Autonomic neural mechanisms in hypertension

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Abstract

Autonomic cardiovascular control is impaired in hypertension, involving both the parasympathetic and sympathetic component of the reflex modulation. The autonomic dysfunction depends on a variety of reflex and non-reflex mechanisms and participates in the complex cardiometabolic alterations, known as "end-organ damage", detectable in the clinical course of hypertensive disease. This paper will review the main features of the vagal and adrenergic dysfunction characterizing essential hypertension, the mechanisms potentially involved in this neural abnormality as well as the effects of therapeutic intervention.

Key words: autonomic nervous system, baroreflex, parasympathetic function, sympathetic nervous system.

Introduction

Cumulative evidence collected over the past few decades strongly indicates that homeostatic control of the cardiovascular system exerted by the autonomic nervous system undergoes marked alterations in a consistent fraction of hypertensive patients. These alterations, which include parasympathetic inhibition coupled with a concomitant sympathetic activation, are already detectable in the earlier stages of hypertensive disease [1, 2]. As hypertension progresses, however, the main features of the autonomic abnormalities undergo further potentiation, thereby contributing directly and indirectly to disease progression, maintenance of blood pressure elevation and development of target organ damage [1, 2]. An additional step in the complex chain of events leading to the development and progression of autonomic abnormalities is represented by the finding that several major pathological states of cardiovascular (heart failure), metabolic (diabetes mellitus, obesity, metabolic syndrome) or renal (renal insufficiency and failure) aetiology, which often accompany and complicate chronic blood pressure elevation, may further aggravate the above-mentioned sympathetic/parasympathetic alterations [3-5]. In some of these conditions (i.e. congestive heart failure, renal failure and stroke) evidence exists that the sympathetic activation may bear prognostic relevance, the magnitude of the adrenergic overdrive being inversely related to patients' survival (Figure 1) [6-9].

The present paper will critically review the autonomic abnormalities described in the clinical course of the hypertensive state and their possible determinants. This will be followed by an analysis of the consequences of

