Sympathetic Control of Circulation in Hypertension and Congestive Heart Failure

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Adrenergic overactivity is a common hallmark of both essential hypertension and congestive heart failure. Indirect and direct measures of sympathetic function have clearly shown that sympathetic activation characterizes essential hypertension. This adrenergic overactivity appears to be related to the severity of the hypertensive state, being detectable in its early stages and showing a progressive increase with the severity of the disease. Essential hypertension is also associated with an impaired baroreflex control of vagal activity, whereas baroreceptor modulation of sympathetic nerve traffic remains unaltered, although undergoing a resetting phenomenon. In contrast, secondary hypertension is not associated with an increased adrenergic activity, thus suggesting that an enhancement in efferent sympathetic outflow is a peculiar feature of essential hypertension. Congestive heart failure is a condition also characterized by sympathetic activation, whose degree is proportional to the clinical severity of the disease. This is paralleled by an impairment in arterial baroreceptor modulation of both vagal and sympathetic activity, thus suggesting that the adrenergic overactivity in congestive heart failure is triggered by a reduced afferent restraint on the vasomotor centre. Chronic angiotensin-converting enzyme inhibition reduces the degree of both sympathetic activation and baroreflex dysfunction occurring in heart failure patients, a finding which documents that the neurohumoral abnormalities can be at least partially reversed by pharmacologic treatment. *Key words: autonomic nervous system, baroreceptors, congestive heart failure, essential hypertension, secondary hypertension, sympathetic nervous system.*

INTRODUCTION

An increase in adrenergic tone and an impaired reflex control of the cardiovascular system have been repeatedly advocated in recent years as key pathophysiological factors in the development of essential hypertension and its complications. Whether the adrenergic abnormalities observed in essential hypertension are present in high blood pressure states of a secondary nature has not yet been clarified. Sympathetic overactivity is also an important feature of another cardiovascular disease, namely, congestive heart failure, and is accompanied by profound abnormalities in autonomic reflex control of the cardiovascular system. Neural mechanisms, in addition to well-known haemodynamic alterations, have been shown largely to contribute to the downward shift of progressive heart failure.

The aim of the present paper is briefly to review available knowledge on the pathophysiological role of abnormalities of sympathetic cardiovascular homeostasis in hypertension and in congestive heart failure. This is done answering three main questions: (1) How early in the clinical progression of each condition do the sympathetic alterations occur? (2) What are the potential underlying mechanisms? (3) Can the described alterations be reversed by pharmacologic treatment?

SYMPATHETIC ACTIVITY IN ESSENTIAL AND SECONDARY HYPERTENSION

Several methodological approaches employed to evaluate adrenergic drive in essential hypertension provide unequivocal evidence that this condition is characterized by sympathetic overactivity. Conflicting data were initially obtained by plasma norepinephrine measurement, however, some studies showing increased, unaltered or even decreased plasma levels of the adrenergic neurotransmitter. A metanalysis of 32 studies performed by Goldstein [1] showed a consistent and significant increase in plasma norepinephrine in hypertensive sub-
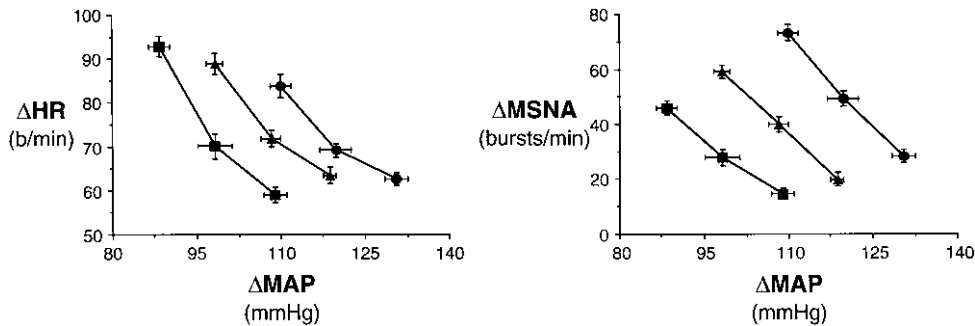
Fig. 1. Curves relating changes in heart rate (ΔHR) and in muscle sympathetic nerve activity (ΔMSNA; expressed as changes in burst frequency) in response to graded increases and reductions in mean arterial pressure (MAP absolute values) induced by phenylephrine or nitroprusside in normotensive subjects (*squares*, n = 13), in patients with moderate essential hypertension (*triangles*, n = 14) and in patients with more severe essential hypertension (*circles*, n = 14). Data are shown as means ± SEM. The overall amplitude of the heart rate responses to mean arterial pressure changes induced by the vasoactive drugs is reduced in both degrees of essential hypertension, while no reduction can be seen in the case of muscle sympathetic nerve activity (MSNA, bursts/min). Mid-line symbols represent baseline.

