Neurogenic Essential Hypertension Revisited: The Case for Increased Clinical and Research Attention

Samuel J. Mann

The management of essential hypertension has increasingly focused on the use of diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, which lower blood pressure (BP) through effects on blood volume and on the renin-angiotensin system. However, in many individuals these agents, whether given alone or in combination, fail to normalize BP. In such cases it is likely that hypertension is at least partly maintained by pathophysiologic mechanisms other than volume and the renin-angiotensin system, and therefore, that pharmacotherapy directed at other mechanisms is needed.

One such form of hypertension is the often overlooked entity of neurogenic hypertension. The purpose of this article is to renew attention to this overlooked entity, to provide a very clinically oriented overview of its possible causes and manifestations, and to discuss the potentially important treatment implications of recognizing this form of hypertension. These implications underscore the need for further clinical and research attention concerning neurogenically mediated hypertension. Am J Hypertens 2003;16:881–888 © 2003 American Journal of Hypertension, Ltd.

Key Words: Sympathetic nervous system, β-blockers, α-blockers, hypertension drug therapy.

Despite advances in treatment, essential hypertension is controlled in only 45% of treated hypertensives. Most single agents lower blood pressure (BP) in only 50% to 60% of patients, likely because of the heterogeneity of underlying hypertensive mechanisms. Not surprisingly, in any given individual, hypertension may be exquisitely responsive to one agent yet completely unresponsive to another.

A logical goal would be to treat individuals with agents matched to the underlying mechanism of their hypertension. Unfortunately, this is a difficult task. Reflecting this, the guidelines for drug selection of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) focus on demographics, co-morbidities, and side effects but not on underlying hypertensive mechanisms. Poignantly, even in patients with severe essential hypertension, we usually do not understand the mechanism or the best-suited drug.

In recent years, the central role of blood volume and of the renin-angiotensin system (RAS) in the development of essential hypertension have been emphasized, and drugs directed at them, including diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), have played an increasingly prominent role in treatment. However, although these agents, given alone or in combination with each other, are highly effective, they fail to normalize BP in a significant proportion of patients. This shortcoming underscores the need for more varied approaches to treatment.

The association between essential hypertension and increased activity of the sympathoadrenal system (SAS), along with the known antihypertensive efficacy of agents directed at the SAS, suggest that essential hypertension also has an important neurogenic component. However, despite ample basic research concerning neurogenic pathways of BP control, the clinical relevance of neurogenic hypertension has received little attention. The purpose of this review is to renew attention to the clinical relevance of neurogenic hypertension, to describe the clinical circumstances in which it might be suspected, and to discuss the potentially important treatment implications of its recognition.

Interaction Between the RAS and the SAS

This review brings attention to two physiologic systems that play a central role in BP regulation, the RAS and the SAS. It is important to emphasize that these systems do


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Published by Elsevier Inc.

0895-7061/03/$30.00
doi:10.1016/S0895-7061(03)00978-6
not operate completely independently of each other. Stimulation by epinephrine of β-adrenergic receptors of the SAS increases not only heart rate and cardiac output but also renin secretion and RAS activity. β-Blockers inhibit both these effects, and it is often unclear which of these two effects is responsible for BP lowering in individual patients.

Conversely, stimulation of the RAS increases SAS tone.6–8 Consistent with this, antagonism of the RAS with ACEIs and ARBs decreases SAS tone, although the relevance of this effect to their antihypertensive effect in human hypertension is not clear.5,9–12

Despite these interactions between the RAS and the SAS, identifying neurogenic forms of hypertension offers the potential to better understand hypertensive mechanisms in individual patients, and guide drug selection, as will be discussed. However, before proceeding, a brief summary of the clinical features of non-neurogenic essential hypertension provides a helpful background.

