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REVIEW SERIES

Neuroadrenergic disarray in pseudo-resistant and resistant hypertension

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Several studies have investigated the behavior of sympathetic cardiovascular drive in essential hypertension, providing conclusive evidence of the adrenergic activation characterizing this condition. These studies have also shown the importance of neuroadrenergic overdrive in the development and progression of the hypertensive state as well as in the pathogenesis of hypertension-related end-organ damage. The information available on the sympathetic nervous system's behavior in 'pseudo-resistant' and 'true resistant' hypertension is much more scarce. This paper will review the available knowledge on this issue by examining the data collected via indirect and direct approaches to investigate adrenergic function in resistant hypertension as well as the effects of pharmacological and non-pharmacological interventions.
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INTRODUCTION

Cumulative evidence collected over the past few decades strongly supports the notion that homeostatic control of the cardiovascular system exerted by the sympathetic nervous system undergoes marked alterations in a consistent fraction of hypertensive patients. These alterations, represented by a marked increase in the adrenergic nervous system's excitatory influences on the heart as well as on the peripheral circulation, are detectable in the earlier stages of hypertensive disease.[1,2] As hypertension becomes more stable, however, the sympathetic abnormalities undergo further potentiation, thereby contributing directly and indirectly to the maintenance of blood pressure elevation, disease progression and the development of target organ damage.[1,2] An additional step in the complex chain of events leading to the development and progression of adrenergic abnormalities relates to the evidence that several major pathological states ascribed to cardiovascular (heart failure), metabolic (diabetes mellitus, obesity, metabolic syndrome, sleep apnea) and renal (renal insufficiency and failure) factors often accompany and complicate chronic blood pressure elevation and may further aggravate the above-mentioned neurogenic alterations.[1–6] In some of these conditions (that is, congestive heart failure, renal failure and stroke), evidence suggests that sympathetic activation may have independent prognostic relevance, with the magnitude of the adrenergic overdrive being inversely related to patient survival.[1–2,4]

There is little information available on the sympathetic nervous system's behavior in resistant hypertension, that is, the clinical condition characterized by elevated blood pressure despite the use of three or more antihypertensive drugs, including a diuretic at a full daily dosage. This lack of information may depend on several factors, including difficulties in diagnosing 'true' resistant hypertension as well as the methodological problems related to direct assessment of sympathetic neural drive in this condition.

This study will first provide an overview of the neuroadrenergic abnormalities characterizing the hypertensive state and the abnormalities' possible determinants. This will be followed by an analysis of the information available on the behavior of direct and indirect adrenergic drive markers in 'pseudo-resistant' and 'true resistant' hypertension. Finally, the implications of these findings for resistant hypertension treatment will be briefly mentioned.

SYMPATHETIC ABNORMALITIES IN EARLY AND ADVANCED HYPERTENSIVE STAGES

Early clinical stages of hypertensive disease (and in some cases, 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.[7] Such reciprocal changes in autonomic cardiovascular modulation have been documented by several studies, which can be summarized as follows.

In young, borderline hypertensive subjects, i.v. administration of atropine (which blocks the effects of the parasympathetic neurotransmitter acetylcholine on muscarinic receptors) triggers a lower increase in heart rate and cardiac output than that reported in pure normotensive age-matched controls.[7] This alteration, which

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demonstrates the impairment of vagal-heart rate control that occurs 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 on indirect sympathetic tone markers, such as plasma norepinephrine, these markers were significantly elevated in essential hypertensive patients compared with age-matched normotensive subjects.[8] Furthermore, by employing a technique based on i.v. tracer infusion of small radiolabelled norepinephrine doses, Australian investigators were able to show that the rate of norepinephrine spillover from neuroeffector junctions is increased in young subjects with borderline blood pressure elevation and that this process takes place in the kidney and in the heart, that is, two organs important to homeostatic blood pressure control.[9] Further evidence comes from the direct measurement of sympathetic nerve traffic to the skeletal muscle circulation, a technique which has documented increased central sympathetic outflow in young, borderline hypertensive subjects.[1,2,4,6]