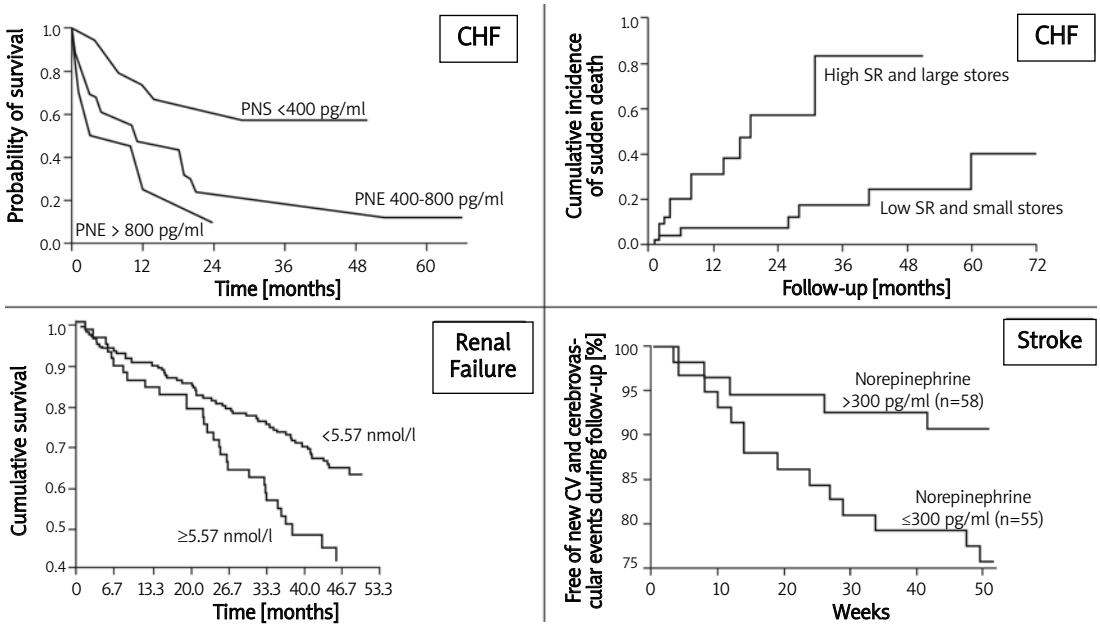

Figure 1. Inverse relationship between different markers of adrenergic activation and survival in congestive heart failure (CHF, upper panels), renal failure and stroke (lower panels). For all the three conditions data on plasma norepinephrine (NE) are shown. For CHF cardiac norepinephrine spillover rate (SR) is additionally shown (upper right panel). Data from ref. [6-8]

autonomic dysregulation in terms of disease progression as well as development of target organ damage. Finally, the therapeutic implications (and issues related to the potential reversibility of the above-mentioned alterations) will be briefly discussed.

Autonomic abnormalities in early hypertensive stages

Early stages of hypertensive disease (and even in some instances of pre-hypertensive stages, particularly in subjects with a family history of hypertension) are characterized by the so-called hyperkinetic circulatory state, which is mediated both by increased adrenergic drive and reduced parasympathetic function [10]. Such reciprocal changes in autonomic cardiovascular modulation have been documented by several studies, whose results can be summarized as follows. In young borderline hypertensive subjects intravenous administration of atropine (which blocks the effects of the parasympathetic neurotransmitter acetylcholine on muscarinic receptors) triggers an increase in heart rate and cardiac output of lesser magnitude than that documented in pure normotensive age-matched controls [10]. This alteration, which demonstrates the impairment in the vagal-heart rate control occurring in hypertension, is not limited to the parasympathetic function, but affects sympathetic cardiovascular control as well. Manifold evidence supports this statement. In a meta-analysis of all published studies, Goldstein reported that, even accounting for some negative results, an indirect marker of sympathetic tone, such as plasma norepinephrine, is significantly elevated in essential hypertensive patients as compared to age-matched normotensive subjects [11]. Furthermore, by employing a technique based on the intravenous tracer infusion of small doses of radiolabelled norepinephrine, Australian investigators were able to show that the rate of norepinephrine spillover from the neuroeffector junctions is increased in young subjects with borderline blood pressure elevation, and that this enhanced release takes place particularly in the kidney and in the heart, i.e. two organs of key importance in blood pressure homeostatic control [12]. Further evidence comes from the direct measurement of sympathetic nerve traffic to the skeletal muscle circulation, a technique which has allowed an increase in central sympathetic outflow to be documented in young borderline hypertensive subjects [13].

The complex borderline hypertension syndrome, however, is characterized by other abnormalities involving the haemodynamic state, the metabolic and hormonal profile as well as the haemorheological condition. Several of these abnormalities are triggered and reinforced by autonomic abnormalities, and specifically by sympathetic overdrive. This appears to be particularly the case for metabolic disarray, which is frequently detected in the early hypertensive phases and include, as components, hyperinsulinaemia, insulin resistance, dyslipidaemia and hypercholesterolaemia [14]. Most of these alterations, which represent the main features of the metabolic syndrome together with

visceral obesity, are characterized by marked adrenergic overdrive, as studies based on the direct recording of muscle sympathetic neural outflow as well as on the norepinephrine spillover technique have unequivocally shown [14].

Autonomic abnormalities in established hypertension

Evidence collected both in experimental animal models of hypertension and in man indicates that while parasympathetic dysfunction remains stable in the hypertensive state characterized by more severe increases in blood pressure, sympathetic activation undergoes progressive and further potentiation [1]. This has been shown by a study performed by our group [15], in which we quantified sympathetic nerve traffic to the skeletal muscle district in three groups of age-matched subjects, i.e. 1) with normal blood pressure, 2) with moderate essential hypertension, and 3) with essential hypertension of a more severe degree. The progressive increase in blood pressure values observed in these three clinical conditions was paralleled by a progressive and marked elevation in sympathetic nerve traffic, suggesting a key role of adrenergic neural factors not only in the development but also in the progression of the hypertensive state. A further demonstration of this phenomenon comes from evidence, collected years ago by our group, that blood pressure variability, i.e. the magnitude of the blood pressure oscillations occurring during the daytime and nighttime, which is largely dependent on adrenergic influences, undergoes an increase in hypertension, and progresses when hypertension becomes more severe [16].