**Clinical Features of Non-Neurogenic Essential Hypertension**

This brief review focuses on volume-dependent and RAS-dependent forms of essential hypertension, as regulation of volume and of RAS expression are well known to be related to human hypertension, and antihypertensive agents directed at them are widely used. Both genetic and lifestyle factors appear contributory to these forms of hypertension.13,14

Hypertension typically develops gradually, with the age of onset and severity affected by lifestyle factors such as diet, weight, and exercise status. Volume-dependent hypertension is characterized by salt sensitivity of BP, reduced levels of plasma renin activity, and responsiveness to salt restriction, diuretics, and calcium channel blockers.15–17 It is highly prevalent among African Americans,18 elderly patients, and patients with renal insufficiency.19–22 In contrast, RAS-dependent essential hypertension is less responsive to diuretics, and more responsive to agents such as ACEIs and ARBs.21

Most patients respond to monotherapy with either a diuretic or an ACEI (or ARB), or to a combination of the two.23 In some nonresponders, factors such as noncompliance with medication, alcohol abuse, and ingestion of sympathomimetic agents may be responsible. Isolated systolic hypertension, whose mechanism differs from essential hypertension, can also be difficult to control. In the absence of such factors, hypertension refractory to a diuretic/ACEI combination traditionally provokes suspicion of secondary hypertension, but diagnostic investigation is usually unrevealing. In this setting, pathogenetic mechanisms other than volume and the RAS, such as neurogenic hypertension, clearly merit consideration.

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**Table 1. Suggested causes of increased sympathetic tone in essential hypertension**

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<th>Cause</th>
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<tr>
<td>Angiotensin II</td>
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<td>Insulin resistance</td>
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<td>Dietary salt sensitivity</td>
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<td>Hyperresponsivity to stress</td>
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<td>Impaired baroreceptor reflexes</td>
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<tr>
<td>Genetic factors</td>
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<td>Vascular compression of the medulla</td>
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<td>Psychologic factors</td>
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**Neurogenic Hypertension**

The SAS is intimately involved in BP regulation. Its components include afferent nerves from arterial baroreceptors, central nervous system pathways including the brainstem, medulla, hypothalamus, limbic system, and spinal cord, and the peripheral sympathetic nerves. Medullary structures, such as the nucleus tractus solitarius and the caudal ventrolateral medulla have inhibitory effects, whereas the rostral ventrolateral medulla exerts excitatory effects on sympathetic outflow.24–26 Excitatory and inhibitory inputs from other central nervous system structures, including the hypothalamus and limbic cortex, are also known to affect sympathetic outflow.24–26

Unfortunately, the neural mechanisms involved in BP regulation in normotensive and hypertensive populations are highly complex and still not well understood. The reader is referred to references 40–42 for more detailed discussion.

The SAS is clearly involved in transient increases in BP, such as those that occur in response to stressors.27,28

Less established is its role in sustained hypertension, although studies assessing plasma catecholamines, norepinephrine spillover, microneurography, and heart rate variability have documented that SAS tone is greater in hypertensive than in normotensive populations.5,29 In addition, agents that reduce SAS activity or antagonize its effects effectively lower BP.

The factors that stimulate sympathetic tone in human essential hypertension are poorly understood. Several have been suggested (Table 1). Angiotensin II stimulates sympathetic outflow, although the importance of this effect in human hypertension is unclear.6,10,11 Some suggest that insulin resistance plays a role,30,31 although it is unclear whether insulin resistance is a cause or a consequence of increased SAS tone.31–33 Evidence argues against another suggested cause, impaired baroreflexes.5 Salt sensitivity and increased salt intake might also lead to increased sympathetic tone.34 Genetic factors are also under investigation.35–38 An association between neurogenic hypertension and vascular compression of the medulla by ecstatic vessels was originally suggested by Janetta et al.,39 but subsequent studies have yielded inconsistent results.40,41

A link between psychological factors and hypertension...
Table 2. Conditions associated with blood pressure elevation and increased sympathoadrenal tone

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<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Stroke</td>
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<td>Sleep apnea</td>
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<tr>
<td>Alcoholism</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Paroxysmal hypertension</td>
</tr>
<tr>
<td>Acute or chronic anxiety</td>
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<tr>
<td>Acute or chronic sinus tachycardia</td>
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</tbody>
</table>

has been widely suspected and studied, although the nature of that link remains unclear. Hyper-responsivity to stress has been postulated, but remains unproven. The popular hypothesis that repeated pressor responses to stress can lead to permanent, self-perpetuating hypertension also has not been validated.

