Assessment of Sympathetic Cardiovascular Drive in Human Hypertension: Achievements and Perspectives
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Assessment of Sympathetic Cardiovascular Drive in Human Hypertension
Achievements and Perspectives

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Abstract—Methodological refinements in the assessment of human sympathetic cardiovascular drive have allowed throughout the years to better define the role of the sympathetic nervous system in the pathophysiology of hypertension. Earlier studies have provided evidence that indirect markers of adrenergic drive, such as plasma or urinary norepinephrine as well as heart rate, often display an increase in the hypertensive state. Direct recording of efferent postganglionic muscle sympathetic nerve traffic via microneurography and regional norepinephrine spillover technique have conclusively documented the occurrence of an adrenergic overdrive in hypertension, showing that the sympathetic activation is directly related to the severity of the hypertensive state and is widespread to different cardiovascular districts. The present review will focus on some major features of the “neuroadrenergic hypothesis of hypertension.” In particular it will examine the mechanisms responsible for the adrenergic overdrive, the relationships between the sympathetic activation and the metabolic disarray of frequent detection in the hypertensive state, and the participation of neuroadrenergic factors at the development of the hypertension-related target organ damage. Further issues addressed will be the contribution of the hyperadrenergic state to the different patterns of the 24-hour blood pressure profile as well as to the day/night blood pressure variability described in the hypertensive state and the behavior of the sympathetic function in the hypertensive states complicated by the presence of other cardiovascular or metabolic disease. Finally, the clinical and therapeutic implications of the neuroadrenergic abnormalities occurring in hypertension, as well as the areas worthy of future research, will be highlighted. (Hypertension. 2009;54:690-697.)

Key Words: sympathetic nervous system ■ hypertension ■ target organ damage ■ 24-hour ambulatory blood pressure ■ cardiometabolic risk

The role of the sympathetic nervous system (SNS) in the pathogenesis of hypertension (HT) has been remarkably changed over the past 50 years. Indeed, until a few decades ago it was believed that sympathetic neural influences were almost univocally involved in the short-term blood pressure (BP) control, with limited or even no impact at all on long-term BP regulation and development of high BP. This concept, however, has drastically changed over the past 20 years, thanks to the development of methodological approaches allowing direct assessment of systemic and regional sympathetic cardiovascular drive in humans.1–5

This review will focus on the changing face of the SNS in HT. This will be done by reviewing how technical refinements in the assessment of human adrenergic function have substantially modified our thinking on this issue. The review will also examine the most recent data collected in the field, allowing to better define the role of the SNS in the pathophysiology of HT-related target organ damage, the relationships with clinic, home, and ambulatory BP as well as the links with the metabolic disarray frequently detected in HT (Figure 1). Finally, the perspectives and expectations of future research in the field will be addressed.

Sympathetic Overdrive in HT: Background Evidence

General Features
Since the first reports describing the behavior of some indirect hemodynamic markers of the adrenergic function, such as resting heart rate and cardiac output, in young essential hypertensives, the hypothesis has been prompted that at least in selected groups of patients with borderline BP elevation coupled with an hyperkinetic circulation sympathetic cardiovascular influences undergo a potentiation.1,4 This has been confirmed via biochemical assay of urinary adrenergic metabolites as well as of circulating plasma levels of norepinephrine (ie, the main adrenergic neurotransmitter).5,6 Although intriguing, the results of the above mentioned studies failed to provide conclusive information on the multifaced profile of the SNS in HT. For example, they were...
unable to clarify whether and to what extent the adrenergic overdrive is hallmark of the hypertensive disease or it rather represents a specific feature of selected hypertensive states. In addition, at that time it was unknown whether the increase in sympathetic drive does homogeneously affect all circulatory districts or it is rather confined to specific organs. Finally, and more importantly, these initial studies did not allow to establish whether the adrenergic dysfunction is a phenomenon selectively involving the peripheral SNS, the central SNS, or both of these two neural compartments.

The development of sophisticated techniques allowing more direct assessment of human sympathetic function, such as the norepinephrine radiolabeled spillover technique, the microneurographic recording of efferent postganglionic muscle sympathetic nerve firing rate and, to some extent, the power spectral analysis of the heart rate signal,1–3,7 has allowed, however, to obtain more conclusive information on the above mentioned issues. Such information can be summarized as follows. First, studies performed by using direct as well as indirect approaches to assess neuroadrenergic function have almost univocally shown that the HT-related sympathetic overdrive is detectable not only in borderline but also in mild to moderate and in more severe essential HT (Figure 2, left panel).8,9 Second, in HT the magnitude of the sympathetic activation goes in parallel with the magnitude of the BP increase,9 thereby supporting the hypothesis that the two phenomena are linked together through a cause/effect relationship. Three, published studies have also shown that

Figure 1. Schematic drawing of the pathophysiological role of the sympathetic activation in hypertension (HT), 24-hour blood pressure (BP) profile, end-organ damage, and metabolic abnormalities associated with a high blood pressure state. OSA indicates obstructive sleep apnea.