jects compared with normotensive controls. This has since been confirmed in recent studies in which the norepinephrine spillover technique has been employed [2], a more sensitive approach allowing the limitations of the plasma norepinephrine technique to be overcome by excluding factors related to tissue clearance and/or peripheral blood flow. Evidence has therefore been provided that hypertensives, particularly at a young age, are characterized by an increased adrenergic tone [3], and that a widespread sympathetic activation, involving outflows to the heart and kidneys [4], but also to the brain [5], characterizes high blood pressure states.

The microneurographic technique providing direct and reproducible assessment of adrenergic tone in humans [6, 7] has allowed the sympathetic abnormalities characterizing the hypertensive state to be defined. These take place in the early stages of the disease, because normotensive subjects with a family history of hypertension [8] and borderline hypertensive patients [9] display an increase in muscle sympathetic nerve traffic compared to age-matched controls. The sympathetic activation, however, is not confined to the early stages of the disease. Indeed, recent data collected by our group clearly demonstrate, again using the microneurographic technique, that stable essential hypertension is also characterized by adrenergic overactivity, which is already evident in mild hypertensives and becomes more marked in more severe hypertensives, its degree thus being related to the severity of the hypertensive state [10]. This is paralleled by a progressive loss of baroreflex modulation of vagal activity, thus confirming what had already been demonstrated about 25 years previously by the Oxford group [11]; what our study has demonstrated, however, for the first time, is that baroreflex control of sympathetic nerve activity in essential hypertension remains unaffected,

although functioning at the higher prevailing blood pressure levels. This has been shown by the evidence of preserved reflex sympathoinhibitory and sympathoexcitatory responses to baroreflex activation and deactivation induced by stepwise phenylephrine and nitroprusside intravenous infusions [10]. This provides a direct demonstration that baroreflex modulation of blood pressure in human hypertension is preserved and undergoes a resetting phenomenon, rather than an impairment (Fig. 1) [10].

Although the precise mechanisms responsible for the sympathetic activation of essential hypertension are still unknown, it is possible to hypothesize that an increased efferent neural adrenergic drive may be centrally mediated. Neurohumoral substances, such as insulin and angiotensin II, for instance, are known to stimulate central sympathetic outflow in man [12, 13]. Sympathetic overactivity characterizing high blood pressure could also derive from an impairment of reflex mechanisms that exert a physiological restraint on central sympathetic outflow, i.e. an alteration of the "afferent" branch of the reflex. As previously mentioned, we have shown that a primitive alteration of arterial baroreceptors represents an unlikely mechanism, at least in middle-aged hypertensives, since baroreflex function in these subjects is preserved although with an upward resetting of its range of action. Severe hypertension leading to left ventricular hypertrophy, however, is associated with a marked impairment of sympathetic control of the cardiovascular system exerted by cardiopulmonary receptors [14, 15]. It can therefore be postulated that impairment of the cardiopulmonary reflex is involved in the origin of the sympathetic activation typical of essential hypertension.