A few other issues related to the autonomic alterations characterizing essential hypertension deserve to be mentioned. First, a state of sympathetic hyperactivity is not only a feature of young and middle-age hypertensives, but it also occurs in elderly hypertensives, even when the blood pressure elevation selectively affects systolic values. Indeed, when sympathetic nerve traffic was recorded in elderly subjects with systodiastolic or isolated systolic hypertension, a clear-cut sympathetic activation was observed when the values were compared to those found in elderly normotensive controls [17]. Second, the hypertension-related increase in adrenergic outflow appears to be specific for some cardiovascular districts, such as the heart, the kidneys, and the skeletal muscle vasculature, and peculiar to the hypertensive state of essential nature [2, 12]. This is documented by the evidence that the secondary forms of high blood pressure elevation caused by primary hyperaldosteronism or by renal arterial stenosis appear not to be characterized by elevated sympathetic cardiovascular outflow. It is further documented by the evidence that in patients with an adrenal pheochromocytoma, central sympathetic outflow is not increased [18]. Thus, in sharp contrast with what has been described for essential hypertension, in secondary hypertensive states, the autonomic imbalance is confined to the parasympathetic control of heart rate, which, in these conditions, also appears to be clearly impaired [15]. Third, independently of the "in-office" or "out-of-office" type of blood pressure elevation, sympathetic activity is increased in hypertension. This has been recently shown to occur both in "white-coat" hypertension, i.e., a condition characterized by elevated clinic but normal ambulatory blood pressure, and in "masked" hypertension, characterized by normal clinic but elevated ambulatory blood pressure [19]. Finally, the adrenergic overdrive (and the accompanying parasympathetic dysfunction) appears to some extent to be related not only to the 24-h absolute blood pressure load but also to the day/night blood pressure difference. This is confirmed by the recent evidence provided by our group that hypertensive patients with the so-called "reverse dipping profile" (i.e. those patients in whom blood pressure values do not undergo any reduction during nighttime but rather show a tendency to increase), are characterized by a more pronounced sympathetic activation than that seen in dipper hypertensives [20]. This adrenergic dysfunction is paralleled by a more pronounced parasympathetic heart rate alteration [20].

Determinants of the autonomic alterations

The autonomic dysfunction occurring in hypertension may depend on several non-mutually exclusive mechanisms (Figure 2). These include: 1) alterations in reflex cardiovascular control, 2) metabolic abnormalities and 3) neurohumoral activation. As far as reflex mechanisms are concerned, there is evidence that both arterial baroreceptor reflexes and cardiopulmonary reflexes are impaired in human hypertension. In hypertension, however, baroreceptor impairment has been demonstrated for the parasympathetic but not for the sympathetic component of the reflex, unless congestive heart failure or left ventricular dysfunction is concomitantly present. Indeed, while the arterial baroreceptor regulation of heart rate has been shown to be reset and blunted, the modulation of both blood pressure and sympathetic nerve traffic exerted by this reflexogenic area does not appear to undergo any impairment, not only in mild but also in severe hypertension [15]. As mentioned above, however, reflex influences stemming from other reflexogenic areas appear to be altered in hypertension. This is the case for the cardiopulmonary reflex, whose

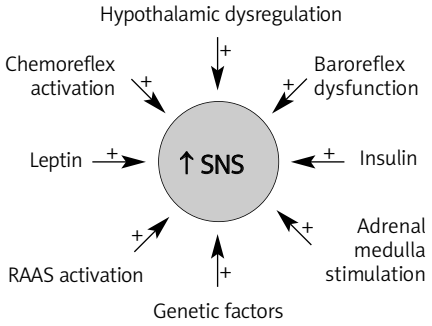

Figure 2. Schematic drawing illustrating the possible mechanisms responsible for the increase in sympathetic activity (↑ SNS) in essential hypertension
RAAS – renin-angiotensin-aldosterone system