**Possible Clinical Indicators of Neurogenic Hypertension**

When hypertension is predominantly driven by the SAS, it is considered to be neurogenic. The problem, however, is how to identify individuals in whom neurogenic mechanisms may be operative. A major barrier to such study is the absence of clinically convenient techniques for assessing SAS tone in individual patients. Plasma and urine catecholamine levels very poorly reflect differences between individuals in SAS tone. Measurement of sympathetic nerve activity is laborious and painful, and its use is limited to research. The role of spectral heart rate analysis remains to be clarified. In this context, clinical rather than biochemical indicators may deserve more consideration as clues of possible neurogenic hypertension.

**Presence of Co-morbid Conditions Associated With Increased SAS Tone** In many instances, individuals with hypertension have co-existing conditions that are associated with both increased SAS tone and BP elevation (Table 2). In the presence of those conditions, SAS tone might be contributory to BP elevation.

Acute BP elevation is frequently seen during and after a stroke. Increased SAS tone has been documented in this setting, due possibly to increased intracranial pressure. Sleep apnea is associated with an increased prevalence of hypertension, particularly in obese individuals, and with increased SAS tone. Obesity itself has been linked to increased SAS tone. Tachycardia is associated with increased SAS tone, and the antihypertensive effect of β-blockers is positively correlated with resting heart rate.

Alcohol abuse is associated with BP elevation, and reducing alcohol intake can cause a sustained lowering of BP. Ironically, the direct effect of alcohol is vasodilatation and, if anything, BP lowering. It is the stimulation of the SAS by alcohol, and by alcohol withdrawal, that appears responsible for its hypertensive effect.

In these clinical circumstances, where hypertension and increased SAS tone co-exist, treatment with agents directed at the SAS would seem to merit consideration. However, the efficacy of such therapy in comparison with other agents has not been studied.

**Atypical Presentation of Hypertension** The possibility that other clinical factors might also serve as indicators of neurogenic hypertension is also largely unexplored.

In many patients, the onset and pattern of hypertension are clearly atypical. For example, hypertension may be severe, refractory, or paroxysmal, or its onset may be sudden or at a young or advanced age. Such atypical patterns regularly provoke clinical suspicion of secondary hypertension, although diagnostic search is usually unrevealing. Even in individuals with severe hypertension, a cause is found in only 10%. Similarly, only 2% of patients with paroxysmal hypertension have a pheochromocytoma. The possibility is largely unstudied that atypical presentations are in some cases clues of a neurogenic origin.

**Psychological Factors and Neurogenic Hypertension** The well-documented association between emotional stressors and changes in BP and SAS tone supports the possibility that neurogenic hypertension is related to psychological factors. Anxiety is associated with increased SAS tone, and neurogenic hypertension is often suspected in anxious and tachycardic individuals who indeed have an adrenergically mediated hyperkinetic form of BP elevation. However, anxiety and tachycardia are often a manifestation of white coat hypertension (BP elevation limited to the physician’s office), rather than of true sustained hypertension, as assessed by ambulatory or home BP monitoring. Thus, although a link between anxiety and hypertension may exist, it is weaker than popularly believed.

