Urinary noradrenaline excretion and renal function in normal and hypertensive 50-year-old men

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Summary
1. Sympathetic nervous system activity, measured by urinary noradrenaline excretion, was determined in a group of untreated hypertensive subjects \((n = 39)\), a reference group \((n = 80)\) and a normotensive group \((n = 51)\), all derived from a random population sample of 50-year-old men. It was compared with casual and resting blood pressure, urinary sodium excretion, urinary creatinine concentration and glomerular filtration rate. Hypertension was defined as systolic pressure >175 or diastolic >115 mmHg on two separate occasions. Normotension was defined as systolic pressure <160 and diastolic pressure <95 mmHg.

2. There was no difference in the average excretion of noradrenaline during the day or night between the reference, normotensive and hypertensive groups. None of the hypertensive patients had values for urinary noradrenaline excretion during the day above the range found in normotensive subjects, indicating that hypertension with increased sympathetic nervous system activity is uncommon when hypertension is defined as above.

3. No correlation between urinary noradrenaline excretion during the day and blood pressure was found in the reference group or in the normotensive group. In the hypertensive group, there was a negative correlation between urinary noradrenaline excretion and blood pressure after rest. This finding might indicate that factors other than sympathetic nervous system activity determine the level of blood pressure in hypertensive subjects.

4. In the hypertensive group, urinary noradrenaline excretion during the day was positively correlated with both urinary sodium excretion during the day and glomerular filtration rate. Urinary noradrenaline excretion per 24 h was positively correlated with urinary sodium excretion during the same time. High resting blood pressure, low urinary sodium excretion, low glomerular filtration rate and a reversed diurnal rhythm of urinary excretion characterized hypertensive patients with low urinary noradrenaline excretion, indicating more severe hypertension in these hypertensive patients with reduced sympathetic nervous system activity.

Key words: blood pressure, glomerular filtration rate, noradrenaline, random population sample, sodium, sympathetic nervous system.

Introduction
Studies on the role of the sympathetic nervous system in the development and maintenance of high blood pressure have given somewhat conflicting results. Studies in spontaneously hypertensive rats have shown that these genetically predisposed animals react with a more intense increase in sympathetic nervous system activity when they are exposed to stress stimuli (Okamoto, 1969; Folkow, Hallbäck, Lundgren, Silvertsson & Weiss, 1973). The increased heart rate in borderline hypertensive subjects (Frohlich, Kozul, Tarazi & Dustan, 1970; Berglund, Wilhelmsen & Werkö, 1974) and in established hypertension (Isacsson, 1972) has been
taken as indirect evidence of increased sympathetic activity, as has also the increased cardiac output in hypertensive patients without organ damage (Sannerstedt, 1969). Haemodynamic studies, however, have shown the hyperkinetic circulation in labile as well as in established hypertension to be caused by a combination of increased sympathetic activity and decreased parasympathetic tone (Julius, Pascual & London, 1971; Korner, Shaw, Uther, West, McRitchie & Richards, 1973). Direct quantification of sympathetic nervous system activity by insertion of needle electrodes into efferent sympathetic nerves has not shown any increase (G. Wallin, W. Delius & K. E. Hagbarth, unpublished work). In a hypertensive, however, even 'normal' sympathetic activity should be regarded as too high, as an increase in blood pressure should be accompanied by a decrease in sympathetic activity via the baroreceptor reflex (Koch-Weser, 1973).

Previous studies have shown increased catecholamine excretion in 5-25% of hypertensive patients (de Quattro, 1971; Esler & Nestel, 1973), and the frequency of increased plasma catecholamine concentrations has varied between 26 and 75% (Engelman, Portnoy & Sjoerdsma, 1970; de Quattro & Chan, 1972). A review of studies concerning sympathetic nervous system activity in hypertension is given by de Quattro & Miura (1973). However, the interpretation of these results is difficult as sympathetic activity is probably influenced by the severity of the hypertensive disease. Thus one study has shown a negative correlation between the sympathetic response to tilt and the severity and duration of the hypertension (Frohlich, Tarazi, Ulrych, Dustan & Page, 1967).

The differences in the findings in previous studies may be due to the fact that they all have been performed in highly selected hospital series. Furthermore, the groups of normal and hypertensive subjects compared have not been homogeneous with respect to age and sex. Differences in age and sex are accompanied by differences in physical activity, body weight and smoking habits, and all these factors are known to influence the excretion of catecholamines (von Euler, 1956; Kershbaum, Khorsandian, Caplan, Ballett & Feinberg, 1963). This paper presents results of determination of urinary noradrenaline excretion and its relation to kidney function in groups of normal and hypertensive males of the same age, derived from blood pressure screening in a total population.

