Sympathetic Neural Mechanisms in Human Hypertension

Ronald G. Victor, MD, and Moiz M. Shafiq, MD

Corresponding author
Ronald G. Victor, MD
Internal Medicine, Hypertension Division, UT Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA.
E-mail: ronald.victor@utsouthwestern.edu

Current Hypertension Reports 2008, **10:**241–247
Current Medicine Group LLC ISSN 1522-6417

Compared with substantial clinical research on the renin-angiotensin-aldosterone system (RAAS), much less is known about the importance of the sympathetic nervous system as a therapeutic target to slow the initiation and progression of human hypertension. Using microelectrode recordings of sympathetic activity and radiotracer measurements of regional norepinephrine spillover in hypertensive patients, recent research has advanced several provocative findings with novel—but still largely potential—therapeutic implications for clinical hypertension. These include a stronger scientific rationale for using 1) combined α/β-blockers in the early phases of primary hypertension and obesity-related hypertension; 2) RAAS blockers as central sympatholytics in hypertension associated with chronic kidney disease; and 3) a higher dialysis dose—either nocturnal or short daily hemodialysis—to reduce uremic stimulation of a blood pressure–raising reflex arising in the failing kidneys. New outcomes trials are needed if we are to translate this largely theoretical body of research into clinical practice.

Introduction

For several decades, the sympathetic nervous system has been the "stepchild" of clinical hypertension. Sympathetic neural mechanisms are given comparatively little time in scientific programs at national meetings of heart and kidney associations and even hypertension societies. Compared with the renin-angiotensin-aldosterone system (RAAS), the activity of the sympathetic nervous system is harder to measure. Compared with RAAS blockers, central sympatholytics and adrenergic blockers have far less favorable side-effect profiles due to multiple sites of action, especially within the central nervous system. Moreover, in recent cardiovascular outcomes trials, α-blockers and β-blockers have not performed as well as other classes of antihypertensives; they are no longer considered first-line therapy for uncomplicated hypertension [1].

However, at the cell and molecular levels, norepinephrine is just as potent as angiotensin II in causing remodeling and hypertrophy of vascular smooth muscle and cardiac muscle [2]. Furthermore, sympathetic activation stimulates renin release and renal sodium retention, contributing to hypertension in numerous animal models [2]. Sustained sympathetic activation has been demonstrated in several forms of human hypertension but large gaps remain in our understanding of the precise mechanisms driving this activity and its contribution to the development and progression of hypertension. A better understanding of sympathetic neural mechanisms of human hypertension is needed to identify more specific therapeutic targets.

In the past 5 years, the field has not seen earth-shattering breakthroughs but significant progress has been made in at least three forms: 1) primary hypertension, 2) renal parenchymal hypertension, and 3) obesity-related hypertension. There is increasing evidence that all three hypertensive states are accompanied by marked sympathetic activation but with distinct differences in apparent mechanisms and patterns of sympathetic activation and in sympathetic responsiveness to specific pharmacologic and nonpharmacologic interventions.

Primary Hypertension

As noted earlier, sympathetic nerve activity is difficult to measure, particularly in the clinical setting. Plasma norepinephrine levels are an insensitive measure [3]. Although easily performed and noninvasive, frequency analysis of heart rate variability is not a valid measure of sympathetic nerve activity [4–6]. The two state-of-the-art techniques that best quantify sympathetic nerve activity in humans are radiotracer measurements of regional norepinephrine spillover and microneurography (microelectrode measurements of sympathetic nerve activity) [3,7,8••]. The former is invasive and requires arterial cannulation. The latter is minimally invasive and requires specialized training.