Figure 2. Behavior of muscle sympathetic nerve traffic (MSNA), expressed as bursts incidence corrected for heart rate (bs/100 hb) in mild-to-moderate (MEH) and severe (SEH) hypertension (left panel), in white coat (WCHT) and masked (MHT) hypertension (central panel) and nondipper (NDHT) and reverse dipper (RDHT) hypertensives (right panel). In each panel, data referring to normotensive control subjects (C) are shown. Values are represented as mean±SEM. Symbols refer to the statistical significance between data obtained in normotensive control subjects (NT1, NT2, NT3) vs other conditions. Modified with permission from Grassi et al.9,12,14

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the adrenergic hyperactivity is detectable in (1) HT affecting young, middle-age, and elderly people,8–10 (2) systolic and isolated systolic HT,10 (3) pregnancy-induced HT,11 (4) white-coat and masked HT (Figure 2, central panel),12,13 and (5) dipping, extreme dipping, nondipping, and reverse dipping condition (Figure 2, right panel).14,15 Although few studies failed to detect any substantial difference in sympathetic drive between normal and high BP state,16,17 the majority of the investigations provided results that consistently indicated the sympathetic overdrive as a hallmark of HT of essential nature.

Further fuel to the “neuroadrenergic hypothesis of HT” came from the evidence that at least in some clinical forms of secondary HT, such as primary hyperaldosteronism, Cushing syndrome, and, although nonunivocally, renovascular HT, sympathetic drive is not augmented, pointing toward the specificity of the hyperadrenergic state to the hypertensive syndrome, and, although nonunivocally, renovascular HT, HT of essential nature.

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The dichotomy of the skin/muscle SNS pattern is likely to depend on the fact that whereas muscle and cardiac as well as renal sympathetic activity is under baroreflex control,21,24 skin sympathetic nerve traffic does not depend on baroreceptor modulation.21–24

Central Versus Peripheral Neuroadrenergic Abnormalities

The microneurographic technique and the jugular veins norepinephrine spillover methodology are at present the only available approaches capable of providing direct information on the behavior of central sympathetic neural drive.1–3,26 Although both the methods do not allow to exclude that mechanisms related to ganglionic transmission of the neural signal may contribute at the HT-related SNS activation, their systematic use in HT research has prompted the hypothesis that the HT-related adrenergic activation is by and large of a central nature. This implies that in HT the increase in circulating norepinephrine mainly originates from a “true” increase in central sympathetic neural outflow. The relevant participation of the central SNS at the HT-related sympathetic overdrive does not deny, however, that peripheral factors may also contribute at a chronic BP elevation. Indeed, by making use of sophisticated methodologies allowing to assess the reactivity of peripheral vascular adrenergic receptors to sympathetic agonists and antagonists or the peripheral turnover of the adrenergic neurotransmitters, it has been found that human HT is characterized by (1) a downregulation of peripheral α-adrenergic receptors,27 (2) an impairment in the neuronal reuptake of norepinephrine from sympathetic nerve terminals,3,6,7 and (3) an altered functional interaction at the level of the vascular wall between norepinephrine, epinephrine, and other humoral (such as angiotensin II), metabolic (including insulin and leptin), or endothelium-derived substances.25 Altogether the above mentioned mechanisms may contribute to the increase in peripheral vasoconstrictor tone as well as to the abnormal vasomotor responsiveness to adrenergic stimuli reported in HT.

Sympathetic Overdrive in HT: New Findings

The unequivocal demonstration that sympathetic activation accompanies HT since its earlier clinical phases and it goes hand by hand with the clinical severity of the disease has provided a definite answer to the question as to whether the hypertensive state can count on a “sympathetic ground” in its pathophysiological profile. This demonstration, however, also generated new questions on the functional role of the HT-related hyperadrenergic state. These refer in particular to (1) the mechanisms responsible for the adrenergic overdrive, (2) the relationships between the sympathetic activation and the metabolic disarray of frequent detection in HT, (3) the participation of neuroadrenergic factors at the development of the HT-related target organ damage, (4) the contribution of the hyperadrenergic state to the different patterns of the 24-hour BP profile and to the day/night BP variability described in HT, and (5) the behavior of sympathetic function in HT complicated by the presence of other cardiovascular or metabolic disease.