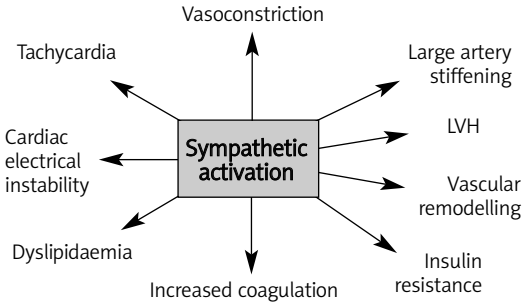

Figure 3. Schematic drawing illustrating the adverse cardiovascular and metabolic effects of the sympathetic activation characterizing essential hypertension
LVH – left ventricular hypertrophy

control of the cardiovascular system (particularly vascular resistance and renin release from the kidney) is markedly reduced, especially when left ventricular hypertrophy accompanies chronic blood pressure elevation [21]. This is also the case for the arterial chemoreflex, whose reflex restraint on adrenergic drive is blunted in hypertension, particularly when obesity, metabolic syndrome or sleep apnoea is concomitantly detected [22]. All together these data underscore the contribution of reflex mechanisms to the sympathetic/parasympathetic dysfunction occurring in hypertension, although the temporal patterns of these alterations may be different according to the vagal or the adrenergic component of the reflex function.

Two other hypotheses advanced in recent years to explain the autonomic dysfunction in hypertension should be briefly highlighted. The first one claims that the sympathetic activation and the parasympathetic inhibition seen in hypertension might depend on a metabolic alteration (i.e., hyperinsulinaemia and the related insulin resistance) accompanying the hypertensive condition [3, 14]. This hypothesis comes from the evidence that in both experimental animals and in humans acute infusion of insulin, without altering glycaemic levels (the so-called euglycaemic clamp infusion technique), markedly stimulates the sympathetic nervous system and inhibits the parasympathetic control of the circulation. This finding is of particular relevance when one takes into account that a large proportion of hypertensive patients (more than 40%) display elevated insulin levels and an insulin resistance state. This means that hyperinsulinaemia and related insulin resistance conditions may represent one of the mechanisms responsible for the autonomic dysfunction that characterizes essential hypertension. It should be mentioned, however, that, at least for the sympathoexcitatory action of insulin, the effect appears to be reciprocal; namely, that a state of sympathetic activation may cause insulin resistance as well [3, 14]. This latter hypothesis has recently received further experimental support by the evidence that, when conditions characterized by insulin resistance, such as obesity and metabolic syndrome, are associated with hypertension, the degree of sympathetic activation is greater than that seen in the uncomplicated high blood pressure state [4, 23].

The second hypothesis claims that the activation of a variety of humoral systems (such as nitric oxide, endothelins, vasopressin, atrial natriuretic peptides, brain natriuretic factors, renin-angiotensin system, etc) may adversely interfere with the main features of the autonomic control of the cardiovascular system. This appears to be particularly the case for the renin-angiotensin system, because elevated levels of circulating (or tissue) angiotensin II, such as those found in hypertension, may impair vagal modulation of sinus node activity and trigger a marked adrenergic activation, presumably *via* the excitatory effects this substance exerts on central sympathetic outflow [24].

Autonomic dysfunction and vascular organ damage

Since the autonomic nervous system has been shown to exert a powerful influence on cardiovascular structures such as the heart and the arteries, it is predictable that sympathetic/parasympathetic dysfunction would be involved to a major extent in the cardiac and vascular alterations described in untreated hypertension. These include: 1) left ventricular hypertrophy, 2) left ventricular dysfunction, 3) arrhythmogenesis, 4) blood hyperviscosity, and 5) arterial stiffness (Figure 3).