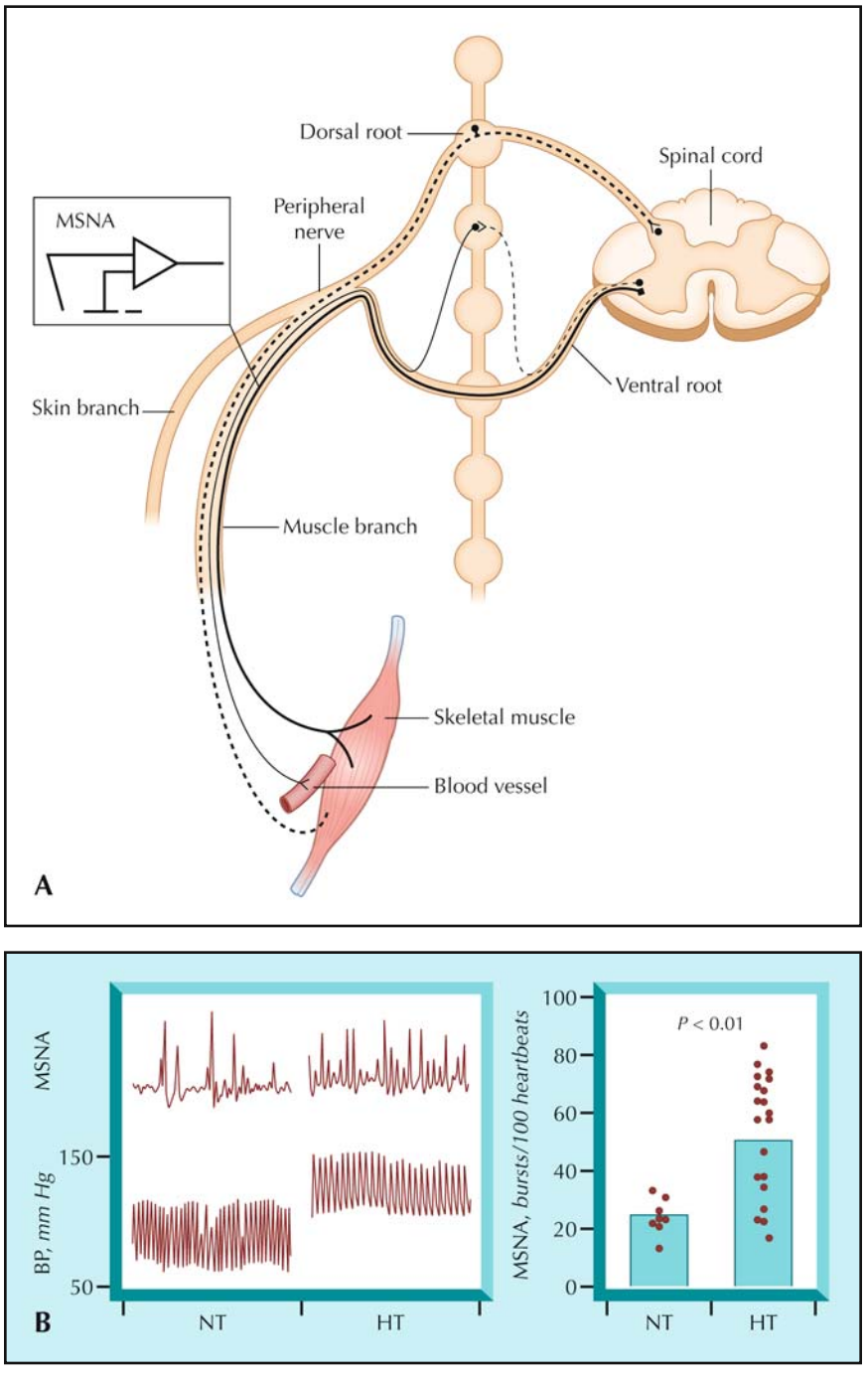

Figure 1. Microneurographic measurements of muscle sympathetic nerve activity (MSNA) in normotensive and hypertensive humans. **A,** Schematic diagram shows insertion site of recording microelectrode into peripheral sympathetic nerve bundle innervating blood vessels in human skeletal muscle. **B,** Multiunit recordings of MSNA and blood pressure (BP) from two illustrative human subjects (*left*) and summary data (*right*) showing higher mean levels of nerve firing in hypertensive (HT) than normotensive (NT) humans. (**A** *adapted from* Guyenet [10]; **B** *adapted from* Schlaich et al. [3].)

