Original Articles

Changes in Plasma Norepinephrine, Blood Pressure and Heart Rate During Physical Activity in Hypertensive Man


SUMMARY We have investigated the changes in plasma norepinephrine and blood pressure and heart rate during a range of physical activities in eight hypertensive subjects in order to determine whether changes in plasma norepinephrine reflect changes in sympathetic activity. Blood pressure was recorded over 24 hours from an intra-arterial cannula. Plasma norepinephrine, measured by a sensitive radioenzymatic method, increased progressively with increasing levels of physical activity. In each subject a statistically significant linear relationship was observed between the logarithm of plasma norepinephrine and systolic blood pressure. Analysis of variance showed that 66% of the variance of plasma norepinephrine was associated with changes in blood pressure and heart rate. These observations support the hypothesis that plasma norepinephrine reflects short-term changes in sympathetic activity. Use of the quantitative relationship described, in conjunction with measurements of norepinephrine metabolism, may help to determine the significance of increased levels of plasma norepinephrine observed in some hypertensive patients. (Hypertension 1: 341-346, 1979)

KEY WORDS • essential hypertension • sympathetic function • sleep

PLASMA levels of norepinephrine are widely used as an index of sympathetic activity and increased levels noted by some observers in a proportion of hypertensive subjects are interpreted as indicating increased sympathetic activity as a cause of the high blood pressure. However, observations which confirm the usefulness of plasma norepinephrine as an index of sympathetic activity in man are limited; activities that increase sympathetic tone such as changes in posture and physical exercise are accompanied by appropriate increases in plasma norepinephrine. Norepinephrine released from the sympathetic nerve endings is subject to a number of influences including local re-uptake mechanisms and enzymatic degradation and only a proportion of released norepinephrine escapes to contribute to the circulating levels of norepinephrine. Therefore, it may be simplistic to suppose that the level of plasma norepinephrine will necessarily reflect the level of sympathetic activity. If plasma levels do reflect sympathetic activity, there should be a quantitative relationship between plasma levels of norepinephrine and physiological measurements which reflect sympathetic activity, such as changes in heart rate and blood pressure. We have investigated how plasma norepinephrine, blood pressure and heart rate change with increasing levels of physical activity in patients with mild to moderate hypertension in order to define the relationship between plasma levels and physiological measures of sympathetic activity.

Patients and Methods

We investigated eight patients (five male, three female) with mild to moderate essential hypertension whose average age was 43 years (table 1). Hypertension was defined as a blood pressure greater than 150/90 mm Hg on three separate occasions as an outpatient. There was no evidence of any underlying cause for hypertension after clinical examination, measurement of urea, electrolytes and creatinine, 24-hour urinary metanephrine excretion and excretion urography. We excluded patients who had evidence of target organ damage defined as 1) history or signs of ischemic heart disease or cerebrovascular disease; 2)
left ventricular hypertrophy on clinical examination, electrocardiogram or chest x-ray; 3) impairment of renal function; or, 4) retinal changes greater than Grade 2 (Keith-Wagener-Barker classification). All patients were previously untreated or had stopped treatment at least 2 months before study. One patient was a smoker (Patient 8). Patients were admitted to hospital for 36 hours for investigation. Sodium intake was standardized by asking them to avoid adding extra salt to the diet, apart from that used in cooking, for 3 days before admission. During their hospital stay they received a diet containing 60 mEq of sodium daily. A 24-hour urine specimen was obtained from each subject and urinary sodium excretion was measured. Ambulatory blood pressure was recorded continuously over 24 hours using the system developed in Oxford. Essentially, pressure is measured from a fine polyethylene cannula in the brachial artery and recorded on magnetic tape by a portable tape-recorder, together with electrocardiograph (The Oxford Instrument Co. Ltd., Osney Mead, Oxford, UK). The cannula was kept patent by perfusion of water at 2 ml/hour from a miniature pump; the frequency response of the transducer and recording system was flat to 7 Hz. Calibration was performed three to four times during the 24-hour period so that allowance could be made for small zero shifts due to battery depletion over the 24-hour period; calibration was linear over the range 50–220 mm Hg. Blood pressure and heart rate during specific activities were measured by playing out the tape recording on ultraviolet-sensitive paper and averaging the measurements over 30–60 seconds. During bicycle exercise, blood pressure was measured from a Gaeltec 3EA/a transducer (Watco Services, Basingstoke, Hants, UK) connected by a three-way tap to the cannula and recorded on a Minograf 81 recorder (Elema-Schönander, Stockholm, Sweden). Frequency response of this system was flat to 20 Hz. Blood pressure and heart rate during bicycle exercise were averaged over the last 3 minutes of an 8-minute exercise period.

