Dissociation of 24-Hour Catecholamine Levels from Blood Pressure in Older Men

NAFTALI STERN, ELIZABETH BEAHM, DENNIS McGINTY, PETER EGGLENA, MICHAEL LITTNER, MICHAEL NYBY, ROBERT CATANIA, AND JAMES R. SOWERS

SUMMARY Increased plasma norepinephrine levels have been observed in some persons with early essential hypertension. Although both plasma norepinephrine level and mean arterial blood pressure rise with age, little is known about the state of catecholamine secretion in elderly patients with essential hypertension. We studied the 24-hour cycle levels of plasma norepinephrine, epinephrine, and dopamine in 12 elderly hypertensive subjects and 13 age-matched normotensive controls (mean ages, 63.8 ± 1.2 yr and 64.8 ± 1.8 yr [SEM] respectively). Blood samples were obtained at bihourly intervals from 0900 to 2100 hours and every 30 minutes from 2100 to 0900 hours, during which time sleep and breathing were continuously monitored. A circadian rhythm was displayed in both groups by plasma epinephrine levels (mesor, 49 ± 2 pg/ml and 38 ± 1 pg/ml; amplitude, 15 ± 2 pg/ml and 11 ± 1 pg/ml; acrophase, 12.20 ± 0.40 hr and 14.41 ± 0.34 hr in the normotensive and hypertensive groups respectively) but not by plasma norepinephrine or dopamine levels. During the 24-hour cycle plasma epinephrine, but not norepinephrine or dopamine, levels were positively related to mean arterial blood pressure (r = 0.60 for the normotensive subjects, r = 0.57 for the hypertensive subjects, p < 0.01 for both). Mean 24-hour plasma norepinephrine (377 ± 9 pg/ml vs 455 ± 9 pg/ml; p < 0.001), epinephrine (34 ± 2 pg/ml vs 45 ± 2 pg/ml; p < 0.01), and dopamine (40 ± 2 pg/ml vs 62 ± 3 pg/ml; p < 0.01) levels were lower in the hypertensive group, although groups did not differ in parameters known to affect catecholamine secretion such as body weight, sodium intake, sleep efficiency, or sleep-related breathing disorders. Mean 24-hour plasma norepinephrine level was inversely related to the 24-hour mean arterial blood pressure (r = -0.48, p < 0.05). High norepinephrine levels in the elderly may reflect decreased baroreceptor sensitivity as well as compensatory response to decreased $\beta$-adrenergic receptor sensitivity. It is unclear why elderly hypertensive persons, unlike younger hypertensive persons, have lower plasma catecholamine levels than do elderly normotensive persons. (Hypertension 7: 1023-1029, 1985)

KEY WORDS • essential hypertension • norepinephrine • epinephrine • dopamine • diurnal rhythm • catecholamines

AGING is associated with a gradual increase in plasma norepinephrine (NE) levels as well as with a tendency for rising blood pressure.1-3 Whereas increased sympathetic outflow has been implicated in the induction of early "neurogenic" essential hypertension, the age-dependent increase in NE is observed in normotensive subjects. Whether the ob-

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served increment in circulating NE is related to the age-associated rise in blood pressure or to the increased incidence of hypertension in aging humans is unclear. The increase in NE with advancing age instead could reflect a compensatory mechanism to a declining peripheral response to adrenergic stimuli or an age-related decrease in clearance of NE. Moreover, a recent study based on single NE samples obtained from a large number of subjects with a wide age range concluded that NE increases with age in normotensive subjects but not in subjects with essential hypertension. However, there is relatively little direct information about the state of plasma catecholamines in hypertension of the elderly. Among 64 studies of plasma NE in hypertensive and normotensive subjects recently reviewed by Goldstein,10 not a single study included hypertensive subjects with a mean age of 55 years or greater. Further, as plasma NE has a short
Subjects and Methods