Complex borderline hypertension syndrome, however, is characterized by other abnormalities involving the hemodynamic state, the metabolic and hormonal profile as well as hemorheological conditions. Several of these abnormalities are triggered and reinforced by autonomic abnormalities, specifically by sympathetic overdrive. This appears to be particularly the case for the metabolic disarray, which is frequently detected in early hypertensive phases and includes hyperinsulinemia, insulin resistance, dyslipidemia and hypercholesterolemia.[6] Most of these alterations, which represent the main features of metabolic syndrome together with visceral obesity, are characterized by marked adrenergic overdrive, as studies based on direct recording of muscle sympathetic neural outflow and the norepinephrine spillover technique have unequivocally shown.[1,2,4,6]

The above-mentioned sympathetic abnormalities reported in the early stages of hypertension appear to be maintained and potentiated in established hypertension. This outcome has been shown by a study performed by our group,[10] in which we quantified sympathetic nerve traffic to the skeletal muscle district in three groups of age-matched subjects, that is, those with normal blood pressure, moderate essential hypertension and more severe essential hypertension. 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 adrenergic overdrive's key role not only in the development but also in the progression of the hypertensive state. A few other issues related to the autonomic alterations that characterize essential hypertension deserve to be mentioned.

First, sympathetic overactivity is not only a feature of young and middle-age hypertensives but also occurs in elderly hypertensives, even when systolic blood pressure values are selectively elevated.[11,12] 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 with those found in healthy, elderly, normotensive controls.[12] Second, the hypertension-related increase in adrenergic outflow appears to be specific to some cardiovascular districts, such as the heart, kidney and skeletal muscle vasculature, and almost peculiar to the essential hypertensive state.[2,10,12–14] Finally, the adrenergic overdrive appears to be related to some extent to the 24-h absolute blood pressure load as well as the day/night blood pressure difference.[15] This finding is supported by the evidence provided by our group and others that hypertensive patients with the 'reverse dipping profile' (that is, patients in whom blood pressure values do not undergo any reduction overnight but rather show a tendency to increase), are characterized by more pronounced sympathetic activation than that seen in dipper hypertensives.[16]

BEHAVIOR OF SYMPATHETIC CARDIOVASCULAR DRIVE IN 'PSEUDO-RESISTANT' HYPERTENSION

A consistent fraction of hypertensive patients labeled as resistant hypertensives are indeed 'pseudo-resistant.' In an analysis, we recently performed of the results collected in two large observational studies carried out and coordinated by our group, the Pressioni Arteriose Monitorate E loro Associazioni (PAMELA) and the Blood Pressure (BP) control rate and CArdiovascular Risk profilE (BP-CARE) study, we found that $\sim$1/3 of the patients originally diagnosed with resistant hypertension are indeed characterized by white-coat hypertension when ambulatory blood pressure monitoring is performed and/or home blood pressure measurements are taken into account.[17,18] Assessment of sympathetic neural drive in white-coat hypertension has been performed by different investigators, and the results are quite different from those collected in true resistant hypertension patients.

All the approaches employed to test adrenergic function (power spectral analysis of the heart rate signal, plasma norepinephrine concentrations in peripheral blood and direct recording of efferent postganglionic sympathetic nerve traffic in a peripheral nerve) show that white-coat hypertension, which is responsible for a consistent number of pseudo-resistant hypertensive states, is characterized by adrenergic overdrive.[19–21] The magnitude of this activation, however, does not appear to be different from that seen in essential hypertensive states in which both 'office' and 'out-of-office' blood pressure values are elevated.

