Autonomic Dysfunctions in Human Hypertension

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SUMMARY Elevated circulating supine or standing norepinephrine (NE) or epinephrine (E) levels were observed in a variable proportion of hypertensive patients by several investigators. In our studies, elevated supine NE levels were found in an important proportion of patients with labile or sustained hypertension, whereas elevated supine E levels were observed only in a small proportion of patients with labile hypertension. Since there was little overlap between patients characterized either by elevated NE or E levels, these amines appear to reflect distinct abnormalities affecting the basal functions of either the sympathetic fibers or the adrenal medulla. In addition, greater increases of either amine, in response to postural change, were also observed in an important subgroup of hypertensive patients suggesting abnormalities in the reactivity of the sympathoadrenal system. It is likely that a variety of mechanisms underlie those elevated supine or standing catecholamine levels. Besides reflecting primary dysfunctions occurring along the sympathetic baroreflex arc, those elevated levels could also reflect dysfunctions occurring outside the sympathoadrenal system through various presynaptic modulatory mechanisms. Among those modulatory influences, the parasympathetic system was found to exert an inhibitory influence on NE liberation by sympathetic fibers through an action of acetylcholine on presynaptic muscarinic receptors. Since muscarinic blockade, by atropine treatment, was found to potentiate the NE response to postural change in hypertensive patients characterized by normal sympathetic response whereas it did not potentiate the response in patients characterized by an increased reactivity before treatment, it may be postulated that the sympathoadrenal hyperreactivity observed in certain patients is probably the consequence of a reduced inhibitory parasympathetic tone. (Hypertension 3 (suppl II): II-124-II-128, 1981)

KEY WORDS • sympathetic system • parasympathetic system • circulating catecholamines • norepinephrine • epinephrine • atropine

ELEVATED circulating catecholamine (CA) (norepinephrine (NE) and epinephrine (E)) levels have been observed in a variable but important subgroup of hypertensive patients by several groups of investigators during the last decade.1 These findings are suggestive of an increased sympathoadrenal tone in a subpopulation of patients suffering from labile or sustained essential hypertension, but little is known concerning the mechanisms underlying those elevated levels. Although it is generally assumed that the amount of NE and E liberated into the circulation is proportional to the sympathetic nerve activity or to the secretory activity of the adrenal medulla, several other putative mechanisms should also be considered. As knowledge is increasing on the inactivation of circulating CA and on the presynaptic modulatory mechanisms of NE release from sympathetic fibers, it is becoming obvious that external events can alter circulating CA levels without change in sympathetic nervous activity.

In light of the demonstration in animal preparations that the parasympathetic system exerts an inhibitory influence on NE liberation by sympathetic fibers presumably through an action of acetylcholine on presynaptic muscarinic receptors,2-3 we have focussed the present study on the evaluation of the possibility that the increased sympathetic reactivity observed in certain patients might be secondary to a reduced parasympathetic tone. Although the present findings suggest such an abnormality in a subgroup of hypertensive patients, this study does not rule out the possibility that other putative external mechanisms could be involved in the apparent sympathoadrenal hyperreactivity observed in an important subgroup of labile or sustained hypertensive patients.
Methods

Normotensive subjects and patients with labile or mild sustained hypertension of either sex were studied between 9:00 am and 1:00 pm while fasting since midnight. Most patients had never been treated previously, but when treated, the treatment was stopped for at least 3 weeks prior to the study. To maintain sodium and calorie intake as close as possible to the habitual intake, the diet was not controlled in the preceding days.

All patients studied were found to have uncomplicated essential hypertension after a complete physical examination and a series of routine laboratory analyses. Basal supine and standing blood pressure levels were established at three distinct medical visits. The hypertension was categorized as sustained when the blood pressure was consistently above 150/90 mm Hg. It was considered labile when levels were occasionally recorded below 150/90 mm Hg.

Determination of basal catecholamine (CA) levels was made after resting in the supine position for 20 minutes. The evaluation of the sympathoadrenal reactivity to postural change was determined by measuring the circulating CA levels after 10 minutes in the standing position. In the study on the evaluation of the parasympathetic tone, an intravenous catheter was positioned in one forearm vein at the beginning of the experiment to facilitate blood sampling without any discomfort to the patient. The NE and E levels were determined in basal and standing positions as well as in response to isometric exercise (handgrip at 30% of maximal force for 2 minutes) before and after intravenous administration of atropine at a dose of 0.02 mg per kilogram. Informed consent was obtained from each patient before undertaking the study.