This paragraph will examine in detail the latter alteration, inviting the reader to seek information related to the other cardiovascular consequences of sympathetic dysfunction in previous publications by our group and others [1, 12, 14, 25-28]. As far as vascular alterations are concerned, several studies have shown that an acute increase in sympathetic nerve activity is accompanied by an immediate reduction of arterial distensibility. Our group, for example, has reported that infusion of phenylephrine in a brachial artery is accompanied by an immediate

reduction of arterial distensibility, as assessed by beat-to-beat changes in vessel diameter in response to the nearby finger blood pressure changes [29]. Other authors have shown that arterial distensibility may be reduced in response to different stimuli capable of eliciting a marked and generalized sympathetic activation [1, 2].

The above data imply that in conditions characterized by increased sympathetic activity, such as essential hypertension, arterial distensibility should be reduced. This is indeed what has been found, particularly in the condition known as isolated systolic hypertension, in which a pathological increase in arterial stiffness has been reported and adrenergic overdrive clearly documented [30]. A variety of mechanisms may be accounted for by the reduction in arterial distensibility (and thus the increase in arterial stiffness and the related development of atherosclerosis) triggered by the adrenergic activation (Figure 4). First, when sympathetic activation is paralleled by a blood pressure rise, distensibility may be reduced because the resulting increase in vessel diameter stretches the most non-distensible component of the vessel wall, i.e. collagen, making the relationship an inverse one also within the blood pressure range from diastole to systole [31]. Second, distensibility can be reduced also because of a sympathetic-dependent acute increase in heart rate, assuming that this increase is associated with a stiffening of middle-size and large elastic arteries both in experimental animals and in humans (Figure 5) [32]. Third, because sympathetic influences reduce arterial distensibility also in the absence of any blood pressure and heart rate change (see above), other mechanisms must be involved.

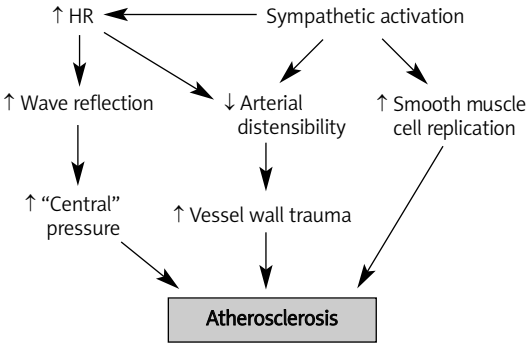

Figure 4. Schematic drawing illustrating the possible mechanisms through which the sympathetic overdrive may reduce arterial distensibility and favour the development of atherosclerosis
HR – heart rate

These may include the contraction of vascular smooth muscle by sympathetic influences, given the evidence that the elastic modulus of contracted muscle tissue is greater than that of the relaxed one. Finally, a contracted vascular smooth muscle may also have greater viscous properties, i.e. it may more prominently oppose resistance to vessel distension in relation to pressure.

Effects of therapeutic intervention

On the basis of the data discussed above, sympathoinhibition should be regarded as an important goal of the therapeutic approach to hypertensive disease. This can be achieved by the

