That hypertension is due to a derangement of sympathetic and parasympathetic cardiovascular regulation is one of the most widely accredited and tested hypotheses in cardiovascular research. Its proposal followed from the demonstration that autonomic cardiovascular influences play a fundamental role in homeostatic control of the cardiovascular system. In animal models of hypertension, both an increased sympathetic nerve activity and a reduction of vagal cardiac tone are associated with and responsible for the appearance and maintenance of high blood pressure, with their role expanding to include hypertension-related sequelae.1–3 Albeit through a longer and more difficult journey, evidence is now available that similar autonomic alterations may have a causative or cocausative role also in the generation and maintenance of human hypertension.4–7

We begin this review by describing the alterations in autonomic cardiovascular control that characterize human hypertension. We then discuss the possible mechanisms underlying these abnormalities and their importance in the development and progression of the structural and functional cardiovascular damage that characterizes hypertension. Finally, we examine the modifications of sympathetic and vagal cardiovascular influences induced by current nonpharmacological and pharmacological interventions aimed at correcting elevations in blood pressure and restoring the normotensive state. (Circ Res. 2014;114:1804-1814.)

Key Words: hypertension ■ parasympathetic nervous system ■ sympathetic nervous system

Abnormal increases in circulating plasma levels of the adrenergic neurotransmitters norepinephrine and epinephrine

Autonomic Dysfunction in Prehypertension

Abnormal increases in circulating plasma levels of the adrenergic neurotransmitters norepinephrine and epinephrine

The Autonomic Nervous System and Hypertension

Giuseppe Mancia, Guido Grassi

Abstract: Physiological studies have long documented the key role played by the autonomic nervous system in modulating cardiovascular functions and in controlling blood pressure values, both at rest and in response to environmental stimuli. Experimental and clinical investigations have tested the hypothesis that the origin, progression, and outcome of human hypertension are related to dysfunctional autonomic cardiovascular control and especially to abnormal activation of the sympathetic division. Here, we review the recent literature on the adrenergic and vagal abnormalities that have been reported in essential hypertension, with emphasis on their role as promoters and as amplifiers of the high blood pressure state. We also discuss the possible mechanisms underlying these abnormalities and their importance in the development and progression of the structural and functional cardiovascular damage that characterizes hypertension. Finally, we examine the modifications of sympathetic and vagal cardiovascular influences induced by current nonpharmacological and pharmacological interventions aimed at correcting elevations in blood pressure and restoring the normotensive state. (Circ Res. 2014;114:1804-1814.)

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have repeatedly been demonstrated in normotensive individuals with a family history of hypertension. Moreover, these abnormalities are detectable when measured during maneuvers that activate autonomic cardiovascular control.9–13 Pressor responses to a variety of laboratory stressors have also been examined and found to predict the subsequent development of hypertension.14,15 Furthermore, in a more refined experimental approach (measurement of the clearance of norepinephrine after the infusion of small amounts of its radiolabeled form), it was shown that the increase in norepinephrine is not due to its reduced tissue disposal but rather to an enhanced spillover rate from neuroeffective junctions and thus to augmented norepinephrine secretion from sympathetic nerve terminals.16 Finally, in microneurographic studies aimed at quantifying postganglionic sympathetic nerve traffic to the skeletal muscle circulation and including normotensive controls, both the number and amplitude of sympathetic bursts were shown to be higher not only in individuals with a family history of hypertension17 but also in those with white-coat and masked hypertension (Figure 1).18–20 that is, conditions in which patients have a markedly greater risk of progressing to true hypertension.21 Thus, there is little doubt that a central sympathetic overdrive is present in individuals predisposed to developing high blood pressure because of either a genetic background or a specific blood pressure phenotype. Interestingly, this sympathetic hyperactivity is likely to be accompanied by an impaired vagal influence on the heart. Evidence for this impairment comes from studies of the normotensive offspring of hypertensive parents. In this group, spectral analysis of the R–R interval showed a reduction of low-frequency fluctuations in heart rate,22,23 that is, fluctuations that are known to be a component of heart rate variability that reflects vagal modulation of the sinus node.24 Thus, not just 1 but both divisions of the autonomic nervous system may be altered in individuals who have a greater risk of developing hypertension, even when an overt blood pressure abnormality is not yet detectable. This points to the causative role of the autonomic nervous system in the development of high blood pressure condition.