Using these techniques, several research teams have provided convincing evidence that stage 1 primary human hypertension is characterized by sympathetic activation targeted to the kidney, heart, and skeletal muscle vasculature [2,9••,10]. As shown in Figure 1, microneurography provides direct measurements of postganglionic sympathetic nerve activity—the proximate neural stimulus to norepinephrine release [10]. This has proven to be a powerful clinical research tool [7,8••]. Muscle sympathetic nerve activity (MSNA) refers to spontaneous bursts of sympathetic activity targeted to the skeletal muscle vasculature. The activity is normally tightly regulated by carotid sinus and aortic arch baroreceptors, accompanied by parallel changes in regional vasomotor tone, and eliminated by ganglionic blockade.

Basal levels of MSNA provide a valid measure of resting sympathetic nerve activity—at least to one major vascular bed—that contributes to total peripheral resistance and blood pressure [8••]. In unrelated persons, basal levels of MSNA show considerable interindividual differences, but have a high degree of intraindividual reproducibility when a given subject is studied repeatedly. Figure 1 is an example of a study showing higher levels of MSNA in hypertensive than

normotensive individuals, but with overlap between the groups [10].

A recent study by Grassi et al. [11•] suggested the overlap is largely eliminated when the normotensive control group is more rigorously defined using 24-hour ambulatory blood pressure monitoring. An important lesson from ambulatory blood pressure monitoring is that 10% to 15% of patients previously considered as normotensive based on office blood pressure measurements are found to have "masked hypertension"—elevated blood pressure only outside the physician's office [12]. In such individuals, the higher out-of-office blood pressures are assumed to indicate sympathetic overactivity. Grassi et al. [11•] now provide experimental support for this assumption by showing increased levels of MSNA in individuals with masked hypertension. These elevations were indistinguishable from those in patients with persistent in- and out-of-office hypertension. When patients with masked hypertension were eliminated from the normotensive control group, mean values of MSNA were 70% higher in the persistent hypertensives (who had mild stage 1 hypertension) compared with true normotensive individuals, with little or no overlap between the two groups.

Thus, from a purely academic standpoint, the newer α/β-blockers would seem a rational choice for treating mild hypertension accompanied by increased MSNA. Additionally, MSNA has been shown to increase further with combination therapy with an angiotensin receptor blocker and a thiazide diuretic, a popular current treatment regimen [13•]. Yet, none of the recently updated practice guidelines recommend α-adrenergic blockers or central sympatholytics as first-line therapy for stage 1 primary hypertension [1,14]. Furthermore, the British Hypertension Society guidelines eliminated β-blockers as first- or second-line therapy [1]. This recommendation did not include the newer α/β-blockers, which seem to be stronger antihypertensives and have better metabolic profiles than traditional β-blockers [15]. Outcomes trials are needed.

For renal parenchymal hypertension, the evidence for a sympathetic contribution to hypertension is even stronger.

Renal Parenchymal Hypertension: Chronic Hemodialysis and Stage II to III Chronic Kidney Disease

Hypertension is present in 80% of chronic hemodialysis patients and contributes to their excessive cardiovascular morbidity and mortality in this patient population [16]. The hypertension is due in part to volume expansion, but evidence is increasing for a major sympathetic component [16,17]. Plasma norepinephrine levels tend to be mildly to moderately increased in hemodialysis patients both because of impaired clearance and increased central sympathetic activity. In nondiabetic hemodialysis patients, MSNA is increased in those with native kidneys but indistinguishable from normal in those with bilateral nephrectomy [18]. These clinical observations suggest that sympathetic activation in end-stage renal disease can be triggered by a pressor reflex arising in the failing kidneys, a concept that was proven conclusively in experimental rat models [19]. In many species, the kidneys are richly innervated by sensory (afferent) fibers that signal the brain in response to chemical changes in urine composition and mechanical changes in the renal pelvis. In rats, some of these afferent fibers are excitatory, reflexively raising blood pressure when activated by ischemia or by urea.

In hemodialysis patients with native kidneys, recent studies show that hypertension is much better controlled—and the need for antihypertensive medication greatly reduced—by increasing the weekly dialysis dose, either by daily daytime hemodialysis or by nocturnal hemodialysis [20,21••,22••]. The dramatic improvements in interdialytic hypertension are accompanied by reduced MSNA, plasma norepinephrine, and systemic vascular resistance. As cardiac output is unchanged, the reduced MSNA and blood pressure may be caused by more effective dialysis of some uremic toxins (or other chemical substances in the uremic milieu) that tonically activate excitatory renal afferents.