This finding was shown years ago by the results of a study we performed in white-coat and essential hypertensives, who were classified by stringent criteria, including ambulatory blood pressure values.[21] As shown in Figure 1, muscle sympathetic nerve traffic, both when expressed as burst incidence over time and when corrected for heart rate values, was elevated in white-coat hypertensive patients compared with true normotensive individuals. However, when the values were compared with those obtained in true essential hypertensive patients, it was clear that the white-coat group showed a lower degree of adrenergic activation (Figure 1).[21] As discussed below, neuroadrenergic function in white-coat and 'pseudo-resistant' hypertension is different from that displayed by 'true' resistant hypertensive patients. In these patients, a potentiation of the sympathetic overdrive, which characterizes essential hypertension, can be detected via the microneurographic nerve traffic recording technique.[22]

It can thus be concluded that 'pseudo-resistant' hypertension differs from 'true' resistant hypertension not only from a hemodynamic view point, that is, the difference between office and out-of-office blood pressure values, but also based on the pathophysiological background (Table 1). As discussed below, resistant hypertension displays more pronounced activation of sympathetic neural influences on the cardiovascular system compared with 'pseudo-resistant' hypertension.

SYMPATHETIC FUNCTION IN 'TRUE RESISTANT' HYPERTENSION

Scanty information is available on sympathetic cardiovascular function in resistant hypertension. Among the likely factors responsible for this lack of data, two appear to have a major role. The first one refers to the already mentioned difficulty in correctly diagnosing 'true' resistant hypertension, accounting for the white-coat effect as well as

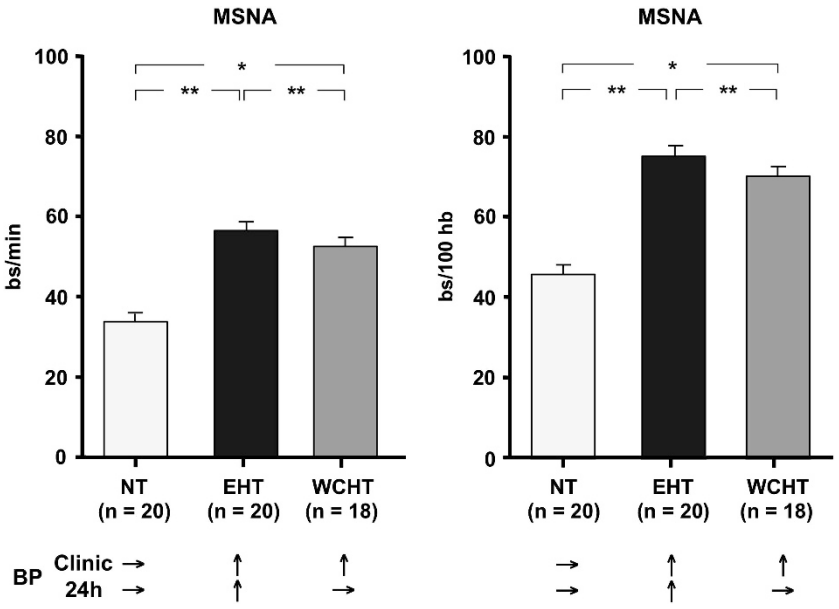

Figure 1 Muscle sympathetic nerve traffic values (MSNA), expressed as burst incidence over time (bs min^{-1}, left panel) and as burst incidence corrected for heart rate (bs per 100 hb, right panel) in normotensive subjects (NT, normal clinical and ambulatory blood pressure), essential hypertensive patients (EHT, elevated clinical and ambulatory blood pressure) and white-coat hypertensive patients (WCHT, elevated clinical but normal blood pressure). Data are shown as the mean ± s.e. Asterisks (*$P<0.05$, **$P<0.01$) refer to the statistically significant differences between groups. BP: blood pressure. Arrows indicate the normality (→) or elevation (↑) of clinical and ambulatory (24 h) blood pressure in the 3 groups of subjects. Figure created using data from Grassi *et al*.[21]

Table 1 Blood pressure and sympathetic profiles of pseudo-resistant and resistant HT

	Pseudo-resistant HT	*Resistant HT*
Office BP values	Increased	Marked increased
Home BP values	Normal	Increased
Ambulatory BP values	Normal	Increased
Sympathetic nervous system	Moderately activated	Markedly activated

Abbreviations: BP, blood pressure; HT, hypertension.

poor patient adherence to prescribed antihypertensive drug regimens. However, the second factor refers to the complicated antihypertensive drug treatment schedules present in resistant hypertensive patients, which affect sympathetic neural function assessments.