**Autonomic Dysfunction in Early Hypertensive Phases**

Further support for a causative or cocausative role of autonomic dysfunction in hypertension comes from the multiple lines of evidence showing that young hypertensive individuals and those in the early stages of hypertension also have an increased sympathetic and a reduced cardiac vagal drive. Seminal studies performed many years ago clearly demonstrated that in young patients with so-called hyperkinetic syndrome, that is, an increase in systolic blood pressure, an increase in cardiac output, and a resting tachycardia,25 the elevations in heart rate depended on a reduced vagal inhibitory influence on the sinus node because the intravenous administration of atropine (which selectively blocks the effect of the vagal neurotransmitter acetylcholine on muscarinic receptors) restored both heart rate and blood pressure to the normal values of the control group.26 Additional evidence of a reduced tonic vagal cardiac inhibition was obtained in subsequent studies, in which atropine was shown to elicit a lower increase in heart rate in young borderline hypertensives than in age-matched controls.27 Finally, smaller reductions in glandular secretions under parasympathetic control, such as salivary flow,28 in borderline hypertensive individuals suggest that in early hypertension, parasympathetic impairment is not confined to the heart or to the cardiovascular system; rather, it is generalized to all parasympathetically dependent functions.

In parallel with the parasympathetic alterations, early hypertension is characterized by increased sympathetic activity and sympathetic cardiovascular influences. Years ago, intravenous injection of the β-blocker propranolol was shown to cause a greater reduction of heart rate in borderline hypertensive individuals than in controls, documenting the association of initial hypertensive status with a greater sympathetic tone to the sinus node.26 Studies with radiolabeled norepinephrine have extended to borderline hypertension the observations made in prehypertensive conditions (see above).29 Finally, direct evidence of a heightened central adrenergic drive in hypertension comes from microneurographic recordings of the efferent postganglionic sympathetic nerve fibers of young individuals with either a high-normal blood pressure or borderline hypertension, in whom sympathetic nerve traffic to the skeletal muscle is significantly reduced compared to normotensive controls.30

![Figure 1. Muscle sympathetic nerve activity (MSNA), expressed as burst frequency over time (bs/min, left) and as burst frequency corrected for heart rate (bs/100 hb), measured by microneurography in the peroneal nerve in normotensive subjects (NT) and in age-matched patients with white-coat hypertension (WCHT) and masked hypertension (MHT). *P<0.05 and **P<0.01 in a comparison between groups. Data are shown as the mean±SE. Adapted with permission from Grassi et al (American Heart Association, 2007).20](image-url)
sympathetic nerve activity; and NA, not assessed.

True resistant pregnancy

Hypertension in failure

Hypertension and renal failure

Hypertension and heart failure

Hypertension and obesity

Hypertension and metabolic syndrome

Hypertension and diabetes mellitus

Hypertension in pregnancy

Table. Conditions Characterized by Blood Pressure Elevation Associated With Sympathetic Activation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Plasma Norepinephrine</th>
<th>MSNA</th>
<th>Norepinephrine Spillover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (males/ females)</td>
<td>↑</td>
<td>↑</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic/diastolic hypertension</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>↑=</td>
<td>↑</td>
<td>↑=</td>
</tr>
<tr>
<td>Hypertension (young age)</td>
<td>↑=</td>
<td>↑</td>
<td>↑=</td>
</tr>
<tr>
<td>Hypertension (middle age)</td>
<td>↑=</td>
<td>↑</td>
<td>↑=</td>
</tr>
<tr>
<td>Hypertension (elderly)</td>
<td>↑</td>
<td>↑</td>
<td>↑=</td>
</tr>
<tr>
<td>Hypertension with/without nocturnal dipping</td>
<td>↑=</td>
<td>↑</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension and obesity</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Hypertension and metabolic syndrome</td>
<td>↑=</td>
<td>↑</td>
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<tr>
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<tr>
<td>Hypertension and renal failure</td>
<td>↑</td>
<td>↑</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension in pregnancy</td>
<td>↑=</td>
<td>↑</td>
<td>NA</td>
</tr>
<tr>
<td>True resistant hypertension</td>
<td>↑=</td>
<td>↑</td>
<td>NA</td>
</tr>
</tbody>
</table>

† indicates increase; =, unchanged vs normotensive controls; MSNA, muscle sympathetic nerve activity; and NA, not assessed.