In a study by Zilch et al. [22••], conversion from conventional three-times-weekly hemodialysis to short daily hemodialysis significantly reduced but did not totally normalize MSNA. The decrease in MSNA was accompanied by parallel reductions in systemic vascular resistance and blood pressure, with unchanged ultrafiltration volume and cardiac output. The need for antihypertensive medication was eliminated in half the patients. All values returned to prestudy levels when patients were switched back to conventional hemodialysis, suggesting a real effect. However, this was a small study of only 11 patients and the provocative findings need to be confirmed in larger studies.

In a study of 10 hemodialysis patients by Chan et al. [21••], conversion to nocturnal hemodialysis completely normalized blood pressure and virtually eliminated the need for antihypertensive medication. The improvement was rapid, occurring within only 2 months, and was associated with improved arterial baroreceptor control of heart rate and arterial compliance, presumably due to a reduced calcium-phosphorus product with less arterial wall calcification. Baroreceptors are pressure-sensitive nerve endings that respond to mechanical deformation of the vascular walls in which they are embedded. The same level of arterial blood pressure should cause greater baroreceptor firing when the aortic arch and carotid sinus vessels are compliant (nocturnal hemodialysis) than when they are stiff (conventional hemodialysis). Thus, the improved blood pressure control could be due to reduced neurogenic vasoconstrictor tone (ie, MSNA) in the resistance arterioles and improved compliance of the conduit

arteries. Large outcome trials are needed to determine if cardiovascular morbidity and mortality are substantially improved by conversion from conventional to nocturnal hemodialysis. If so, nocturnal hemodialysis should become part of Medicare benefits.

The sympathetic nerves are activated not only in patients with end-stage renal disease but also in those with stage 2 to 3 chronic kidney disease [16,17]. Interestingly, the activation mechanism seems to involve a central action of angiotensin II—a central rather than peripheral (reflex) mechanism of action [17,23]. Thus, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can reduce elevated levels of MSNA in patients with hypertension and chronic kidney disease but not in those with hypertension and normal renal function [9••,16,24]. However, the initial studies by Koomans et al. [16] and by Neumann et al. [24] were limited to small numbers of patients with chronic kidney disease.

A recent study by Neumann et al. [25••] confirmed and extended the previous conclusions with 10 times the number of patients with chronic kidney disease. The new data substantiate that either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker reduces sympathetic activation in chronic kidney disease. However, MSNA was not completely normalized, indicating that other mechanisms almost certainly are involved.

From a clinical standpoint, it would be important to know whether more complete normalization of sympathetic nerve activity—by adding sympatholytics to the antihypertensive regimen—slows progression of chronic kidney disease and reduces cardiovascular morbidity and mortality beyond that achieved by blood pressure reduction and RAAS inhibition alone [26]. Some animal data suggest this may be the case [16], but unfortunately industry has little monetary incentive to sponsor clinical trials involving generic sympatholytics. Government and foundation sponsorships are needed.

The sympathetic nervous system may be an even more important therapeutic target for obesity-related hypertension, which is increasingly important in the initiation and progression of chronic kidney disease and other forms of hypertensive target-organ disease [9••,27].

Obesity-Related Hypertension: With and Without Obstructive Sleep Apnea

It is estimated that obesity contributes to as much as 60% of all hypertension [28]. Sympathetic activation is considered one of the most important mechanisms linking obesity to hypertension and hypertensive target-organ damage [29]. With weight gain, increased sympathetic nerve activity is thought to be a compensatory mechanism to burn more fat, but at the expense of sympathetic activation in tissues regulating blood pressure—kidney and vascular smooth muscle [30]. However, a recent study questions this teleology. Shibao et al. [31] found that ganglionic blockade caused a greater decrease in blood pressure in obese than in lean hypertensive patients but surprisingly had a smaller effect on resting energy expenditure.