A total of 25 men, 12 essential hypertensive subjects (blood pressure >140/115, 90/115, 170/115 mm Hg based on multiple determinations) and 13 age-matched normotensive subjects (blood pressure <135/85 mm Hg) older than 55 years of age were studied. Subjects were recruited by advertising in local community and veterans organizations. Inpatients were not considered for this study, and all participating subjects were relatively healthy. Specifically, secondary forms of hypertension, concomitant cardiac, neurological, renal, metabolic, psychiatric, or chronic lung (defined as forced expiratory volume in 1 min < 80% using age-corrected norms) diseases as well as habitual alcohol consumption or regular use of hypnotic drugs were carefully excluded, leading to the selection of 25 subjects out of the 179 initially screened. Subjects signed approved informed consent statements. All medications were withheld for at least 3 weeks preceding the study, and no medications, including hypnotics, were used throughout the hospitalization period. On admission to the metabolic-geriatric ward, subjects were placed on a diet containing 100 mEq of sodium and 80 mEq of potassium per day. They underwent 3 nights (Nights 1, 2, 4) of adaptation and graded familiarization with the sleep laboratory and monitoring equipment. The following parameters were recorded between 2100 and 0900 hours: blood pressure and heart rate (indirectly, Sentry 2000 automated monitor, Costa Mesa, CA, USA), electroencephalogram (2 channels: C3-A2, P3-A1), electrooculogram (2 channels), chin electromyogram, electrocardiogram (lead I), airflow (nasal-buccal thermistor, Somnitech, Inc., Van Nuys, CA, USA), chest and abdominal respiratory movement (mercury strain gauges, Parks Electronics, Beaverton, OR, USA), hemoglobin saturation (continuous ear oximetry, Biox IIA, Boulder, CO, USA, or Hewlett-Packard, Palo Alto, CA, USA), and left and right anterior tibialis electromyogram (to detect nocturnal myoclonus). Nighttime studies were conducted in a soundproofed room. Sleep stages were quantified using standard criteria. Subjects were classified as having sleep apnea if they exhibited at least 12 episodes/hr of 4% or more hemoglobin desaturation. Simulated and real blood sampling was carried out by a venous catheter connected to a sampling line passing through a port in the wall. Twenty-four hour sampling for hormone levels was conducted on Day 5 and Night 5. Between 0900 and 2100 hours, blood samples were obtained at bihourly intervals through a previously inserted venous catheter after the subject had been supine for at least 30 minutes. Between 2100 and 0900 hours, samples were obtained every 30 minutes just before blood pressure was measured. Samples were collected in prechilled heparinized tubes (4 °C) and centrifuged at 750 g within 10 minutes, and immediately stored at −80 °C until assayed (within 2 wk). Plasma NE, E, and DA were determined by a single isotope radioenzymatic assay, as previously described. The sensitivity of this assay is 10 pg/ml for NE and E and 15 pg/ml for DA. Plasma renin activity (PRA) was determined by radioimmunoassay at 0900 hours on the second morning (following overnight recumbency); sensitivity is 0.2 ng/ml/hr. Differences in mean arterial pressure (MAP) and plasma catecholamines were analyzed by analysis of variance with repeated measures. Chronobiological characteristics of blood pressure, NE, E, and DA were assessed by previously outlined methods using the Apple II Cosinor Program obtained from the Institute of Work Physiology, Oslo, Norway.

Results

Clinical characteristics of the hypertensive and normotensive subjects in this study are summarized in Table 1. The two groups were matched for age, daily sodium intake, weight, and prevalence of sleep apnea. Characterization of sleep parameters of the two groups is given in Table 2. The normotensive and hypertensive subjects studied were indistinguishable as regards total sleep time, sleep efficiency, distribution of sleep stages, number of changes in sleep stages, and number of arousals (defined as interruption in sleep > 10 sec). Basal PRA was 1.4 ± 0.3 ng/ml/hr for the normotensive group and 0.8 ± 0.1 ng/ml/hr for the hypertensive group (p < 0.05). The NE levels (Figure 1) peaked in the midday hours in both groups (p < 0.01 for the comparison of...
TABLE 1. Clinical Characteristics of the Elderly Subjects Studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.8 ± 1.2</td>
<td>64.8 ± 1.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>131 ± 3</td>
<td>166 ± 3*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>76 ± 2</td>
<td>97 ± 2*</td>
</tr>
<tr>
<td>Sodium excretion (mEq/24 hr)</td>
<td>104 ± 6</td>
<td>112 ± 4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.5 ± 2.8</td>
<td>83.9 ± 3.6</td>
</tr>
<tr>
<td>% ideal body weight</td>
<td>115.8 ± 3.2</td>
<td>120.1 ± 4.0</td>
</tr>
</tbody>
</table>