isolated elevation of systolic blood pressure. The same has been found in patients with both high blood pressure and metabolic risk factors, such as obesity, metabolic syndrome, or diabetes mellitus. These observations have led to the conclusion that in hypertension, sympathetic hyperactivity is a generalized phenomenon, irrespective of the heterogeneous clinical aspects that accompany a high blood pressure state. Indeed, in studies that included matched controls, sympathetic activity was significantly greater in obese hypertensives than in lean ones, possibly because obesity is frequently accompanied by an insulin-resistant state that elevates the level of circulating insulin, whose sympathostimulating effect has been documented (see the discussion below on Mechanisms of Autonomic Alterations in Hypertension section). Because obesity, metabolic syndrome, and diabetes mellitus all have a high prevalence in the population and are frequently associated with hypertension, hypertensives can be expected to have in general an even greater degree of sympathetic activity than shown in studies on more selected groups of patients.

Sympathetic Activation and Hypertension Severity

Studies performed by our group and by others found that the adrenergic overdrive that characterizes hypertension is not stable but instead follows the blood pressure increase and the progression from uncomplicated to complicated stages that may occur in the course of the disease. The relationship between adrenergic outflow and blood pressure values is illustrated in Figure 2, which refers to data obtained from microneurographic recordings of sympathetic nerve traffic in normotensive individuals versus those with mild and more marked blood pressure elevations. Compared with the normotensive group, the number of neural bursts was progressively greater in the 2 hypertensive conditions. This was also the case when nerve traffic was quantified as burst amplitude, and the data were adjusted for between-group differences in heart rate. Other studies revealed that sympathetic activation is normally more pronounced in complicated than in uncomplicated stages of hypertension. Indeed, sympathetic nerve firing was not found to differ in hypertensive patients with a blunted versus a normal nocturnal blood pressure fall, despite the notoriously greater severity of cardiovascular risk in the former (nondippers) than in the latter (dippers) category of patients. However, for a similar increase in blood pressure, hypertensive patients with impaired renal function have a sympathetic nerve overactivity that steadily increases as renal function progressively deteriorates. Likewise, compared with the respective controls, sympathetic activations were shown to be more pronounced in hypertensive patients with (1) left ventricular hypertrophy, (2) impaired left ventricular diastolic function, (3) systolic heart failure (Figure 3), and (4) ventricular arrhythmias of an advanced Lown class. Finally, for a similar blood pressure elevation, muscle sympathetic nerve firing is much less pronounced in patients with hypertension who respond to antihypertensive drug administration with an adequate blood pressure fall than in so-called resistant hypertensives, in whom the concurrence of a variety of factors result in a
high blood pressure state that is severe enough to prevent a therapeutically effective blood pressure fall, despite treatment with multiple antihypertensive drugs.63 There are thus consistent data to suggest that activation of the adrenergic nervous system evolves from less to more severe hypertensive states, that is, it increases with the increase in blood pressure values, the development of organ damage, and the appearance of clinically apparent renal or cardiac disease or of treatment ineffectiveness.

Although much less evidence is available, and despite an already marked initial functional impairment,1 a similar progressive activation likely explains the hypertension-related alteration of the parasympathetic division of the autonomic nervous system. This can be inferred from the finding that from normotension to mild and more severe degrees of blood pressure elevation, there is a gradual reduction of the bradycardic and tachycardic responses to baroreceptor stimulation and deactivation, respectively (Figure 4, left),41 a major mechanism of heart rate control. Because these responses are largely reduced, or even abolished, by the administration of atropine,64 the mechanism is likely to be a progressive impairment of cardiac vagal modulation.

**Regional Distribution of Sympathetic Activation**

Although addressed in only a limited number of studies, it nonetheless seems clear that the sympathetic overactivity associated with the established hypertensive phase is not uniformly distributed throughout the body; rather, regional differences are such that it is marked in some districts and modest or even absent in others. For example, radiolabeling studies have shown that in established hypertension, there is increased norepinephrine spillover into the cerebral, coronary, and renal circulation but not at the level of the splanchnic and pulmonary vascular districts.7 In microneurographic measurements of sympathetic nerve traffic, skin neural outflow was not increased in hypertension, whereas an increase was observed in muscle.65 The discrepancy, however, does not seem to be peculiar to the essential hypertensive state because a sympathetic nerve traffic that is augmented in muscle but normal in skin occurs in several other clinical conditions, for example, heart failure, cirrhosis, obesity, obstructive sleep apnea, and metabolic syndrome (Figure 5).6,66,67 We can therefore speculate that the preservation of skin sympathetic outflow in diseases characterized by an overall enhanced sympathetic drive is secondary to the body’s crucial need to modulate
heat dissipation rapidly (thereby preserving an effective temperature control) via prompt alterations of vasomotor tone to cutaneous vessels.