Other psychological factors may also be involved with hypertension and with neurogenic hypertension, in particular. Hypertension and severe hypertension have been associated with emotional defensiveness. One form of hypertension in particular, recurrent paroxysmal hypertension, or pseudopheochromocytoma, appears to be neurogenic and psychosomatic in origin, and has been successfully treated based on this understanding. A neurogenic origin is suggested by the transience of the hypertensive episodes, increases in catecholamine levels during episodes, and the efficacy in some patients of combined α plus β blockade. An underlying psychosomatic cause is evident, although patients uniformly insist that episodes are unrelated to stress or emotional distress. A common thread among patients is a pattern of repression of emotions, related either to a past history of severe abuse or trauma or to a more generalized pattern of repressing unwanted emotions. Consistent with this, psychotherapy alone has cured some patients, and antidepressants have been reported to be extremely effective in preventing recurrent hypertensive paroxysms.
Responses to Antihypertensive Regimens. Finally, responses to mechanistically different antihypertensive regimens also may be indicative of underlying hypertensive mechanisms. Logically, one can suspect that hypertension resistant to treatment with an ACEI/diuretic combination is mediated by mechanisms other than volume and the RAS. Recent studies demonstrate an interesting association between psychological factors and resistance to these agents. Resistant hypertension has been reported to be associated with psychological factors such as a paucity of emotional attachment to others. Inhibited anger expression and childhood abuse history have been associated with a reduced response to monotherapy with an ACEI or a diuretic.

Drug Therapy in Neurogenic Hypertension

Identification of patients with neurogenically mediated hypertension is not a mere hypothetical issue. It might bear considerable relevance to treatment in terms of selection of agents directed at the SAS. Such agents include α- and β-adrenergic receptor blockers, central α-agonists (eg, clonidine, α-methyldopa), older agents such as reserpine, guanethidine, and guanadrel, and the recently introduced imidazoline receptor agonists (eg, rilmenidine, moxonidine).

The efficacy of central α-agonists in neurogenic hypertension is supported by the positive correlation of the antihypertensive effect of clonidine with pretreatment plasma norepinephrine level. However, their widespread use is discouraged by a high incidence of side effects, particularly fatigue. The imidazoline receptor agonists cause less fatigue, but are not currently available in the United States. Reserpine is not widely used, largely due to adverse effects associated with the high doses used decades ago. Guanethidine and guanadrel are also effective but are not widely used.

The remainder of this discussion will therefore focus on α- and β-adrenergic receptor blockers, which remain the most widely used antiadrenergic agents. The discussion may pertain as well to other agents with mechanisms directed at the SAS.

α-Blocker and β-Blocker Monotherapy. The SAS elevates BP by stimulating increases in cardiac output and vascular resistance through its epinephrine-mediated adrenal limb (adrenal medulla) and its norepinephrine-mediated neural limb (sympathetic nerves). Its effects are mediated by stimulation of cardiac and vascular α- and β-adrenergic receptors. Epinephrine, secreted by the adrenal medulla, stimulates cardiac β-receptors, which increases heart rate, stroke volume, and cardiac output. In the vasculature, it stimulates both the vasoconstricting α receptors and the vasodilating β-2 receptors, with a net effect of reduction of peripheral resistance. Norepinephrine, secreted by sympathetic nerve endings, also stimulates cardiac β receptors, but peripherally stimulates largely the α receptors, resulting in increased vascular resistance and reflex slowing of heart rate. Stimuli that are mediated preferentially by the adrenal limb and epinephrine, such as anxiety and hypoglycemia, elevate BP predominantly by increasing cardiac output, whereas stimuli that are preferentially neurally and norepinephrine mediated, such as isometric exercise or immersion of the hand in ice water, elevate BP predominantly by increasing vascular resistance.

The involvement of α and β receptors in SAS-mediated BP elevation provides a rationale for antihypertensive therapy with α or β receptor blockade. β-Blocker monotherapy lowers BP by reducing both renin secretion and cardiac output, and it still remains unclear which of these two effects is more involved in its antihypertensive effect in any given individual. α-Blocker monotherapy lowers BP by reducing peripheral resistance. However, its use has been discouraged by recent findings of increased cardiovascular end points, particularly congestive heart failure, in comparison to treatment with the diuretic chlorthalidone. Nevertheless, α-blockers are highly effective when used in combination with other antihypertensive agents, and their use should not be discouraged in patients whose hypertension is not controlled by other regimens.