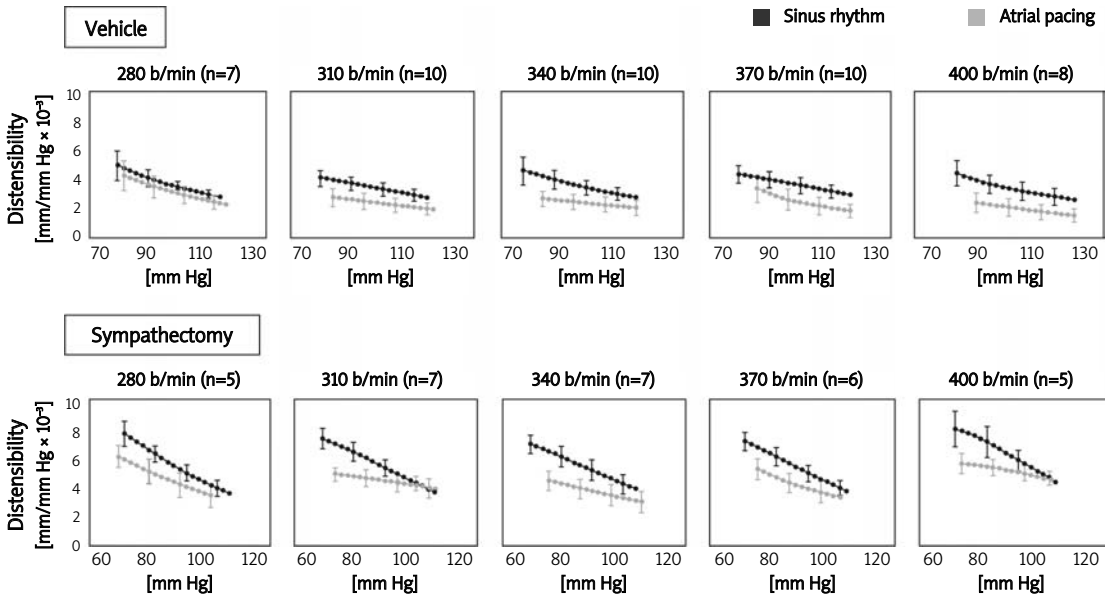

Figure 5. Effects of a progressive increase in heart rate *via* atrial pacing on arterial distensibility in experimental animals. Data are shown before (vehicle) and after sympathectomy, which markedly blunts the impairment in arterial distensibility induced by the pacing manoeuvre. Data from ref. [33]

lifestyle changes recommended by the Guidelines as the main therapeutic step to adopt, i.e. energy-restricted diet and physical training [33]. Either intervention is capable of improving the haemodynamic and metabolic profile, but also of exerting clear-cut sympathoinhibitory effects. Physical training programmes have repeatedly been shown to reduce sympathetic influences on the heart and peripheral circulation [34, 35]. In normotensive obese individuals, a 16-week low calorie diet has been found to reduce by 30% muscle sympathetic nerve traffic and concomitantly to improve the baroreflex modulation of sympathetic function [36]. Similar findings have recently been reported in patients with the metabolic syndrome, in whom a 12-week low-calorie diet decreased total body norepinephrine spillover by 35-40% [37]. Interestingly, the sympathetic deactivation was paralleled by a clear-cut improvement in insulin resistance, a finding that further supports the relationship existing between adrenergic and metabolic function. It should be emphasized that low-calorie diets should be administered without an undue reduction in sodium intake, because of evidence that a restriction in dietary sodium intake triggers adverse sympathometabolic effects, thus possibly potentiating the adrenergic activation and the insulin resistance state described in the metabolic syndrome [38].

Sympathetic deactivation should also be a goal of pharmacological antihypertensive interventions employed in hypertension, an approach that is mandatory when the disease is associated with diabetes, obesity or metabolic syndrome, given the high cardiovascular risk profile characterizing these conditions [39]. In this context, diuretics and β-blockers may be contraindicated because through a worsening of insulin resistance, lipid profile and an increase in body weight (β-blockers) they adversely affect several components of the metabolic syndrome, thus favouring rather than opposing the tendency of metabolic syndrome patients to develop diabetes [39]. Calcium antagonists are lipid neutral and do not adversely affect insulin sensitivity [39]. Some of them, however, increase sympathetic activity and none persistently reduces it, thereby failing to counteract its adverse contribution to metabolic function [39]. This can, on the other hand, be observed with angiotensin-converting enzyme inhibitors and angiotensin II antagonists, both of which exert sympathoinhibition by reducing the sympatho-excitatory effects of angiotensin II [39]. Sympatho-inhibition, however, can also be achieved by peripheral or central sympathomoderating agents. Alpha 1-receptor blockers have been shown to reduce plasma triglyceride levels, increase plasma HDL cholesterol, and improve insulin sensitivity [39], thereby favourably affecting various key components of the metabolic syndrome, in addition to blood pressure. Similar findings have been obtained in animals and humans with drugs acting centrally on α2-adrenergic or I1 imidazoline receptors such as moxonidine and rilmenidine [39]. Central agents of either class cause marked inhibition of the sympathetic drive, which leads to blood pressure reduction and an improvement in the metabolic glucose profile [39].

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