Mechanisms Responsible for the Adrenergic Overdrive

Because one of the major servomechanisms responsible for the sympathetic/parasympathetic homeostatic BP control is the baroreflex function, some years ago it has been proposed that a derangement in this reflex modulation might be responsible for the adrenergic abnormalities reported in HT.1–29 In particular the hypothesis has been prompted that baroreflex control of vagal and sympathetic influences to the heart and the peripheral circulation undergoes an impairment in HT, thus favoring on one side the increase in resting heart rate and on the other the potentiation of the adrenergic drive to peripheral vessels.30 However, although conclusive evidence has been provided that vagal-heart rate control exerted by arterial baroreceptors is impaired in HT, no available data support the hypothesis that a similar impairment does affect the sympathetic component of the baroreflex, which on the contrary appears in HT to be preserved and resetted toward
higher BP values.9 The above findings generated new research aimed at defining some other factors responsible for the HT-related adrenergic overdrive, leading to a number of not necessarily mutually-exclusive working hypotheses. These include the possibility that reflexes stemming from volume-sensitive receptors located in the so-called cardiopulmonary region, which tonically restrain adrenergic outflow and are indeed impaired in HT, might be responsible for the adrenergic alteration.9,29,31 They also include the possibility that a similar impairment would affect arterial chemoreceptors, whose control of sympathetic outflow is altered particularly when obesity or overweight-dependent obstructive sleep apnea accompanies HT.32–34 They additionally include the evidence that the HT-related adrenergic overdrive retains an humoral origin, namely that it is triggered by the central and/or peripheral sympathoexcitatory effects exerted by angiotensin II, leptin, insulin9,28,35,36 (ie, substances whose circulating plasma levels are all increased in HT). Finally, evidence has been provided that nutritional or behavioral factors, such as low sodium intake or increased alcohol consumption, may trigger marked sympathoexcitatory effects,37,38 which may be responsible, at least in part, for the HT-related adrenergic overdrive.

**Relationships Between Sympathetic Activation and Metabolic Disarray**

In recent years the hypothesis has been prompted that a consistent portion of the sympathetic overactivity described in HT could depend on the metabolic disarray frequently detectable in the hypertensive state and known under the term of “metabolic syndrome.” Particular emphasis has been given to the hyperinsulinemic state (and to the related insulin resistance condition),39 which represents one of the hallmarks of the disease. The link between insulin and sympathetic overdrive is founded on the evidence that in both experimental animals and man insulin may trigger marked sympathoexcitatory effects, which are likely to depend on the direct stimulatory action this hormone has on central adrenergic neural outflow.40–42 To make the whole picture more complex, however, it should be mentioned that an increased adrenergic state has been shown per se to favor the development and progression of an hyperinsulinemic state.43 This makes it hard to determine whether in HT the sympathetic activation is the consequence or rather the cause of the insulin resistance state (so-called “chicken and egg question”).44 although some data collected in longitudinal studies seem to support the latter hypothesis.45 As above-mentioned, a further metabolic factor potentially involved in the HT-related sympathoexcitatory activation is leptin,46 whose circulating plasma levels are increased in HT and appear to parallel the magnitude of the adrenergic overdrive.47

**Adrenergic Overdrive and Organ Damage**

Until a few years ago it was unsettled whether and to what extent HT-related target organ damage was triggered only by hemodynamic factors (ie, by the pressure and the volume overload) or also by neurohumoral factors, which may promote directly or indirectly the development and progression of the cardiovascular structural alterations.48 Many humoral factors have been proposed, including the adrenergic neurotransmitters. Indeed, in vitro and in vivo studies in experimental animals have shown that exogenously-administered norepinephrine may trigger a myocardial cell hypertrophic process independently on its hemodynamic effects.49–50 The evidence in man, however, was scant until a few years ago, when microneurographic studies allowed to show that, for a similar BP elevation, hypertensive patients with left ventricular hypertrophy display a sympathetic activation greater for magnitude than that seen in hypertensives without cardiac organ damage.9,31,52 This finding has been strengthened by the evidence that left ventricular mass, detected by magnetic resonance, is directly related to sympathetic nerve traffic.53 All together these data suggest that the adrenergic overdrive may participate at the development and progression of the cardiac structural alterations. This hypothesis has been recently reinforced by the results of a longitudinal study performed in hypertensive patients showing that plasma norepinephrine predicts left ventricular mass values at the follow-up, independently on confounders.54

Another cardiac abnormality associated with HT (ie, left ventricular diastolic dysfunction) appears to be also accompanied by an increased adrenergic drive, independently on the presence of cardiac hypertrophy.55 In this instance, however, it is more difficult to determine whether the sympathetic dysfunction is the cause, or rather the consequence, of the cardiac functional alteration.