Whether the heterogeneity in regional sympathetic drive that occurs in hypertension also applies to the heart versus the peripheral circulation must be considered as well. Compared with normotensive controls, hypertensive individuals have a significant, albeit small, increase in heart rate. Given the markedly impaired cardiac baroreflex control typical of those with high blood pressure (see above), reduced vagal influences on the sinus node are most likely involved. However, the previously mentioned smaller bradycardic effect of β-blockade and the increase in cardiac norepinephrine spillover together suggest the additional participation of an increased cardiac sympathetic drive. Studies performed by our group have shown that in healthy people but also in those with hypertension and other diseases, there is a significant correlation between heart rate and both muscle sympathetic nerve traffic and plasma norepinephrine. Thus, as far as its sympathetic drive is concerned, the heart seems to reflect, at least qualitatively, the changes taking place in several important vascular districts.

Sympathetic Activity, Organ Damage, and Cardiovascular Complications

Because associations do not necessarily mean cause–effect relationships, an important question is whether the increasing sympathetic activity that accompanies the gradual increase in...
the severity of hypertension reflects a pathogenetic role. In animal models, sympathetic influences have been documented to cause or at least favor alterations in cardiac and vascular structure or function. Those studies have also shown that this occurs independently of blood pressure changes. To cite a few examples: (1) the addition of norepinephrine or epinephrine to vascular smooth muscle cell cultures is followed by an increase in cell replication, a key step in the cascade of events that lead to atherosclerotic plaque formation; (2) in rabbits, wall thickness is markedly greater in the intact common carotid artery than in the contralateral chronically denervated vessel; (3) in rats, carotid artery distensibility increases after long-lasting nonhypotensive chemical sympathectomy; and (4) chronic infusions of subpressor doses of norepinephrine in rats increase cardiac cell volume and lead to cardiac hypertrophy.

Evidence that sympathetic influences promote organ damage is available also in humans. In a group of patients undergoing surgical treatment of Dupuytren disease, anesthesia of the brachial plexus was followed by a marked reduction in ipsilateral radial artery stiffness in the absence of blood pressure modifications. A reduction of ipsilateral femoral artery stiffness not related to blood pressure occurred after hemianesthesia of the lower spinal cord performed in patients undergoing arthroscopic surgery of the knee or after unilateral lumbar sympathectomy to treat peripheral artery disease. Compared with the contralateral intact vessel, distensibility was markedly higher in the radial artery of a heterotransplanted hand, with a return to control values after reinnervation occurred.

Most importantly, sympathetic nerve activity may be, either directly or indirectly, a predictor of cardiovascular morbidity and mortality. First, sympathetic activity is associated with and is probably a determinant of blood pressure variability, which itself is a cardiovascular risk factor independent of average blood pressure values. Second, although no studies
have been done in hypertension, sympathetic hyperactivity, as measured by plasma norepinephrine, systemic norepinephrine spillover, or microneurography, is known to be an independent prognostic factor for cardiovascular-related morbid or fatal events in patients with heart failure, end-stage renal failure, major cardiac arrhythmias, obstructive pulmonary disease, or after an acute stroke (Figure 6).77–83