Subjects with sleep apnea

Total                   | 8            | 7            |
Central                 | 4            | 4            |
Occlusive               | 4            | 3            |

Values are means ± SEM. *p < 0.005, between groups.

TABLE 2. Sleep Parameters of the Normotensive and Hypertensive Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (min)</td>
<td>371 ± 13</td>
<td>352 ± 10</td>
</tr>
<tr>
<td>Percent sleep efficiency*</td>
<td>78.7 ± 3.1</td>
<td>74 ± 1.6</td>
</tr>
<tr>
<td>Percent awake</td>
<td>21.3 ± 3.1</td>
<td>24.8 ± 1.9</td>
</tr>
<tr>
<td>Percent stage 1–2</td>
<td>53.5 ± 1.4</td>
<td>52.3 ± 3.9</td>
</tr>
<tr>
<td>Percent delta sleep (stage 3–4)</td>
<td>8.9 ± 1.3</td>
<td>6.1 ± 3.2</td>
</tr>
<tr>
<td>Percent REM sleep</td>
<td>14.5 ± 1.7</td>
<td>13.1 ± 1.2</td>
</tr>
<tr>
<td>Number of arousals/hr (&gt;10 sec)</td>
<td>60.6 ± 6.8</td>
<td>54.8 ± 8.4</td>
</tr>
<tr>
<td>Number of stage changes/hr</td>
<td>53.1 ± 7.0</td>
<td>40.8 ± 7.6</td>
</tr>
<tr>
<td>Number of desaturations/hr</td>
<td>20.9 ± 4.9</td>
<td>17.5 ± 4.4</td>
</tr>
<tr>
<td>Percent minimal oxygen saturation</td>
<td>85.6 ± 1.1</td>
<td>82.0 ± 2.3</td>
</tr>
</tbody>
</table>

Values are means ± SEM; no significant differences between groups.

REM = rapid eye movement.
*Sleep efficiency was calculated as (total sleep time/time in bed) x 100.

NE levels at 1300 hours with those at 0900 hours in both groups). However, mean daytime (0900–2100 hours) NE levels were not significantly different from mean nighttime NE levels in both normotensive and hypertensive subjects. When analyzed individually, 19 subjects exhibited no day/night differences (9 normotensive and 10 hypertensive subjects), four had a higher mean daytime NE level (3 normotensive subjects and 1 hypertensive subject) and two had a higher nighttime NE level (1 normotensive and 1 hypertensive subject). An increase in plasma NE levels in the early morning hours, between 0600 and 0800 hours, was consistently detectable in the normotensive group (p < 0.01 for the comparison of NE levels at 0800 hours with those at 0600 hours), but not in the hypertensive group. Overall there appeared to be no circadian rhythm of mean NE levels in either of the two groups, although by individual analysis three normotensive and four hypertensive subjects retained a circadian pattern, albeit with relatively weak correlation to the best fitting cosine curve (r = 0.202–0.404). The intradian individual sample to sample variation of plasma NE level was high: based on 31 determinations per subject the mean standard deviation was 29.3 ± 2.5% of the mean 24-hour level in the normotensive group and 31.4 ± 3% in the hypertensive group.