Information on the relationships between sympathetic overdrive and target organ damage in HT is not limited, however, to the cardiac district. Indeed, studies performed in both experimental animals and humans have shown that HT-related vascular remodeling process may be mediated by sympathetic factors. In particular the hypothesis has been prompted that at least at the level of small resistance arteries adrenergic mechanisms play a role in the development of the eutrophic remodeling process.6,7,48 Although adrenergic mechanisms are deeply involved in the regulation of vascular distensibility, stiffness and compliance at the level of large- and medium-size arteries,7,48 no data are available in HT on the relationships between adrenergic overdrive and vascular alterations.

Finally, in recent years a number of studies have examined whether sympathetic factors play a role in the development as well as in the progression of the renal organ damage, frequently detected in HT. The above-mentioned hypothesis is based on pioneering studies in experimental animals showing that a renal sympathetic activation contributes at the abnormal natriuresis and diuresis reported in HT.56 The information collected in man refers in particular to end-stage renal failure, in which a marked adrenergic overdrive has been documented.57 Interestingly, in this condition the sympathetic abnormalities closely and directly relate to (1) asymmetrical dimethylarginine (ADMA) plasma levels and thus presumably endothelial dysfunction and (2) left ventricular mass.58 Because both of these two variables represent in renal failure important markers of cardiovascular risk, it was not unexpected to discover, in a prospective study, that the degree of sympathetic overdrive was directly related to cardiovascular mortality.59
In contrast, much less information is available on whether the earlier alterations in renal function, frequently detected in the hypertensive disease, are linked to sympathetic abnormalities. Preliminary data from an ongoing study by our group seem to indicate that this may indeed be the case. If confirmed in a large number of patients, this finding suggests that, similar to what is seen in heart failure, also in renal insufficiency the degree of the adrenergic activation parallels the clinical severity of the disease.

**Adrenergic Overdrive, 24-Hour BP Profile, and BP Variability**

Sympathetic neural mechanisms exert a powerful control not only on absolute BP values but also on their spontaneous oscillations occurring during the daytime and nighttime. This evidence encouraged investigators to examine whether and to what extent the different patterns of the 24-hour BP profile might be characterized by a different behavior of the SNS. Data were collected in hypertensive patients displaying at night a dipping or a nondipping BP state. The results showed no difference in the resting sympathetic activation, this being the case also in the extreme dipping pattern (ie, in the condition characterized by a marked nighttime BP reduction). In contrast, when sympathetic nerve traffic was assessed in patients showing during nighttime a reverse BP dipping pattern (ie, no change or even an increase in nighttime as compared to daytime BP), a potentiation of the sympathetic activation observed in the other above-mentioned 3 groups of patients was seen (Figure 2, right panel). This allowed to conclude that SNS may participate at determining the pattern of the nighttime BP profile in hypertensive patients. This conclusion, although intriguing, faces an important limitation, namely that the relationship sought between sympathetic activity and day/night BP difference is based on SNS measurements performed during daytime. Because in physiological conditions sympathetic nerve traffic, and more in general other markers of sympathetic drive, such as heart rate and plasma norepinephrine, undergo a marked reduction during sleep, it should be crucial to determine in future studies whether the degree of sympathetic inhibition occurring at night is different in presence of different nighttime BP patterns (see below).

Research in this area has been further expanded in the past few years with investigations aimed at determining whether and to what extent sympathetic neural mechanisms contribute at modulating not only absolute BP values but also BP variability (ie, the spontaneous BP oscillations physiologically occurring during the 24-hour period). A recent study has shown that in normotensive subjects BP variability undergoes a progressive increase as the degree of the resting sympathetic activation also increases. Interestingly, in this study greater levels of sympathetic activity were linked to greater BP falls at night. The results of the present study and those obtained by our group in dippers, nondippers, and extreme and reverse dippers suggest that the pattern of nighttime BP may be differentially modulated by sympathetic factors in normotensive and hypertensive people. This indicates, in other words, that sympathetic modulation of nighttime BP reported in the normotensive state may undergo profound alterations in presence of HT.