Secondary forms of hypertension are characterized by different sympathetic neural function behaviour. Indeed,
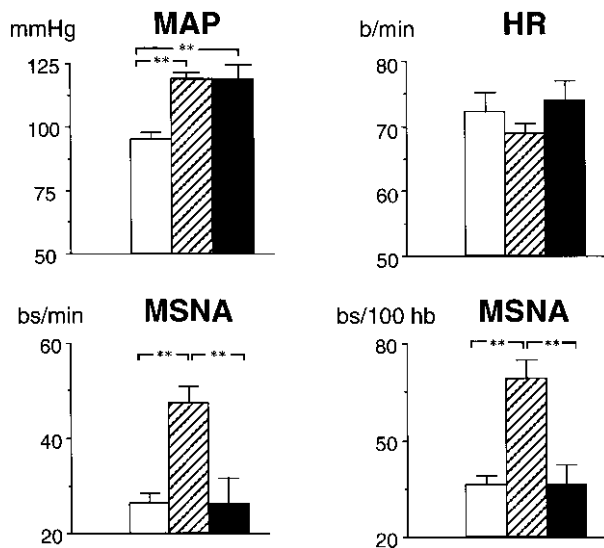
Fig. 2. Bar graphs showing mean arterial pressure (MAP), heart rate (HR) and muscle sympathetic nerve activity (MSNA) expressed as burst frequency over time (*left*) or corrected for heart rate values (*right*) in normotensive controls (*white hystograms*, n = 10), essential hypertensives (*dashed hystograms*, n = 10), and secondary hypertensives (*black hystograms*, n = 12). Data are means ± SEM. Asterisks: **$p < 0.01$. For similar MAP and HR values, MSNA is markedly and significantly increased only in essential hypertensives, while no such increase is observable in secondary hypertensives.

we have found that, in secondary hypertensives affected by either adrenal pheochromocytoma or renovascular hypertension, adrenergic tone is not increased, a finding which suggests that the sympathetic activation is a peculiar feature of essential hypertension (Fig. 2) [10]. This is accompanied by a selective impairment of vagal baroreflex modulation, while sympathetic baroreflex control is once again unaltered, although reset. Therefore, baroreflex changes associated with hypertension, i.e. upward resetting and impairment of cardiac control, do not seem to be specific for a given hypertensive condition and probably follow the blood pressure elevation. As a whole, these findings indicate that the increase in blood pressure in secondary hypertension is not neurogenically mediated but depends more on peripheral factors, such as the increase in peripheral plasma catecholamine synthesis or angiotensin II levels.

SYMPATHETIC ACTIVATION IN HEART FAILURE

Several lines of evidence collected in past decades have demonstrated that congestive heart failure, along with the inherent haemodynamic changes, is characterized by a wide spectrum of neurohumoral alterations. The imbalanced neurohumoral control of the cardiovascular system, while primarily related to a selective failure of the heart to provide an adequate peripheral tissue perfusion, gradually becomes a generalized phenomenon contributing to the progression of the failing heart syndrome. A key feature of these alterations is represented by sympathetic over-activity which can induce deleterious effects, such as: (1) increased cardiac work and myocardial oxygen consumption; (2) myocardial necrosis; (3) down-regulation of β-adrenergic receptors; (4) cardiac arrhythmias; (5) tissue anoxia; (6) fluid retention and peripheral oedema; (7) reduced renal blood flow; (8) sodium retention and potassium loss.

The sympathetic nervous system in heart failure has been extensively studied using different methodological approaches. Measurement of norepinephrine concentrations in plasma or urine in wide populations of heart failure patients has clearly shown that the levels of this adrenergic neurotransmitter are not only increased [16, 17] but also closely related to the patient's survival [18, 19], thus representing an important prognostic marker of heart failure. Studies performed by directly measuring the clearance of norepinephrine and thus calculating the "net" spillover of the sympathetic neurotransmitter from the neuroeffector junctions, through the radiolabelled norepinephrine technique, have demonstrated that sympathetic activation in heart failure patients involves several regional cardiovascular districts, such as the heart, the kidneys, the skeletal muscle and the brain [20, 21]. The increase in norepinephrine spillover in these vascular districts is due more to an augmented release rate of the adrenergic neurotransmitter from adrenergic nerve endings than to flow-dependent changes in the tissue clearance of this substance [22, 23]. Finally, microneurographic studies performed by directly assessing muscle sympathetic nerve activity in a peroneal nerve have documented that congestive heart failure is characterized by an increased neural adrenergic drive, which is accompanied by a clearcut impairment in sympathetic cardiovascular control, exerted by both arterial baroreceptors and cardiopulmonary volume receptors [24–26]. Eckberg and co-workers [27] proved the ability of arterial baroreceptors to modulate vagal activity, i.e. heart rate, as long ago as the early 1970s. This has subsequently been confirmed in later reports [28, 29].