Mean transverse 24-hour NE levels were significantly lower in the hypertensive subjects (377 ± 9 pg/ml vs 455 ± 9 pg/ml; p < 0.001). That difference was almost entirely attributed to markedly higher nighttime NE levels in the normal group (460 ± 9 pg/ml vs 369 ± 7 pg/ml), as the daytime differences were not significant. When all subjects were considered (i.e., both normotensive and hypertensive subjects), mean transverse 24-hour plasma NE level was inversely related to mean transverse 24-hour MAP (r = 0.48, p < 0.05; Figure 2). Overall 24-hour E levels were highly related to clock time in both the normotensive (r = 0.56; p < 0.001) and the hypertensive group (r = 0.61, p < 0.001). On individual analysis three hypertensive subjects and four normotensive subjects failed to display such correlation. The overall mesor E values for the normotensive and hypertensive groups respectively were 49 ± 2 pg/ml and 38 ± 1 pg/ml (p < 0.001), the amplitudes were 15 ± 2 pg/ml and 11 ± 1 pg/ml, and the acrophase values were 12.20 ± 0.40 hours and 14.41 ± 0.34 hours (p < 0.01). Mean 24-hour E levels were again higher in the normotensive subjects than in the essential hypertensive subjects (45
Mean 24-hour plasma DA level also showed no circadian pattern by cosinor analysis. By individual analyses 24-hour DA levels in only one normotensive subject and three hypertensive subjects could be correlated with clock time. Mean 24-hour plasma DA level was higher in the normotensive subjects (62 ± 3 pg/ml) than in the hypertensive group (40 ± 2 pg/ml; p < 0.001; Figure 4).

In all subjects MAP was significantly related to clock time. Heart rate and MAP showed a clear circadian rhythm in all subjects, and the nocturnal decreases in both normotensive and hypertensive subjects were of similar magnitude. Maximal nocturnal decreases in MAP were 24.8 ± 4.4 mm Hg and 27.2 ± 3.2 mm Hg, and the maximal decrements in heart rate were 11.6 ± 1.9 beats/min and 9.2 ± 1.7 beats/min in the normotensive and hypertensive groups respectively, which was not significantly different. During the 24-hour analysis MAP declined during sleep and rose sharply in the early morning hours. The MAP was related to mean plasma E but not to NE or DA levels in both the normotensive (r = 0.60, p < 0.01) and the hypertensive (r = 0.57, p < 0.01) groups (Figure 5).

Discussion

In this study, the mean 24-hour plasma levels of NE, E, and DA were lower in older subjects with essential hypertension than in age-matched controls. In the assessment of NE levels in elderly subjects in whom the overall prevalence of various organic diseases is relatively high, care must be taken to eliminate the possible role of multiple conditions associated with established or possible alterations in plasma NE levels. These include thyroid disease, iron deficiency anemia, congestive heart failure, depression, chronic obstructive lung disease, diabetes, orthostatic hypotension, duodenal ulcer, chronic renal failure, liver dysfunction, and alcohol abuse. These considerations, in conjunction with the need to avoid concomitant drug therapy, led to the exclusion of the majority of the 179 elderly men initially screened for this study. Because hypertensive and normotensive subjects in this study were closely matched for weight and percent ideal body weight and were studied after a metabolic balance on a constant sodium intake had been achieved, variations in weight or dietary salt are unlikely explanations for the lower NE levels in the hypertensive group.

As daytime NE levels of the two groups in this study were only slightly and insignificantly different, the lower overall 24-hour NE levels in the elderly hypertensive subjects should be attributed mainly to the greater nighttime difference in NE levels. Therefore,
Further evidence for lower sympathetic tone in elderly hypertensive subjects relative to elderly normotensive subjects is presented by their lower E levels. Usually, E and DA have not been implicated in the pathogenesis of hypertension. While plasma E and DA are derived mainly from adrenomedullary secretion rather than from sympathetic nerve endings, they nevertheless increase in parallel to NE levels in response to a host of stressful stimuli such as upright posture, exercise, restraint, dorsal column stimulation, and surgical stress. Unlike NE levels, E and DA levels do not increase with age, and the levels observed in this study are within the range reported in younger subjects using similar assays.