Circulating NE and E levels were determined by the radioenzymatic technique of Peuler and Johnson. Statistical analysis was carried out with the calculation of Student's t test.

Results

Circulating NE and E Levels in Labile and Sustained Hypertension

In our most recent study in which NE and E levels were differentially measured, we observed elevated NE and E levels in subgroups of patients with labile and sustained hypertension (fig. 1). As we had previously reported with two other radioenzymatic techniques for the determination of total CA or NE, NE and supine and standing circulating NE levels were found to be significantly elevated in groups of patients with labile or sustained hypertension. However, as we and others have previously observed, NE levels were increased in only one subgroup of patients. In the present study, elevated supine NE level values greater than one standard deviation from the normal mean were observed in 37.5% of labile hypertensive patients and in 30% of patients with sustained hypertension, while elevated standing NE levels were found respectively in 32.5% and 22% of the same groups of patients. Abnormalities were also observed in circulating E levels, and average supine E levels were significantly increased only in patients with labile hypertension. The study of the distribution of those values revealed that supine E levels were present in 22.5% of labile hypertensive patients, while only a few patients with sustained hypertension had elevated levels. However, patients with sustained hypertension demonstrated a greater E reactivity to standing as reflected by an incidence of elevated standing E levels of 26% in those patients, while elevated standing E levels were present in only 17.5% of patients with labile hypertension.

Effects of Parasympathetic Blockade on the Sympathoadrenal Reactivity

To investigate the possibility that a change in parasympathetic tone might be responsible for the sympathethic abnormalities observed in some hypertensive patients, we studied the effects of parasympathetic blockade by treatment with atropine on circulating NE and E levels under basal conditions and on their variations following postural change and a period of isometric exercise in a group of labile hypertensive patients (fig. 2). Following that study, patients were separated in two groups based on the effect of atropine on variations of NE levels following postural change. Patients in whom the atropine treatment increased the NE response following the change from supine to standing position constituted the potentiated group while all other patients in whom that treatment did not increase or else inhibited the NE response to postural change constituted the nonpotentiated group. No differences were observed in basal NE levels between the two groups either before or following the treatment with atropine. It was of interest to observe that the potentiated group had a normal NE reactivity to standing and to isometric exercise prior to atropine treatment, whereas the nonpotentiated group was characterized by an enhanced NE reactivity to both forms of stimulus before atropine administration. The chronotropic response to atropine treatment was also found to be significantly greater in the potentiated group compared to the nonpotentiated group of hypertensive patients (fig. 3). These observations suggest that the parasympathetic tone is probably inhibited or decreased in the nonpotentiated group and that the initial increased NE reactivity observed in these hypertensive patients may be secondary to a lower inhibitory parasympathetic tone on the sympathetic fibers. Although the parasympathetic tone does not appear to affect basal NE levels, marked differences were observed between basal E levels in the two groups of patients (fig. 2). Circulating E levels were significantly greater at all points of the study in the potentiated group of patients.
Discussion

Over the last decade, elevated resting CA or NE have been reported in human hypertension by several groups of investigators using various radioenzymatic assays, but this field of research still remains controversial. In our laboratory, using two different radioenzymatic techniques, we had consistently observed previously elevated supine and standing CA or NE levels in 30% to 40% of patients with labile or sustained hypertension. We had also reported that the CA or NE response to standing was enhanced in a subgroup of hypertensive patients, thus suggesting an increased sympathetic reactivity. Moreover, the observation that basal CA or NE could be significantly correlated with the heart rate or pre-ejection period in hypertensive patients suggested that CA or NE levels reflected physiologically significant alteration in the sympathetic activity.

In the present study, it was still possible to confirm that circulating supine or standing NE levels are elevated in a subgroup of hypertensive patients and it was observed that circulating E levels are elevated in a subgroup of patients with labile hypertension. Since little overlap was observed between patients presenting either elevated E or NE levels, it appears that increases in the circulating levels of these two amines might reflect distinct abnormalities. An elevation in circulating NE levels probably reflects dysfunctions related to sympathetic nerve functions whereas an increase of E levels would probably reflect dysfunctions affecting more specifically the adrenal medulla. From the evaluation of supine and standing circulating NE or E levels, it is possible to suspect a variety of sympathoadrenal dysfunctions affecting the basal tone and/or the reactivity of either component of the sympathetic system.