The sympathetic abnormalities seem to take place in the early phase of the disease, since in large trials plasma norepinephrine levels have been shown to be increased not only in severe heart failure patients, belonging to New York Heart Association (NYHA) classes III or IV, but also, although to a less extent, in milder stages of disease. This finding has been further confirmed in a study by our group [28], in which we found that muscle sympathetic nerve activity, directly recorded via the microneuro-graphic technique, is significantly higher in mild heart failure patients (NYHA classes I–II) compared with
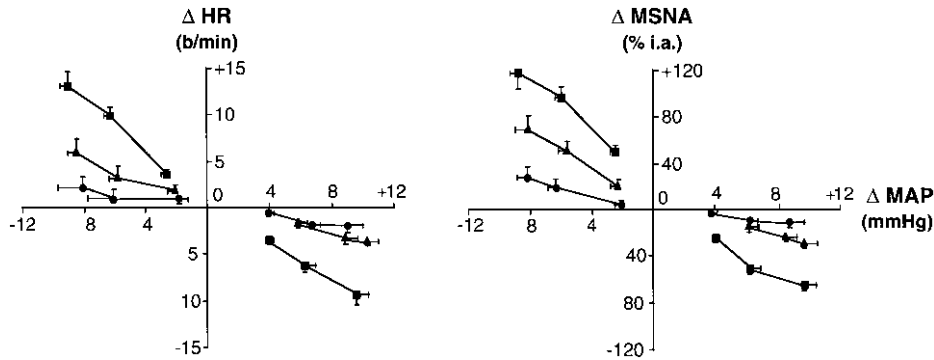
Fig. 3. Plots showing changes in heart rate (ΔHR, expressed as beats per minute [b/min]) and in muscle sympathetic nerve activity (MSNA, expressed as percent integrated activity [% i.a.]) accompanying stepwise reductions and increases in mean arterial pressure (ΔMAP) induced by intravenous infusions of nitroprusside and phenylephrine, respectively. Data are expressed as means ± SEM. Stepwise HR and MSNA responses to nitroprusside and phenylephrine in control subjects (*squares*, n = *17*) and in patients with mild (*triangles*, n = *17*) and severe (*circles*, n = *19*) congestive heart failure (CHF) were always significantly different ($p < 0.01$, control subjects vs severe CHF patients; $p < 0.05$, control subjects vs mild CHF patients) but not between patients with mild and severe CHF. From reference 26, with permission.

control subjects, a further increase being observed in patients with severe heart failure (NYHA classes III–IV). We also examined baroreflex control of heart rate and of sympathetic nerve traffic in these patients by means of the already described vasoactive drug infusion technique. Both vagal and sympathetic control of the cardiovascular system exerted by arterial baroreceptors appeared to be virtually abolished in severe heart failure and significantly reduced in mild heart failure patients compared with normal controls (Fig. 3). Thus, both sympathetic activation and baroreflex impairment occur in the early phase of the heart failure condition, with the degree of these abnormalities proportional to the severity of the disease [28].

These impaired reflex responses appear to be specifically related to arterial baroreceptors, since generalized sympathetic responses to a non-specific stimulus such as the cold pressor test remained unaffected in our heart failure patients [28]. Furthermore, the increase in neural sympathetic drive appeared to be specific to vascular districts under direct baroreflex control, since sympathetic outflow to the skin vasculature, which is mainly influenced by emotional and/or thermoregulatory factors, did not show any increase [30].