Mechanisms of Autonomic Alterations in Hypertension

Several mechanisms have been proposed to explain the sympathetic overdrive seen in individuals with essential hypertension (Figure 7). An attractive hypothesis is that overdrive depends on an excessive adrenergic response to environmental stimuli, leading initially to greater blood pressure variability and later to a sustained hypertensive state.84 Although this hypothesis has found support in experimental models of hypertension, in which induced chronic stresses lead to a permanent elevation in blood pressure,1 there is no similarly conclusive evidence in humans, in whom the definition of real-life stress is difficult and the availability of standardizable and reproducible laboratory stress maneuvers with which to study its long-term effects is limited.85 It has also been proposed that sympathetic overdrive originates from a reduced inhibitory influence of the arterial baroreceptors because cellular impairment or a stiffening of the arterial wall where these baroreceptors are located attenuates their responsiveness to blood pressure changes. In several animal species, however, arterial baroreceptor denervation is followed by a marked increase of blood pressure variability, with little or no change in long-term mean blood pressure values.86–88 Accordingly, this reflex mechanism is thought to be more involved in blood pressure stabilization than in the determination of its average levels.6 Furthermore, in hypertensive humans, the arterial baroreflex loses much of its ability to control heart rate, but it continues to effectively modulate blood pressure and sympathetic activity (Figure 4, right).41 These observations weaken the baroreflex hypothesis, although they do not completely rule out its possible role in the maintenance and progression of sympathetic drive as blood pressure severity increases. There are 2 reasons for this, as also shown in Figure 4. First, as blood pressure increases, so does the range of blood pressure and sympathetic modulation exerted by the baroreflex; this resetting phenomenon helps to stabilize both blood pressure and sympathetic activity at the higher values.41 Second, an increased sympathetic drive may be favored by the reduced inhibitory influence of cardiac stretch receptors, which occurs when hypertension-related diastolic dysfunction and left ventricular hypertrophy

Figure 8. Effects of physical training, diet-induced weight loss, and a marked or mild low-sodium diet on systolic (S) and diastolic (D) blood pressure (BP, top), muscle sympathetic nerve activity (MSNA, central), and MSNA baroreflex sensitivity (bottom). The data were obtained before (black bars, continuous lines) and after (dashed bars, dashed lines) each intervention. Note that while physical training and weight loss induce, along with a reduction in BP, a significant decrease in MSNA together with an improvement in baroreflex control of MSNA, dietary sodium interventions cause a marked sympathetic stimulation together with baroreflex impairment. *P<0.05 and **P<0.01 in a comparison of the data obtained before and after each nonpharmacological intervention. Data are shown as the mean±SE. MAP indicates mean arterial pressure. Redrawn with data derived from references 104–106.
reduce the stimuli (changes in cardiac volume and myocardial contractility) to which these receptors respond.89

Other possible mechanisms are chemoreceptor stimulation by ischemic hypoxia,89 an increased influence of afferent sympathetic nerve fibers,91 and a reciprocal excitatory influence between the sympathetic nervous system and the metabolic and humoral systems also involved in cardiovascular regulation.9 Chemoreceptor stimulation was long ago proposed as a cause of hypertension.90 Evidence for its potential role as a sympathostimulating factor has recently been strengthened by the observation that hypoxia is important for the increased sympathetic activity seen in individuals with sleep apnea,92 a condition frequently associated with obesity and, as such, highly prevalent in hypertension as well.93 Support for a hypothesis that includes a role for afferent sympathetic nerve fibers, originally proposed based on the cardiovascular effects of their stimulation or removal in animals,91,94,95 comes from observations of the blood-pressure-lowering effect of renal denervation (which severs afferent signals from the kidney to the brain) in humans with resistant hypertension (discussed below).7,96 Finally, evidence is available from animal and human studies that insulin and leptin increase postganglionic sympathetic drive97 and that central and peripheral sympatho- stimulating effects are also exerted by angiotensin II.98,99 In these instances, the stimulation is reciprocated by the sympathetic nervous system in a kind of positive feedback relationship.5,46,47,97 Thus, several mechanisms are potentially capable of activating sympathetic nervous influences in essential hypertension, but the relative importance of each one in the different stages or types of hypertension remains to be clarified. Although the claim has been made that sympathetic hyperactivity is perhaps the earliest abnormality,100 the temporal sequence of sympathetic versus other alterations have not yet been conclusively established.

**Autonomic Alterations During Pharmacological and Nonpharmacological Antihypertensive Treatment**

Several studies have measured sympathetic activity or cardiovascular influences during antihypertensive drug treatment. Sympathetic activity usually increases in the first few days after the administration of antihypertensive drugs, including those with central or peripheral sympathomodulating effects. This can be attributed to the reflex activation brought about by the unloading of arterial baroreceptors in response to an acute fall in blood pressure.101,102 During long-term antihypertensive drug treatment, however, the initial acute activation fades (because the baroreflex is reset toward the lower blood pressure value achieved by treatment), with a return of sympathetic activity to levels that are more similar to those of the untreated condition.102 Sympathetic activity does not entirely return to the pretreatment condition with thiazide diuretics and calcium channel blockers (especially the short-acting ones) whose administration is thus characterized by a further degree of chronic sympathetic activation compared with the untreated state.102 This is the case also for blockers of α-adrenergic receptors the administration of which is associated with a reflex increase of central sympathetic drive (offset by the peripheral α-blockade) and a marked cardiac stimulation.103 This is, by contrast, not the case for central agents (clonidine and moxonidine), β-blockers, blockers of the renin–angiotensin system, or mineralocorticoid receptor antagonists, which may reduce sympathetic activity compared with the level measured in untreated patients and improve vagal cardiac control.102,103 However, these agents are not able to restore the sympathetic activity characteristic of individuals with a normal blood pressure.102 That is, compared with controls, sympathetic hyperactivity and parasympathetic impairment continue to be evident also in patients with hypertension whose blood pressure is effectively reduced by treatments based on these drugs.