The release of CA by the sympathetic system has been generally assumed to be proportional to the level of activity within that system. Although it is possible that elevated CA levels could be secondary to intrinsic dysfunctions within the sympathoadrenal reflex arc in certain patients, it is also possible that circulating CA levels could reflect functional abnormalities occurring outside the sympathetic system. It is now accepted that the amount of transmitter released by sympathetic fibers is not solely dependent upon the number of nerve impulses, but that the quantity of transmitter released per impulse may be modulated by a variety of transmitters and hormones acting on presynaptic receptors. In periphery, presynaptic receptors sensitive to NE, E, dopamine, acetylcholine, angiotensin, endorphin, and prostaglandins have been demonstrated to mediate positive or negative feedback mechanisms on the liberation of NE by the sympathetic fibers. Since several of those mechanisms were found to be of functional significance un-
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The group of patients termed POTENTIATED included those in whom atropine increased the NE response to postural change; the NON-POTENTIATED group included all remaining patients. The numbers in brackets indicate the number of patients in each group. The SEM are given only for points where the differences were significant (p < 0.05) between the values of the two groups of patients.

The recent experimental demonstration that the parasympathetic system can inhibit the liberation of NE presumably through an action of acetylcholine on presynaptic muscarinic receptors has provided a sub-stratum for the understanding of the close functional integration of the sympathetic and parasympathetic components of the autonomic nervous system. In light of previous suggestions of a decreased parasympathetic tone in humans, it was logical to postulate that the apparent increased sympathoadrenal tone and reactivity in hypertensive patients might be reflecting a loss of parasympathetic inhibition on the sympathetic system. The present study suggests that the parasympathetic tone is probably diminished in a subgroup of hypertensive patients since their chronotropic response following atropine administration is decreased. The observation that atropine treatment failed to potentiate the NE response following postural change also supports the hypothesis of a decreased parasympathetic tone.

FIGURE 2. Effect of intravenous administration of atropine (0.02 mg/kg) on basal NE and E levels and on the responses to postural change or isometric exercise (handgrip for 2 minutes at 30% of maximal force) in groups of labile hypertensive patients. The patients remained in the supine position through the whole protocol except for two 10-minute periods of standing. The group of patients termed POTENTIATED included those in whom atropine increased the NE response to postural change; the NON-POTENTIATED group included all remaining patients. The numbers in brackets indicate the number of patients in each group. The SEM are given only for points where the differences were significant (p < 0.05) between the values of the two groups of patients.

FIGURE 3. Effect of atropine treatment on the average basal heart rate and blood pressure and on the responses to postural change or isometric exercise in the same group of patients described in figure 2. The SEM is given for points where the differences between the two groups were statistically significant (p < 0.05).
reduced parasympathetic tone in that group of patients since the postural NE response was found to be potentiated by atropine in the other group of patients. Therefore, the enhanced NE reactivity observed before atropine treatment in the nonpotentiated group of patients may well be a consequence of a reduced parasympathetic tone in these patients. However, the parasympathetic tone does not appear to influence basal NE levels since the average NE levels were identical in both groups of patients and since atropine treatment did not significantly alter basal NE levels.

This lack of parasympathetic influence on circulating NE levels could be explained by the possibility that the parasympathetic system would exert its inhibitory influence only when a certain level of sympathetic activation is reached, as it occurs during postural change or isometric exercise. On the other hand, it was observed that circulating E levels were significantly greater at all times in the group of patients with a normal or greater parasympathetic tone. Although no explanations can be provided at this point for the understanding of this phenomenon, it nevertheless indicates that the degree of basal parasympathetic tone may be important in the establishment of circulating E levels.

These studies suggest that circulating CA levels could reflect dysfunctions affecting presynaptic modulatory mechanisms. The present observations do not rule out the possibility that the effect of atropine might be mediated through an action on the brain, but the fact that similar mechanisms were demonstrated on peripheral sympathetic fibers in experimental animals support the possibility that the effect of atropine could be mediated through peripheral mechanisms. An abnormal parasympathetic tone may not explain all abnormalities observed in circulating CA in human hypertension but this mechanism should be considered as a possible explanation for the sympathoadrenal hyperreactivity observed in certain patients. This study does not exclude the possibility that dysfunctions in other presynaptic mechanisms, in the NE clearance, or in the conjugation of CA might be also implicated in the maintenance of elevated supine and standing CA levels in subgroups of hypertensive patients. Whatever the underlying mechanisms, it appears that elevated CA levels could reflect an increased biologic sympathoadrenal tone at the effector cell level in an important subgroup of hypertensive patients.

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References
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