Manifold and of different nature are the causes advanced for explaining the arterial baroreceptor impairment. Vascular factors, of a functional or structural nature, capable of altering the viscoelastic properties of
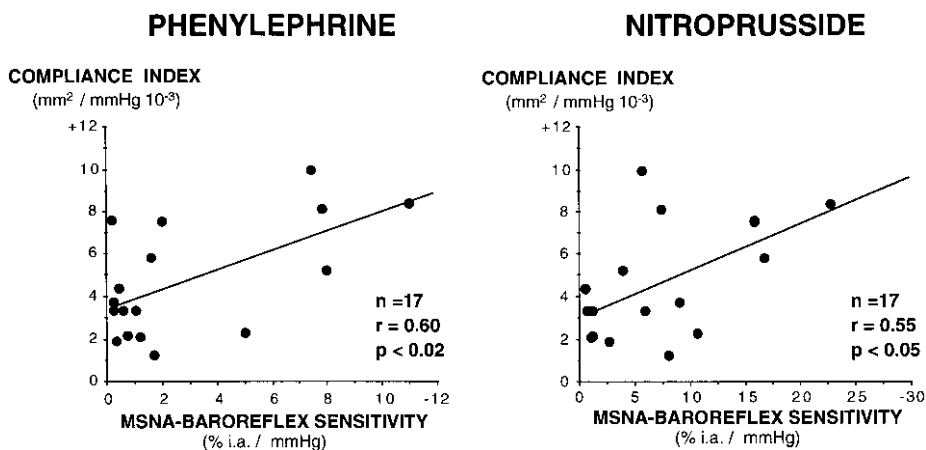

Fig. 4. Scatterplots showing the direct relationship between radial artery compliance and the sensitivity of arterial baroreflex control of muscle sympathetic nerve activity (MSNA, expressed as ratio between percent integrated activity changes and mean aterial pressure changes), assessed for baroreceptor stimulation (*phenylephrine, left panel*) and baroreceptor deactivation (*nitroprusside, right panel*) in 17 patients with congestive heart failure. Compliance is expressed as compliance index. From reference 31, with permission.
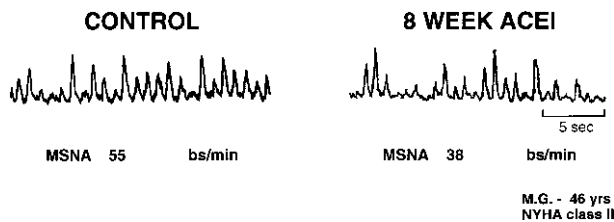
Fig. 5. Original microneurographic recordings depicting the sympatho-inhibitory effect of 8 week ACE-inhibitor treatment in a patient with mild congestive heart failure (NYHA class II). MSNA = muscle sympathetic nerve activity. From reference 35, with permission.

the vessel wall at the site of their anatomical location, have been hypothesized. This has been indirectly confirmed by our group in a study showing that the baroreflex function is inversely related to arterial compliance values, assessed on a beat-to-beat basis via a new ultrasonographic device (Fig. 4) [31].

Along with arterial baroreceptor impairment, congestive heart failure is also characterized by an alteration in the cardiopulmonary receptor control of the cardiovascular system [28, 29]. Reflex increases in forearm vascular resistance following non-hypotensive reductions in central venous pressure induced by lower body negative pressure have been found to be reduced in mild heart failure and virtually abolished in severe heart failure patients compared to control subjects [32–34]. This further contributes to the altered neurohumoral control of circulation in congestive heart failure.

Finally, since sympathetic activation in congestive heart failure is significantly related to the patient's prognosis and is associated with several adverse consequences capable of stimulating progression of the disease, it should represent an important target of medical treatment. A successful therapeutic reduction of adrenergic overactivity would thus be expected to improve patient survival. In a recent study [35] we demonstrated that chronic pharmacological treatment with an ACE-inhibitor drug is capable of reducing the degree of both the sympathetic activation and the baroreflex dysfunction occurring in heart failure patients (Fig. 5), thereby providing evidence that these important adverse prognostic alterations can be at least partially reversed by medical therapy. This improvement may at least in part explain the pathophysiological mechanisms through which ACE inhibitors reduce the elevated morbidity and mortality rate of heart failure patients [36–39].

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