What stimulates the sympathetic nerves in obese individuals? There are two hypotheses, which are not mutually exclusive: 1) adipokines (leptin and other substances released by adipocytes) cross the blood-brain barrier and activate sympathetic nerve activity centrally, and 2) obstructive sleep apnea causes hypoxia and activates the carotid body chemoreceptors [9••,28].

In obstructive sleep apnea, repeated arterial desaturation during sleep triggers wild swings in MSNA and blood pressure [32]. Furthermore, the chemoreflex seems to reset, causing sustained sympathetic activation even during the day. A recent study in rats implicates the neuronal isoform of nitric oxide synthase (nNOS) in this resetting process [33]. Intermittent hypoxia reduced brain levels of nNOS. Neuronally generated nitric oxide is involved in the signaling pathways that tonically restrain sympathetic outflow from the brainstem [34]. Thus, sympathetic nerve activity increases during hypoxia-induced reductions in brainstem nNOS. In patients with obstructive sleep apnea, the increased nighttime and daytime levels of MSNA can be so severe as to produce plasma and urine norepinephrine levels mimicking a pheochromocytoma [35].

If obstructive sleep apnea leads to a common form of neurogenic hypertension, why is continuous positive airway pressure (CPAP)—the best available treatment for obstructive sleep apnea—so underwhelming as an antihypertensive therapy? Three recent meta-analyses show that CPAP lowers blood pressure by only 2 mm Hg on average [36–38]. Is this because sympathetic nerve activity had not been normalized? We do not have sufficient data to tell. However, the meta-analyses indicate considerable interindividual variation in blood pressure reduction with CPAP; the greatest effect being in patients with congestive heart failure, whose daytime systolic blood pressure fell by 15 mm Hg and daytime MSNA by 17% [39].

The clearest evidence linking MSNA and blood pressure reduction with correction of obstructive sleep apnea comes from a single case report: blood pressure, MSNA, and obstructive sleep apnea all were normalized with CPAP but unaffected by uvulopalatopharyngoplasty [40]. In another study, short-term withdrawal of CPAP led to worsening of obstructive sleep apnea and increased urinary norepinephrine [41]. The field needs prospective, adequately powered long-term randomized controlled trials of CPAP for obstructive sleep apnea-related hypertension with sizeable microneurographic substudies. Even if the outcomes are positive, newer therapeutic approaches are needed to overcome the adherence problems inherent with CPAP.

In this regard, investigators have shown that obstructive sleep apnea is not only a hyperadrenergic state but also a state of hyperaldosteronism [42–44]. Excessive stimulation of mineralocorticoid receptors in the brainstem has been shown to increase sympathetic nerve activity—at least in animals [44]. Furthermore, hyperaldosteronism can cause laryngeal edema, which consequently can aggravate obstructive sleep apnea [45]. Recent evidence suggests that mineralocorticoid receptor antagonists can ameliorate obstructive sleep apnea–induced hypertension, but further studies are needed to determine if this is a robust effect and mediated at least in part by reduced sympathetic nerve activity [44].

Most overweight and obese hypertensive individuals do not have obstructive sleep apnea. Despite initial evidence suggesting that obstructive sleep apnea is a prerequisite for sympathetic activation in human obesity, subsequent data have shown convincingly that this is not the case [9••]. Esler et al. [9••] and Lambert et al. [46••] have provided evidence that without obstructive sleep apnea, obesity-related hypertension is accompanied by a highly characteristic pattern of sympathetic activation—one that differs qualitatively from that in lean hypertensive individuals.

In obese and nonobese hypertensive patients, previous work has shown that sympathetic activation is targeted to the kidneys and the skeletal muscle bed [9••]. In nonobese hypertensive patients, the sympathetic activation also is targeted to the heart, presumably contributing to left ventricular hypertrophy and ventricular arrhythmias. However, in obese patients with hypertension, the heart somehow is spared this sympathetic activation [9••]. Thus, the earlier work by Esler, Lambert, and colleagues has implicated the cardiac sympathetic nerves in pressure-overload cardiac hypertrophy (ie, hypertension-related left ventricular hypertrophy) but not in obesity-related cardiac remodeling and hypertrophy. Their latest work uses a higher power "microscope" to dissect out fundamental differences in sympathetic discharge patterns in obese and nonobese hypertensive individuals [46••].