Despite these caveats and limitations, in the past few years, some indirect and direct data have been collected on the neuroadrenergic profile of resistant hypertensive patients. The first data set is based on an analysis of regional norepinephrine spillover, obtained via the previously mentioned norepinephrine radiolabelled technique.[9] In 10 patients with resistant hypertension who underwent renal denervation, Esler and coworkers and Schlaich and coworkers reported data related to renal norepinephrine spillover, showing a consistent reduction (on average 47%) of this direct marker of sympathetic renal function 30 days after radiofrequency ablation of the renal nerves.[23–25] Baseline renal norepinephrine spillover data, assessed by the authors before the renal nerve ablation procedure, however, may explain, although indirectly, whether and to what extent the sympathetic nervous system is activated in resistant hypertension.

When we compare the data of the renal norepinephrine spillover reported in these patients with those observed in a previous study carried out by the same authors in essential non-resistant hypertensive patients,[26] the values tend to be greater in the resistant hypertensive group. This is particularly the case when the data are analyzed for the age range between 60 and 79 years, which is a common age for detecting resistant hypertensives. Although these data need to be interpreted with some caution, given the 'historical' nature of the control group, they may indirectly suggest the presence of high adrenergic overdrive in these patients.

More direct information on the patterns of the sympathetic neural function in resistant hypertension come from data collected in a series of studies carried out by our group through the PAMELA study, with the aim to assess indirectly or directly the behavior of the adrenergic neural influences on the heart and peripheral circulation in this hypertensive state. In the first set of studies, we examined the two cyclic components of systolic and diastolic blood pressure residual variability identified via a fast Fourier transform spectral analysis of 24-h ambulatory blood pressure tracings.[27]

The first of these two components has been shown to be closely related to sympathetic nerve traffic values, for both systolic and diastolic blood pressure values.[27,28] When this analysis was applied to a selected group of hypertensive patients from the PAMELA study, we found that this first component was significantly greater in the case of systolic blood pressure in resistant hypertensives compared with the values seen in controlled and uncontrolled hypertensives (Figure 2). This was also the case for the second cyclic component and the residual variability values for systolic but not for diastolic blood pressure (Figures 2 and 3).

Taken together, these data support the hypothesis that sympathetic cardiovascular influences undergo greater potentiation in resistant hypertension than that characterizing non-resistant hypertension. Recently, this hypothesis has received further experimental support from the finding that sympathetic nerve traffic values are significantly greater in resistant than in non-resistant hypertensive patients with similar levels of blood pressure elevation.[29]

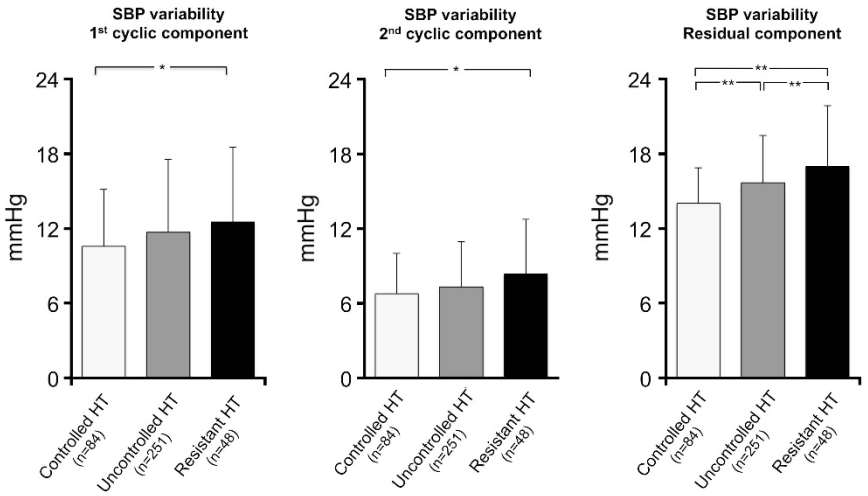

Figure 2 Behavior of the cyclic and residual components of systolic blood pressure (SBP) variability in controlled, uncontrolled and resistant hypertensive (HT) patients of the Pressioni Arteriose Monitorate E loro Associazioni study. Data are shown as the mean ± s.e. Asterisks (*$P<0.05$, **$P<0.01$) refer to the statistically significant differences between groups.