The purpose of the 24-hour blood pressure recording was to confirm that blood pressure elevation was sustained before treatment. Informed consent was obtained from each subject for arterial cannulation and blood sampling and the investigations were approved by the Hospital Ethics Committee.

The severity of hypertension was quantitated in each subject, by averaging 10 observations of blood pressure from the 24-hour blood pressure recording at arbitrary points during quiet afternoon activity. This activity was chosen to reduce the effects of variation in blood pressure with physical activity.

Venous blood specimens were obtained for norepinephrine from a forearm venous cannula (Venflon 17G) without occlusion, transferred to ice-cool heparinized tubes and the plasma separated by centrifugation at 4°C for 7 minutes and stored at −20°C within 30 minutes of sampling.

Plasma norepinephrine was measured by a single isotope radioenzymatic method within 4 weeks of sampling. This method utilizes a partially purified preparation of phenylethanolamine N-methyl transferase specific for norepinephrine and sensitive to 0.05 µg/liter. Norepinephrine was determined in duplicate; intra-assay variation was 8% and inter-assay coefficient of variation 15%. Norepinephrine decreased by less than 10% during storage at −20°C for 4 weeks.

Exercise Tests

Over the 24-hour period specimens were obtained during a range of physical activities, most of which were repeated several times. Table 1 shows the number of observations made in each subject during each activity. Venous blood samples (10 ml) were obtained during the following activities: 1) sleeping (without waking the patient); 2) lying quietly supine (10–20 minutes after resting during daytime activities); 3) sitting after 5 to 10 minutes; 4) standing after 5 to 10 minutes; 5) immediately after walking for 5 to 10 minutes; 6) immediately after 8 minutes of upright bicycle exercise. The bicycle ergometer load (Elema-Schönander ergometer) was determined from a previous multi-stage exercise test to exhaustion and was that load which caused 85% of maximum heart rate. After walking or cycling, at least 40 minutes elapsed before taking further resting specimens.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yrs), Sex</th>
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<td>8</td>
<td>42, M</td>
<td>0 2 1 3 1</td>
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</table>
Data Analysis

Group data are expressed as mean ± SEM. A one-tailed Student's t test, using Bessel's correction for small samples, was used to test the significance of differences between means; correlation coefficients and analysis of variance were performed using standard methods.11

Results

The numbers of observations made in each subject during each activity varied slightly between patients (Table 1). Observations during sleep were not made in two subjects (Patients 2 and 8) and during bicycle exercise in two subjects (Patients 1 and 5) because of difficulty in obtaining satisfactory blood specimens or damping of the intra-arterial pressure recordings. The average number of observations made in each subject was 13 and varied from eight to 19. Mean 24-hour sodium excretion was 82 ± 13 mEq and varied from 30 to 129 mEq. Mean afternoon intra-arterial blood pressure during quiet activity was 148/88 mm Hg compared to a mean of 182/118 mm Hg for mean outpatient readings (Table 2).

Mean Norepinephrine Values During Each Activity

The mean level of plasma norepinephrine during each activity increased progressively from 0.28 ± 0.13 during sleep (n = 16) to 0.48 ± 0.38 lying awake (n = 25), 0.61 ± 0.24 (n = 16) sitting, 0.66 ± 0.24 (n = 27) standing, 1.15 ± 0.57 (n = 16) during walking and 2.97 ± 1.31 (n = 6) after cycling. The following differences were statistically significant: between sleeping and lying (t = 1.98, p < 0.05), lying and standing (t = 3.82, p < 0.0005) and walking and cycling (t = 4.32, p < 0.0005).

Figure 1 shows the mean level of log. plasma norepinephrine plotted against mean systolic blood pressure during each activity; it is apparent that both values increased in a linear manner with increasing level of physical activity.

No significant relationship was noted between mean log. plasma norepinephrine during lying or standing and 24-hour sodium excretion (r = 0.50 and 0.47, respectively).

Relationship Between Plasma Norepinephrine and Systolic Blood Pressure in Individual Patients

Table 2 shows the correlation coefficients and parameters of the relationship between plasma norepinephrine, plotted logarithmically, and systolic blood pressure in each subject. The correlation coefficient varied from 0.52 to 0.91 and was statistically significant in each subject. Figure 2 shows the regression lines of log. plasma norepinephrine on systolic blood pressure for each subject. There is considerable variation in the position of these lines between individuals with some variation in slope. Neither of these parameters was related to mean afternoon blood pressure (for relationship between plasma norepinephrine at 150 mm Hg against mean afternoon systolic blood pressure, r = -0.25; for relationship between slope and mean afternoon systolic blood pressure, r = -0.06).