Most microneurographic studies report MSNA as multiunit activity—the integrated electrical activity of 10 to 100 individual axons firing at different rates. With refinement in the technique, it now is possible to record the discharge rates of single axons within a human muscle nerve fascicle [8••]. Using such single-unit recordings, Lambert et al. [46••] recently found that hypertension in nonobese patients is associated with an increased firing rate of single axons that already are active. In contrast, obesity increases MSNA by recruiting previously silent fibers, without an increase in firing rate. The remarkable implication is that the central neural circuits driving postganglionic MSNA are frequency modulated in lean patients with hypertension but amplitude modulated in obesity-related hypertension—"FM" versus "AM"! If distinct signaling mechanisms could be delineated, perhaps more specific drug targets could be established.

Whatever the precise mechanisms by which obesity begets sympathetic activation, a recent study shows that—at least in dogs—obesity-related hypertension can be completely normalized by sustained reflex sympathetic inhibition with an implanted carotid baroreceptor pacemaker [47]. In the 1960s, carotid baroreceptor pacing was shown to be an effective therapy for refractory hypertension and angina [48]. However, this therapy was short lived due to rapid development of much better antihypertensive drugs and technical limitations of pacemaker surgery—tissue secretions shorted out the electrical contact between the pacing electrodes and the baroreceptor nerves within days or weeks after pacemaker implantation. Now, 50 years later, there is renewed interest in developing a baroreceptor pacemaker for human hypertension [48]. In the past decade, new antihypertensive drug discovery has slowed considerably, and technical breakthroughs in electrode manufacturing allow long-term baroreceptor pacing in dogs and apparently even in humans [48]. A new-generation baroreceptor pacemaker currently is undergoing evaluation in multicenter clinical trials, and could be a radical nonpharmacologic treatment for obesity-related hypertension and other forms of human hypertension with a strong sympathetic neural component [48].

Conclusions

Using microelectrode recordings of sympathetic activity and radiotracer measurements of regional norepinephrine spillover in human hypertensive patients, recent research has advanced several provocative findings with novel—but still largely potential—therapeutic implications for clinical hypertension. These include a stronger scientific rationale for using 1) combined α/β-blockers in the early phases of primary hypertension and obesity-related hypertension; 2) RAAS blockers as central sympatholytics in hypertension associated with chronic kidney disease; and 3) a higher dialysis dose—either nocturnal or short daily hemodialysis—to reduce uremic stimulation of a blood pressure-raising reflex arising in the failing kidneys. New outcomes trials are needed if we are to translate this largely theoretical body of research into everyday clinical practice.

Disclosures

Dr. Victor has received a research grant from Pfizer, has served on the speaker and advisory boards for Novartis, and has served on the advisory board for CVRx.

Dr. Shafiq reports no potential conflict of interest relevant to this article.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. National Institute for Health and Clinical Excellence: **Hypertension: Management in adults in primary care: pharmacological update.** Available at http://www.nice.org.uk/nicemedia/pdf/HypertensionGuide.pdf. Accessed January 2008.
2. Victor RG, Kaplan NM: **Systemic hypertension: mechanisms and diagnosis.** In *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine,* edn 8. Edited by Libby P, Bonow RO, Mann DL, Zipes DP. Philadelphia: Saunders/Elsevier; 2007:1027–1046.
3. Schlaich MP, Lambert E, Kaye DM, et al.: **Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation.** *Hypertension* 2004, **43:**169–175.
4. Esler M, Lambert E: **Reduced HRV and baroreflex sensitivity as universally applicable cardiovascular "risk factors"; waiting for the bubble to burst.** *Clin Auton Res* 2003, **13:**170–172.
5. Taylor JA, Studinger P: **Counterpoint: cardiovascular variability is not an index of autonomic control of the circulation.** *J Appl Physiol* 2006, **101:**678–681.
6. Vongpatanasin W, Taylor JA, Victor RG: **Effects of cocaine on heart rate variability in healthy subjects.** *Am J Cardiol* 2004, **93:**385–388.
7. Vallbo AB, Hagbarth KE, Wallin BG: **Microneurography: how the technique developed and its role in the investigation of the sympathetic nervous system.** *J Appl Physiol* 2004, **96:**1262–1269.
8.•• Wallin BG, Charkoudian N: **Sympathetic neural control of integrated cardiovascular function: insights from measurement of human sympathetic nerve activity.** *Muscle Nerve* 2007, **36:**595–614.