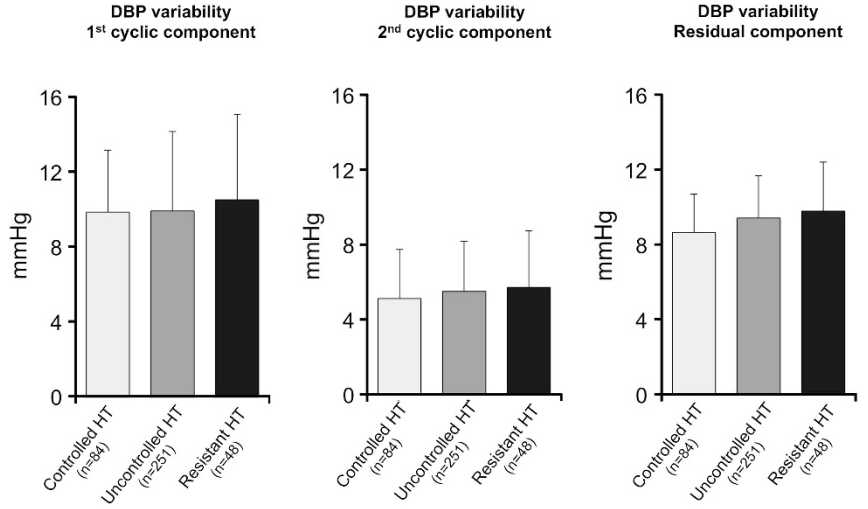

Figure 3 Behavior of the cyclic and residual components of diastolic blood pressure (DBP) variability in controlled, uncontrolled and resistant hypertensive (HT) patients of the diastolic blood pressure study. Data are shown as the mean ± s.e. Values are not significantly different between the three study groups.

Two further issues related to the neuroadrenergic abnormalities characterizing resistant hypertension deserve to be mentioned. The first abnormality refers to the evidence that a consistent fraction of hypertensive patients resistant to antihypertensive drug treatment also displays sleep apnea syndrome.[30] This condition, characterized by a marked elevation in sympathetic nerve traffic values in both obese and lean subjects,[31,32] may participate in the profound sympathoexcitation occurring in the resistant hypertensive state. The second abnormality refers to the finding that an aldosterone excess has been repeatedly reported in these patients.[30,33] Taking into account the sympathoexcitatory effects of this hormone,[13,34] this pathway may represent another pathophysiological mechanism that determines the adrenergic overdrive seen in these patients.

THERAPEUTIC IMPLICATIONS

The evidence described in the previous sections represents the background for considering sympathetic deactivation as an important therapeutic goal of non-pharmacological and pharmacological interventions for resistant hypertension treatment. This is the case, for example, for antialdosterone drugs, such as spironolactone, whose administration has been shown to reduce norepinephrine spillover rate as well as sympathetic neural outflow.[35,36] This is also the case for electrical stimulation of carotid sinus baroreceptors, which has been shown to consistently reduce sympathetic nerve traffic values and concomitantly elevated blood pressure values.[37] Finally, this is the case for radiofrequency ablation of renal nerves, a procedure capable of exerting marked sympathoinhibitory effects in resistant hypertension, as confirmed by the reduction in renal and total norepinephrine spillover rate as well as in muscle sympathetic nerve traffic observed a few weeks after the renal denervation procedure.[23,24,37] However, further studies are warranted to better define the time course of the sympathoinhibitory effects of the renal denervation approach, their qualitative and quantitative relationships with the blood-pressure-lowering responses and their potential impact on clinical outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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