A reduction in sympathetic nerve activity and an increase in cardiac vagal drive have also been reported for the lifestyle interventions used in clinical practice to lower an elevated blood pressure, such as physical exercise and loss of body weight.104,105 As seen in the 2 left parts of Figure 8, the fall in blood pressure is accompanied in either case by a reduction of muscle sympathetic nerve traffic and the increased ability of baroreceptor activation or unloading to regulate the sympathetic drive. The 2 right parts of Figure 8, however, show that these autonomic modifications are not achieved with all lifestyle interventions. Namely, in established cases of hypertension, dietary sodium restriction seems to further alter sympathovagal balance, ie, to impair reflex sympathetic control, and to concomitantly further increase the number of sympathetic bursts to the skeletal muscle circulation.106–108 The effect is marked when the sodium restraint is marked as well but present even with moderately low-sodium intake (80 mmol NaCl/d),107 suggesting that a low-sodium diet, as usually implemented in daily life, enhances the hypertension-related alterations of autonomic cardiovascular control.

Recently, 2 invasive approaches, continuous carotid baroreceptor stimulation and renal denervation, have been proposed as therapeutic procedures to lower blood pressure effectively in patients with resistant hypertension.7,96,109 Bilateral (and, more recently, monolateral) carotid baroreceptor stimulation via an implanted device has been shown to lower blood pressure on a long-term (4 years) basis. As expected, the antihypertensive effect is accompanied by a reduction of sympathetic nerve activity but not, or to only a minor degree, by a concomitant bradycardia.110 Bilateral renal nerve ablation (by catheters delivering high-frequency current or ultrasound) has similarly been found to lower blood pressure on a similar chronic basis.111,112 However, negative results have also been reported113–115 including those from a recent randomized trial in which the office and ambulatory blood pressure effects of renal denervation were not significantly greater after 6 months than those seen in a properly designed control group, that is, a group in which sham denervation was used.116 Renal denervation has also been found to be followed by sympathetic inhibition,117–119 although again the procedure has no effect on sympathetic nerve activity in some studies,114 and the association between the changes in sympathetic activity and those in blood pressure changes has been at best only minor.111–113,117–119 Thus, whether renal denervation is therapeutically effective and the extent to which the positive results are
explained by sympathetic deactivation remains a matter for further investigation.

Conclusions

The data reviewed in this article provide evidence of an attenuation of autonomic cardiovascular control in essential hypertension and that adrenergic overdrive is a major component of this autonomic dysregulation. They also show that adrenergic activation has an early appearance in the course of the disease and becomes more pronounced with the increasing severity of the hypertensive state. They finally show that adrenergic mechanisms also participate in the development of target-organ damage, which is frequently detectable in patients with hypertension. Taken together, the findings discussed herein provide a rationale for pursuing sympathetic deactivation by nonpharmacological as well pharmacological interventions aimed at lowering elevated blood pressure values and protecting patients from hypertension-related complications.

It should additionally be emphasized, however, that many questions remain about the pathophysiological and clinical aspects of hypertension-related adrenergic activation. For example, the identification of patients with hypertension in whom the pathogenetic role of sympathetic hyperactivity predominates over other potential pathogenetic factors is difficult in the clinical setting. Furthermore, in patients in whom sympathetic hyperactivity is suspected or confirmed, it is virtually impossible to detect among the multiple potential candidate mechanisms, the one(s) responsible. Finally, the prognostic importance of adrenergic overdrive, especially with respect to its independent impact on cardiovascular morbidity and mortality, has been documented in several diseases but never studied in hypertension. Despite the disappointing results of a large-scale outcome trial, on the protective effect of an antihypertensive agent in the treatment of hypertension, the Framingham heart study. Circulation. 1999;99:1831–1836.


Renal denervation: current implications and future perspectives. 


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