Superb, comprehensive review.

9.•• Esler M, Straznicky N, Eikelis N, et al.: **Mechanisms of sympathetic activation in obesity-related hypertension.** *Hypertension* 2006, **48:**787–796.

Reviews the recent results in the field.

10. Guyenet PG: **The sympathetic control of blood pressure.** *Nat Rev Neurosci* 2006, **7:**335–346.
11.• Grassi G, Seravalle G, Trevano FQ, et al.: **Neurogenic abnormalities in masked hypertension.** *Hypertension* 2007, **50:**537–542.

Demonstrates increased levels of MSNA in individuals with masked hypertension that are indistinguishable from those in patients with persistent hypertension both in and out of the office.

12. Pickering TG, Eguchi K, Kario K: **Masked hypertension: a review.** *Hypertens Res* 2007, **30:**479–488.
13.• Fu Q, Zhang R, Witkowski S, et al.: **Persistent sympathetic activation during chronic antihypertensive therapy: a potential mechanism for long term morbidity?** *Hypertension* 2005, **45:**513–521.

Provocative study indicating that losartan-hydrochlorothiazide exacerbates sympathetic activation in hypertension.

14. Mancia G, De BG, Dominiczak A, et al.: **2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).** *Eur Heart J* 2007, **28:**1462–1536.
15. Bakris GL, Fonseca V, Katholi RE, et al.: **Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial.** *JAMA* 2004, **292:**2227–2236.
16. Koomans HA, Blankestijn PJ, Joles JA: **Sympathetic hyperactivity in chronic renal failure: a wake-up call.** *J Am Soc Nephrol* 2004, **15:**524–537.
17. Kotanko P: **Cause and consequences of sympathetic hyperactivity in chronic kidney disease.** *Blood Purif* 2006, **24:**95–99.
18. Converse RL Jr, Jacobsen TN, Toto RD, et al.: **Sympathetic overactivity in patients with chronic renal failure.** *N Engl J Med* 1992, **327:**1912–1918.
19. Campese VM, Krol E: **Neurogenic factors in renal hypertension.** *Curr Hypertens Rep* 2002, **4:**256–260.
20. Chan CT, Harvey PJ, Picton P, et al.: **Short-term blood pressure, noradrenergic, and vascular effects of nocturnal home hemodialysis.** *Hypertension* 2003, **42:**925–931.
21.•• Chan CT, Jain V, Picton P, et al.: **Nocturnal hemodialysis increases arterial baroreflex sensitivity and compliance and normalizes blood pressure of hypertensive patients with end-stage renal disease.** *Kidney Int* 2005, **68:**338–344.

Conversion from conventional hemodialysis to nocturnal hemodialysis led to improved arterial baroreflex function and a substantial fall in blood pressure.

22.•• Zilch O, Vos PF, Oey PL, et al.: **Sympathetic hyperactivity in haemodialysis patients is reduced by short daily haemodialysis.** *J Hypertension* 2007, **25:**1285–1289.

Conversion from conventional three-times-weekly hemodialysis to short daily hemodialysis significantly reduced MSNA and blood pressure.

23. Campese VM, Shaohua Y, Huiquin Z: **Oxidative stress mediates angiotensin II-dependent stimulation of sympathetic nerve activity.** *Hypertension* 2005, **46:**533–539.
24. Neumann J, Ligtenberg G, Klein II, et al.: **Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment.** *Kidney Int* 2004, **65:**1568–1576.
25.•• Neumann J, Ligtenberg G, Klein IH, et al.: **Sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment.** *Hypertension* 2007, **49:**506–510.

Confirmed that RAAS blockers reduce sympathetic nerve activity in patients with chronic kidney disease.