Relationship between Plasma Norepinephrine and Diastolic Blood Pressure in Individual Subjects (Table 3)

The relationship between log. norepinephrine and diastolic blood pressure was less consistent than for systolic blood pressure and was statistically significant in only five of the eight subjects (Patients 2, 3, 4, 7, 8).

Relationship Between Plasma Norepinephrine and Heart Rate in Individual Subjects (Table 3)

The relationship between log. norepinephrine and heart rate was consistent and was statistically significant in all except one subject (Patient 5) in whom few observations were made during exercise because of difficulty in obtaining venous blood.

Analysis of Variance

Ninety-nine observations of systolic blood pressure, diastolic blood pressure and heart rate were available.
for analysis of variance. Seven of the 106 original observations were rejected because on close examination of the arterial pressure trace it was possible that slight damping had occurred.

Analysis of variance confirmed that there was a strong association between log. plasma norepinephrine and systolic blood pressure \((r = 0.59)\) and between log. norepinephrine and heart rate \((r = 0.69)\) with a weaker relationship between log. norepinephrine and diastolic blood pressure \((r = 0.36)\) when the patients were considered as a group. Clearly, heart rate, systolic blood pressure and diastolic blood pressure are not independent variables; when allowance was made for this, the multiple correlation coefficient was 0.81, indicating that changes in heart rate and blood pressure accounted for 66% of the total variance of plasma norepinephrine. Using an F test to compare variance within and between individuals, significant differences between subjects were found for all four variables (norepinephrine: \(F = 5.5, p < 0.001\); systolic blood pressure: \(F = 4.0, p < 0.001\); diastolic blood pressure: \(F = 7.0, p < 0.001\); heart rate: \(F = 2.8, p < 0.01\)). We then considered the residual variance (34%) left after removal of the association between plasma norepinephrine and blood pressure and between plasma norepinephrine and heart rate with physical activity. After a repeat analysis using covariance adjusted means for norepinephrine, significant differences between individuals with respect to norepinephrine no longer remained (\(F = 1.4\)). This

<table>
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<th>Patient no.</th>
<th>Log. plasma norepinephrine &amp; HR</th>
<th>Log. plasma norepinephrine &amp; DBP</th>
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<td></td>
<td>Correlation coefficient</td>
<td>Probability</td>
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<td>NS</td>
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<tr>
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<td>&lt; 0.001</td>
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</tr>
<tr>
<td>8</td>
<td>0.92</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
suggested that the differences in norepinephrine between subjects were due to differences in the relationship between norepinephrine and the physiological variables, blood pressure and heart rate, rather than to some unidentified and independent factor.

Discussion

We consider that there are two conclusions which can be drawn from our observations; first, they support the hypothesis that plasma norepinephrine reflects short-term changes in sympathetic activity in man; and second, they suggest ways in which the importance of the sympathetic nervous system in initiating or maintaining hypertension can be further elucidated in man.

We selected patients who had no evidence of target organ damage, particularly cardiac enlargement, in order that the effects of disordered cardiovascular function consequent upon prolonged hypertension should be minimized. The modestly elevated intra-arterial blood pressure of our patients, 148/88 mm Hg, indicates that we were successful in selecting patients with only mild to moderate hypertension; in fact only three patients had sustained intra-arterial pressures greater than 140/90 mm Hg.

We deliberately studied our patients in an informal ward environment in order to reduce any effect of anxiety induced by a strange laboratory environment on sympathetic function and plasma catecholamines. We attempted to minimize the effects of anxiety by delaying blood sampling for at least 1 hour after arterial and venous cannulation and by reducing the contact of patient and doctor to blood sampling and general supervision of the physical activities performed.

The method of continuously recording intra-arterial blood pressure is well established; the cannula causes minimal restriction of the patient's physical activity, and sleep disturbance is small. We considered that the frequency response and stability of the recording system were satisfactory for the purposes of demonstrating changes in blood pressure over the wide range which occurs between sleeping and sub-maximal exercise.