In recent years, attempts have been made also to clarify which of the different cyclic, noncyclic, as well as residual components of the BP variability display a closer relationships to sympathetic activity. The preliminary results of this investigation, performed in the context of the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, suggest that while cyclic components of BP variability (which are directly related to cardiovascular risk) are under sympathetic influence, the 2 other components not displaying any significant dependence on the SNS.

**Sympathetic Activation in HT Complicated by Metabolic Disease**

The HT-related adrenergic overdrive has been found to be greater for magnitude when metabolic diseases are detected in conjunction with a high BP state. This has been shown to be the case in obesity-related HT, in which the SNS activation is increased as compared to the one seen in the obese or hypertensive state alone. The same phenomenon has been also documented when diabetes mellitus accompanies HT or when the various components of the metabolic syndrome include HT. Finally, evidence has been provided that the hyperadrenergic state typical of a congestive heart failure state is progressively more and more pronounced as HT and obesity alone or combined together are detected. At variance from what is reported in uncomplicated HT, however, when HT is combined to obesity, metabolic syndrome, congestive heart failure, or diabetes, an increase in heart rate and in plasma norepinephrine values can be frequently observed. This may suggest that in clinical conditions characterized by a marked adrenergic overdrive also markers of sympathetic activity less specific and sensitive than the microneurographic ones, such as heart rate and plasma norepinephrine, may provide valuable information.

**Future Developments and Perspectives**

Despite the remarkable achievements in our understanding the role of SNS in the development of HT, several issues still remain almost completely unaddressed or partially defined. These include methodological, pathophysiological, clinical, and therapeutic aspects. From a methodological view point, the use of microdialysis techniques allowing continuous and direct measurement of norepinephrine levels in different tissues should be implemented. Another approach to be implemented is represented by the single fiber nerve traffic recording, which would allow to obtain more in-depth information of the possible mechanisms underlying HT-related SNS activation. Another area of implementation should be dynamic assessment of sympathetic nerve traffic during sleep stages in patients with uncomplicated and complicated HT (including sleep apnea). This would allow to clarify whether (1) sympathetic activity is inhibited to a similar extent in all hypertensive conditions, (2) the various dipping patterns are really characterized by sympathetic nerve traffic differences during nighttime, and (3) the magnitude of the morning BP surge (which, according to some authors, retains an important impact on cardiovascular risk) displays a relationship with...
the sympathetic activation occurring in the early morning hours.

From a pathophysiologic point of view, future research should also attempt to solve the enigma related to the possible influences of genetic factors on sympathetic activation in HT. Indeed, evidence has been provided that (1) interindividual differences in sympathetic activity have a genetic background,72 (2) single gene mutations (specifically melanocortin-4 receptor gene) may affect blood pressure as well as SNS activity,73 and (3) α-adrenoreceptor gene polymorphisms might be related to sympathetic activation.74 However, although interesting, these contentions require further investigation, not allowing at the moment a clear-cut unifying hypothesis to be drawn. Future research should also clarify whether the relationship between systemic arterial BP and adrenergic drive are also shared by BP measurements made at the site of the aortic artery (so called “central” BP). Because this variable appears to exert an important pathogenic role in the development of cardiovascular disease,75 this information should also provide important clinic insights. Additional areas of research are represented by the assessment of sympathetic drive (1) in the so-called prehypertensive state (ie, the clinical condition characterized by BP levels between 130 to 139 mm Hg systolic and 85 to 89 mm Hg diastolic) and (2) in presence of earlier vascular and renal alterations, such as retinal arteriolar-venular ratio and microalbuminuria, respectively. In addition, although the role of sympathetic neural factors in the development and progression of target organ damage is well documented, it is still unsettled whether the adrenergic overactivity of the hypertensive state exerts such dangerous consequences as to have an independent impact on cardiovascular morbidity and mortality, as documented for other disease.6,7,28,59 Finally, future investigations in the field of the adrenergic nervous system should also provide information of therapeutic relevance. This has been already provided for some antihypertensive drugs or lifestyle interventions.76 A pilot study of recent publication seems to expand these therapeutic implications by showing that in resistant HT a catheter-based renal sympathetic denervating procedure may be of potential help in reducing elevated BP and lowering by 28% and 47% systolic and diastolic BP.77,78

Conclusions

In conclusion, the information achieved so far and the results expected in the near future confirm that the research aimed at testing the so-called “neuroadrenergic hypothesis of HT” has been, and it is still at present, an active and productive one, capable of providing new insights in the field of the pathophysiology of HT.

Disclosures

None.

References