The loss of circadian rhythmicity of plasma NE in most aged subjects in this study is in striking contrast to the distinct pattern observed in younger subjects studied under similar conditions in this laboratory. Based on the correlation between plasma NE levels and blood pressure in young subjects in these earlier studies, it was postulated that the circadian rhythm of blood pressure is regulated in part by ambient levels of plasma NE. The absence of nocturnal decrease of blood pressure in pheochromocytoma provided further, though indirect evidence for the role of NE as a determinant in the diurnal pattern of blood pressure. This is clearly not the case in elderly men, in whom the NE-blood pressure relationship over the 24-hour cycle did not hold up: blood pressure in this age group decreased at night, but NE levels did not. In the absence of a consistent circadian rhythm of NE in the elderly, the importance of multiple sampling in the search for representative NE levels is underscored by the high sample to sample variance in both normotensive and hypertensive subjects.

Detailed, multiple sampling studies of 24-hour plasma levels of E and DA have not been previously reported, but a number of reports have suggested the existence of circadian rhythm of plasma and urinary £[18,19,22,24] detectability of a diurnal rhythm of plasma E level in the aged and its obvious relation to the 24-hour cycle blood pressure levels suggest that at least some inherent chronobiological functions related to sympathetic outflow are preserved in the elderly. The reason for the dichotomy between the nocturnal decline in plasma E levels, MAP, and heart rate and the persistent high NE levels (Figure 5) is not clear. One explanation is that plasma levels of epinephrine are not as readily affected by environmental factors as are levels of NE. Although both circulating DA and E are thought to reflect largely adrenomedullary discharge, DA levels were erratic, thus resembling the inconsistency displayed by peripheral NE levels. Since we only measured free DA levels, the possibility that conjugated DA levels might be more closely related to plasma E levels cannot be excluded.

Overall these results reflect a reversal of the state of catecholamine secretion encountered in early hypertension (i.e., increased plasma NE and E levels in some young hypertensive persons). In fact, plasma NE levels appear to be particularly elevated during
sleep in young hypertensive persons compared with those in young normotensive persons. In contrast, the sleep period was the time at which the plasma NE levels were lower in our elderly hypertensive subjects in comparison with those in our elderly normotensive subjects. That plasma NE levels are relatively lower in association with hypertension of the elderly might have been predicted from the results of two previous independent observations. If plasma NE levels increase significantly with age only in normotensive subjects, then ultimately NE levels could be expected to be higher in normotensive subjects in extreme old age. Contrary to findings in young and middle-aged hypertensive persons, in whom plasma catecholamine levels are positively related to arterial blood pressure, an inverse relation between plasma NE level and both systolic and diastolic blood pressure has been recently noted in older hypertensive persons. This inverse correlation was confirmed in the present study. Thus, if the high catecholamine levels in the elderly reflect a compensatory mechanism to a decreased peripheral pressor sensitivity rather than a primary hyperadrenergic state, the elevated blood pressure per se in older hypertensive persons might obviate a major stimulus for enhanced catecholamine secretion. Alternatively, the lower sympathetic tone, taken together with the lower PRA, may be compatible with "hypervolemic hypertension." This idea seems unlikely, however, since a number of studies have demonstrated that older hypertensive subjects with low PRA actually display low blood volumes. Even in younger hypertensive persons, the combination of low renin and suppressed sympathetic nervous function was observed in both normal volume and low volume states. Finally, the possibility that the lower catecholamine levels in elderly hypertensive subjects resulted from enhanced clearance cannot be excluded. It would thus seem that the role of NE level in essential hypertension may undergo a full cycle, from a possible cause in some young hypertensive persons, through a "sustaining phase" in which NE secretion is within the normal range but may still be viewed as inappropriately high for the increased blood pressure to, ultimately, lower levels in older age. The dissociation between plasma catecholamine levels and blood pressure in the elderly suggests that despite the age-related increase in plasma NE levels, hypertension in older persons is not "neurogenic." Thus, the age-associated rise in blood pressure and the increased incidence of hypertension in aging men appears to be independent of the parallel age-dependent increase in NE.

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