of age-associated SNS activation have potentially important implications for both physiological function and disease risk.

The tonically elevated leg vasconstrictor state associated with increased MSNA could limit the ability of older adults to augment limb blood flow in response to increased functional demand imposed physical stress such as acute exercise (41), energy intake (30), and warm ambient temperatures (38), posing a challenge to the maintenance of circulatory homeostasis under these conditions. With respect to disease risk, chronically augmented SNS-mediated reductions in peripheral blood flow and vascular conductance are believed to contribute mechanistically to the etiology of the metabolic syndrome, a key antecedent to clinical atherosclerotic diseases that includes visceral obesity, glucose intolerance, insulin resistance, dyslipidemia, hypertension, and chronic inflammation (4, 37, 42). The prevalence of the metabolic syndrome and atherosclerotic vascular diseases increase progressively with advancing age.

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Fig. 9: A: cardiac β-adrenergic chronotropic responsiveness, measured as the increase in heart rate per unit increase in the plasma concentration of the β-adrenergic receptor agonist isoproterenol during GB, was reduced in older compared with young healthy men. B: cardiac β-adrenergic chronotropic responsiveness was significantly and negatively related to both basal plasma norepinephrine concentrations and MSNA, supporting the concept that chronic elevations in sympathetic activity with aging lead to cardiac β-adrenergic receptor desensitization (from Jones PP and Seals DR, unpublished data).
The fact that the sustained SNS activation with aging is associated with a corresponding increase in tonic autonomic support of arterial blood pressure likely has important implications for the older adult in at least two respects. First, there is accumulating evidence that elevations in SNS activity play a key role in the etiology of essential hypertension with aging, even in initially normotensive adults such as those studied in our investigations (44, 71, 72, 76). The findings of Jones and colleagues (36) are consistent with the idea that this SNS-associated hypertensive effect may be mediated, at least in part, via increased tonic autonomic support of arterial blood pressure. Second, antihypertensive drugs that inhibit central SNS outflow or the peripheral vasoconstrictor effects of SNS activity often cause orthostatic hypotension in elderly patients, particularly after meals when marked gastrointestinal vasodilation is present (postprandial orthostatic hypotension) (39). Our findings may provide a mechanistic explanation for this clinical observation; namely, that the older adult relies to a greater extent on the SNS for tonic blood pressure support. Thus, when this support is partially removed via administration of these antihypertensive medications, the older adult loses an important mechanism for maintaining arterial pressure, especially under challenging physiological conditions.

The effects of augmented SNS activity in reducing limb and systemic vascular β-adrenergic responsiveness has obvious relevance for the control of peripheral blood flow as well as the regulation of arterial blood pressure in the aging adult (15, 36). Control of blood flow is mediated by the interaction among neural, humoral, and local factors. Thus the marked impairment in arterial β-adrenergic responsiveness with aging would presumably alter the fine balance between these factors leading to limitations in vascular control or, at the least, requiring compensatory adjustments in other effector mechanisms to prevent regulatory failure. Moreover, the chronic elevation in SNS activity and associated reduction in β-adrenergic responsiveness are the two primary determinants of impaired baroreflex buffering of arterial blood pressure with aging (33). The age-related impairment in baroreflex buffering, in turn, has important implications concerning the ability of older adults to maintain perfusion pressure and, thus, cardiovascular homeostasis in response to vasoactive drugs, as well as physiological conditions (e.g., exercise, upright posture, and warm ambient temperatures) that produce acute changes in arterial blood pressure (33).

Increased femoral IMT is a strong, independent predictor of the age-associated increase in risk of developing clinical atherosclerotic diseases (9). The chronic activation of the SNS that occurs with aging appears to increase baseline arterial wall thickness from which the superimposed effects of other cardiovascular risk factors could increase femoral IMT to pathophysiological levels (16). This SNS-linked vascular hypertrophy could also contribute to reductions in arterial compliance with aging, as well as to increases in peripheral vascular resistance, thus contributing to hypertensive diseases in the elderly (16).

Finally, the reduced β-adrenergic tissue responsiveness produced by the chronic SNS activation with aging has clear implications for the regulation of blood flow and cardiac function. An inability to produce β-adrenergic-mediated peripheral vasodilation in response to epinephrine release could limit the physiological adjustments to certain types of physical stress in the older adult. Most importantly, the reduced chronotropic and inotropic effects of β-adrenergic desensitization on the heart are believed to be key mechanisms underlying the reductions in maximal heart rate, left ventricular contractility, cardiac output, and aerobic exercise capacity with advancing age (60, 74). The decrease in exercise tolerance with aging, in turn, limits submaximal work capacity and can restrict the functional independence of older adults, significantly impacting their quality of life.

Recent findings from a novel experimental animal model may provide additional insight into the role of chronically augmented SNS activity in the cardiac limitations that occur with aging. Transgenic mice without functional α2A- and α2C-adrenergic receptors in the midbrain, which normally inhibit neuronal release of norepinephrine and the stimulation of SNS outflow to the periphery, had chronically elevated cardiac SNS activity and within a few months developed cardiac dysfunction (8). These mice also demonstrated reduced exercise capacity, peak oxygen consumption, and cardiac contractility compared with their wild-type controls. These effects of increased SNS stimulation on the heart may reflect over a shorter period of time a similar process to that observed with the sustained cardiac SNS activation and elevated norepinephrine release that occurs with primary adult aging in humans.

Summary and Conclusions

Primary human aging is associated with chronic SNS activation to a number of peripheral tissues, including the heart, the gut-liver circulation, and skeletal muscle. This sustained activation of the peripheral SNS may be an attempt of the central nervous system to increase thermogenesis to prevent further storage of excess energy intake as fat. However, as has been proposed to occur in obesity hypertension, this sustained stimulation of the peripheral SNS in human aging has a number of adverse secondary cardiovascular effects. These cardiovascular consequences have important implications for the maintenance of physiological function and homeostasis and the risk of developing clinical cardiovascular and metabolic diseases in middle-aged and older adults.

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