In each patient studied, a significant linear relationship was noted between the logarithm of plasma norepinephrine and systolic blood pressure with increasing physical activity; a linear relationship between log. norepinephrine and heart rate was also seen in seven of the eight subjects. The poorer relationship between log. norepinephrine and diastolic blood pressure is probably accounted for by the less predictable changes in diastolic pressure that occur with physical activity. When the patients were considered as a group, changes in heart rate and blood pressure accounted for 66% of the variance in plasma norepinephrine that occurred with physical activity. These observations lend considerable support to the hypothesis that plasma norepinephrine is an index of short-term sympathetic activity in man and suggest that sympathetic activity is an important determinant of changes in blood pressure during physical activity. The relationship we found does not establish a direct causal relationship between systolic blood pressure and plasma levels of norepinephrine; rather it suggests that both measurements depend on sympathetic activity.

Our observations are consistent with those of other workers in suggesting a relationship between plasma norepinephrine and sympathetic activity in man. Norepinephrine levels increased during postural stimulation and handgrip and a quantitative relationship was noted between the decrease in heart rate and plasma norepinephrine levels during rest after venepuncture. Christensen and Brandsborg separated the increases in plasma norepinephrine with physical activity into separate components related to change in posture and change in heart rate; plasma norepinephrine increased during dynamic exercise of moderate intensity but not during light exercise. In contrast, our observations suggested a continuous relationship between plasma norepinephrine and physiological variables during physical activity. Further evidence supporting a relationship between norepinephrine and sympathetic activity is that drugs which reduce blood pressure by influencing sympathetic outflow from the central nervous system, such as clonidine or peripheral ganglion blocking agents such as pentolinium reduce plasma norepinephrine; diabetic and quadriplegic patients have reduced plasma levels, in association with decreased autonomic function, as do those with primary postural hypotension.

After release from the sympathetic nerve ending, norepinephrine is subject to many influences including re-uptake into nerve endings, uptake into smooth muscle and local enzymatic degradation. Therefore, only a portion of the norepinephrine released which escapes from these mechanisms is able to diffuse into blood. In addition, it is likely that net release and uptake of norepinephrine varies from one tissue to another, although precise information on this matter is lacking. Therefore, changes in forearm venous
blood may not reflect changes in blood at other sites. When one considers these factors, in addition to the technical problems of measurement of norepinephrine, even with radioenzymatic methods, it is perhaps surprising that we were able to account for 66% of the variance of norepinephrine during varying physical activities by the three physiological variables measured.

The positions and slopes of the regression lines of log. norepinephrine on systolic blood pressure varied between individuals and the analysis of variance demonstrated that there were significant differences between individuals in the relationship of plasma norepinephrine to the physiological variables measured. Our observations support the concept that plasma levels of norepinephrine reflect the level of sympathetic activity. These inter-individual differences could be interpreted as indicating either that subjects may vary in their sensitivity to released norepinephrine or alternatively that the fate of norepinephrine after release varies between subjects. There are, however, a number of other reasons why the observed differences could have occurred. First, there were differences between individuals in the numbers of observations made during each activity. Second, we chose to standardize the sodium intake by a diet causing mild sodium restriction: the 24-hour urinary sodium excretion varied considerably and it is quite possible that the ability of the kidneys to conserve sodium influenced the parameters of the norepinephrine/blood pressure relationship; this aspect has been somewhat neglected in the consideration of the cause of increased plasma norepinephrine levels in hypertensive patients. Third, the two parameters, slope and position, could be altered by the physical characteristics of the resistance vessel wall, whereby hypertrophied vascular smooth muscle produces a bigger resistance change than a normal vessel for the same norepinephrine/receptor interaction. However, we found no support for this last observation since we observed no relationship between the severity of hypertension, as reflected by the mean afternoon blood pressure, and either the slopes or the positions of the regression lines of log. norepinephrine on systolic blood pressure.

Our observations support the hypothesis that changes in plasma norepinephrine during physical activity reflect sympathetic activity within an individual subject, but there is little evidence to support the widely held assumption that differences in resting levels of norepinephrine between individuals necessarily indicate differences in sympathetic activity. This assumption may not be justified as there is evidence from experiments in which norepinephrine is infused intravenously that distribution volume and norepinephrine clearance rates may vary widely between individuals. Therefore, plasma levels may vary between individuals for reasons other than changes in sympathetic activity. The question of whether differences in plasma norepinephrine between individuals reflect differences in the level of sympathetic activity is crucial to the study of norepinephrine levels in human hypertension. In conjunction with measurements of norepinephrine clearance rate, it may be possible to use the linear relationship described to determine whether differences in vascular sensitivity or norepinephrine metabolism are important in determining differences in plasma norepinephrine levels between individuals.

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Changes in plasma norepinephrine, blood pressure and heart rate during physical activity in hypertensive man.
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