26. Neumann J, Ligtenberg G, Oey L, et al.: **Moxonidine normalizes sympathetic hyperactivity in patients with eprosartan-treated chronic renal failure.** *J Am Soc Nephrol* 2004, **15:**2902–2907.
27. Biaggioni I: **The sympathetic nervous system and blood volume regulation: lessons from autonomic failure patients.** *Am J Med Sci* 2007, **334:**61–64.
28. Biaggioni I: **Should we target the sympathetic nervous system in the treatment of obesity-associated hypertension?** *Hypertension* 2008, **51:**168–171.
29. Mancia G, Bousquet P, Elghozi JL, et al.: **The sympathetic nervous system and the metabolic syndrome.** *J Hypertens* 2007, **25:**909–920.
30. Landsberg L: **A teleological view of obesity, diabetes and hypertension.** *Clin Exp Pharmacol Physiol* 2006, **33:**863–867.
31. Shibao C, Gamboa A, Diedrich A, et al.: **Autonomic contribution to blood pressure and metabolism in obesity.** *Hypertension* 2007, **49:**27–33.
32. Narkiewicz K, Wolf J, Lopez-Jimenez F, Somers VK: **Obstructive sleep apnea and hypertension.** *Curr Cardiol Rep* 2005, **7:**435–440.
33. Huang J, Tamisier R, Ji E, et al.: **Chronic intermittent hypoxia modulates nNOS mRNA and protein expression in the rat hypothalamus.** *Respir Physiol Neurobiol* 2007, **158:**30–38.
34. Thomas GD, Zhang W, Victor RG: **Nitric oxide deficiency as a cause of clinical hypertension: promising new drug targets for refractory hypertension.** *JAMA* 2001, **285:**2055–2057.
35. Young WF Jr: **Adrenal causes of hypertension: pheochromocytoma and primary aldosteronism.** *Rev Endocr Metab Disord* 2007, **8:**309–320.

36. Alajmi M, Mulgrew AT, Fox J, et al.: **Impact of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea hypopnea: a meta-analysis of randomized controlled trials.** *Lung* 2007, **185:**67–72.
37. Bazzano LA, Khan Z, Reynolds K, He J: **Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea.** *Hypertension* 2007, **50:**417–423.
38. Haentjens P, Van MA, Moscariello A, et al.: **The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials.** *Arch Intern Med* 2007, **167:**757–764.
39. Usui K, Bradley TD, Spaak J, et al.: **Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure.** *J Am Coll Cardiol* 2005, **45:**2008–2011.
40. Donadio V, Liguori R, Vetrugno R, et al.: **Parallel changes in resting muscle sympathetic nerve activity and blood pressure in a hypertensive OSAS patient demonstrate treatment efficacy.** *Clin Auton Res* 2006, **16:**235–239.
41. Phillips CL, Yang Q, Williams A, et al.: **The effect of short-term withdrawal from continuous positive airway pressure therapy on sympathetic activity and markers of vascular inflammation in subjects with obstructive sleep apnoea.** *J Sleep Res* 2007, **16:**217–225.
42. Calhoun DA, Nishizaka MK, Zaman MA, Harding SM: **Aldosterone excretion among subjects with resistant hypertension and symptoms of sleep apnea.** *Chest* 2004, **125:**112–117.
43. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, et al.: **Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension.** *Chest* 2007, **131:**453–459.
44. Pimenta E, Calhoun DA: **Resistant hypertension and aldosteronism.** *Curr Hypertens Rep* 2007, **9:**353–359.
45. Shiota S, Ryan CM, Chiu KL, et al.: **Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects.** *Thorax* 2007, **62:**868–872.
46.•• Lambert E, Straznicky N, Schlaich M, et al.: **Differing pattern of sympathoexcitation in normal-weight and obesity-related hypertension.** *Hypertension* 2007, **50:**862–868.
Fascinating study showing different patterns of single unit sympathetic activity in obese and nonobese hypertensives.
47. Lohmeier TE, Dwyer TM, Irwin ED, et al.: **Prolonged activation of the baroreflex abolishes obesity-induced hypertension.** *Hypertension* 2007, **49:**1307–1314.
48. Filippone JD, Bisognano JD: **Baroreflex stimulation in the treatment of hypertension.** *Curr Opin Nephrol Hypertens* 2007, **16:**403–408.