Rationale for Combining α and β Blockade. Surprisingly, although β-blocker monotherapy reduces resting BP, studies consistently show that it does not prevent stress-induced increases in BP. Other studies explain why. They demonstrate that in the face of β blockade, the BP response to adrenergic stimuli such as mental stress is maintained by a shift in the hemodynamic response from one of increased cardiac output to one of increased peripheral resistance. Likewise, β blockade does not attenuate the hypertensive response to other adrenergic stimuli such as hypoglycemia or epinephrine infusion. Conversely, in the face of stressors that elevate BP predominantly by vasoconstriction, α-blocker monotherapy does not attenuate the pressor response, but shifts the response pattern from one of increased vasoconstriction to one of increased cardiac output. The pressor response to distressful emotions such as anger and sadness, which involves increases in both cardiac output and vascular resistance, would also seem unlikely to be antagonized by either α-blocker or β-blocker monotherapy.

In contrast, as elegantly described by Julius, blocking both α and β receptors does reduce SAS-mediated BP elevation. Combined α and β blockade blunts BP reactivity, whereas monotherapy with an ACEI, diuretic, α or β blocker does not.

A regimen combining α and β blockade differs mechanistically from ACEI/diuretic combinations. It also confines the advantage of modifying adrenergic effects on atherosclerosis, thrombosis, insulin resistance, and hyperlipidemia. Nevertheless, this regimen has received little attention as a management alternative.

Its efficacy in treating hypertension may have been
understated in studies using labetolol or carvedilol, which have variable oral bioavailability. However, studies using an α blocker (eg, doxazosin or terazosin) in combination with a β blocker, report a large antihypertensive effect. The combination of a β blocker with a dihydropyridine calcium channel blocker (CCB) also reduces both cardiac output and peripheral resistance, although studies have not compared β blocker/CCB and β blocker/α blocker combinations.

Clinical Implications of Identifying Neurogenic Hypertension

In patients with hypertension that is at least partially neurogenically mediated, a regimen directed at the SAS would seem physiologically well suited. A treatment algorithm (Fig. 1) can be proposed that differentiates neurogenic from other, more frequently encountered forms of hypertension. However, to date, studies have not compared such regimens with ACEI/diuretic regimens, even in specific clinical situations in which hypertension is likely to be neurogenic, such as post-stroke hypertension.

A major barrier to such studies is that SAS tone cannot be reliably measured, and therefore, neurogenic hypertension cannot be reliably identified in individual patients. It would seem important to assess in future studies the value of the clinical clues discussed in identifying individuals with neurogenic hypertension. This could be achieved by assessing responses to mechanistically different drug regimens, particularly in patients with hypertension in the setting of stroke, sleep apnea, alcoholism, or other conditions known to be associated with increased SAS tone. Consideration of neurogenic mechanisms might also be of value in understanding and treating hypertension that is unresponsive to a diuretic/ACEI combination, or whose clinical presentation is atypical. Similarly, the relationship between psychological characteristics and responses to different antihypertensive agents also merits more study.

Finally, it is important to note that not all individuals with increased SAS tone develop hypertension. Genetic predisposition and lifestyle factors, such as diet, weight, and exercise, contribute substantially to the development and severity of hypertension. Thus, in thin, fit individuals with no family history of hypertension, increased SAS tone can exist without hypertension. In other individuals, particularly in those with refractory hypertension, multiple mechanisms, both neurogenic and non-neurogenic, might all be contributory. In such individuals, BP normalization might require regimens directed at multiple mechanisms.

Conclusions

Essential hypertension is a heterogeneous disorder whose treatment can be improved if drugs are selected based on pathophysiology in the individual patient. Greater awareness of the role of the SAS, and of the likely contribution of neurogenic mechanisms in some proportion of hypertensive patients, will likely help in pursuing this goal.

Although we cannot reliably assess SAS tone in individual patients, the possibility that readily available clinical clues might serve as indicators of neurogenic hypertension merits study. More research and clinical trials designed to identify individuals with neurogenically mediated hypertension, and assess their responses to different antihypertensive regimens, are needed if we are to move from “cookbook” treatment to more physiologically appropriate individualized care of hypertensive patients.

References


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