### Material

From a screening examination, which was a part of a multifactor, primary preventive trial (Wilhelmsen, Tibblin & Werkö, 1972) in a randomly selected third \( n = 1122 \) of the 50-year-old male population in Göteborg, Sweden, all subjects with previously untreated, newly discovered essential hypertension formed a hypertension group \( n = 35 \); Fig. 1. The diagnosis of essential hypertension was based on casual blood pressure above 175 mmHg systolic and/or 115 mmHg diastolic on two separate occasions 2 weeks apart, and a negative standard diagnostic examination for secondary hypertension (Wilhelmsen, Berglund & Werkö, 1973). Of the hypertension group, eighteen subjects were classified as belonging to WHO stage 1, thirteen to stage 2 and four to stage 3. A reference group \( n = 80 \) was obtained from the same trial by drawing a 10% subsample at random. The non-participation rate in the reference group was 18% (20/110). Five subjects in the reference group fulfilled the criteria for hypertension and joined the hypertension group. Subjects in the reference group with casual blood pressure above 175 mmHg systolic and/or 115 mmHg diastolic only at the first measurement \( n = 5 \) remained in the reference group. A normotensive group \( n = 51 \) was created by excluding subjects in the reference group with casual blood pressure above 160 mmHg systolic or 95 mmHg diastolic.
Methods

Investigations

The reference, normotensive and hypertensive groups were subjected to the same investigations, which were performed in parallel for the three groups during the spring of 1972. The screening examination was performed between 16.30 and 19.30 hours, when blood pressure has been shown to be highest (National Health Survey, 1966). When casual blood pressure was taken at 08.00 hours in the same age cohort, the limits 175/115 mmHg corresponded to 162/101 mmHg. At the screening examination the participants were asked to take part in an examination of heart and kidney function. The day before this investigation a 24 h urine sample was collected. The hypertensive group also underwent a standard diagnostic investigation including X-ray of the chest, electrocardiography and isotope renography and routine laboratory tests (Wilhelmsen et al., 1973). At this diagnostic investigation urine specimens were collected for the determination of urine osmolality after 13 h abstinence from fluid.

Casual blood pressure was measured at the screening examination after a few minutes interview in the seated position with a 12.5 cm broad and 26 cm long cuff connected to a mercury manometer. Diastolic pressure was recorded as phase 5, i.e. when the sounds disappeared. Blood pressure was determined to the nearest 2 mmHg in order to avoid digital preference. As part of a non-invasive investigation of cardiac function (J. Wikstrand, G. Berglund, L. Wilhelmsen & T. Wallentin, unpublished work), blood pressure after 1 h rest was measured in the supine position on a randomly selected half of the reference, normotensive and the hypertensive groups. A microphone was placed over the brachial artery. The same type of cuff as used at screening but with automatic inflation and deflation was used. The cuff pressure, the Korotkoff sounds and ECG were recorded on a Mingograf 81 (Siemens-Elema, Sweden). Blood pressure was calculated to the nearest 1 mmHg. Recordings were not obtained for four subjects in the reference group. Heart rate at screening and after 1 h rest was measured from five consecutive beats on the ECG.

Height and weight were measured according to Rose & Blackburn (1968). Relative body weight was calculated as weight/height −100.

Two hypertensive subjects with extreme obesity (relative body weight 1.38 and 1.48) and high noradrenaline excretion were excluded as a previous study has shown a much higher urinary noradrenaline excretion in grossly obese subjects (P. Björntorp, L. Sjöström & J. Häggendal, unpublished work).

Determinations of urinary noradrenaline excretion were performed for the day (07.00-19.00 hours) and night (19.00-07.00 hours) separately. A modified method according to von Euler & Floding (1956), measuring only free noradrenaline, was used. Subjects who were suspected of inadequate urine collection were excluded (see below) from analysis of variables requiring urine collection.

Glomerular filtration rate was determined as clearance of $^{51}$Cr-EDTA by using the single-injection technique (Bröchner-Mortensen, 1972), and the rate was corrected to 1.73 m² body surface area, which was calculated according to Isacsson (1958). The day-to-day variation for determinations in the same subjects was 5%. Two subjects in the reference group, one with a chronic glomerulonephritis verified by biopsy and one in whom the injection of $^{51}$Cr–EDTA was given partly subcutaneously, were excluded from analysis of glomerular filtration rate, the latter also being excluded from the normotensive group. In the hypertensive group one subject with low glomerular filtration rate and insulin-treated diabetes mellitus was excluded.

Determinations of urine volume, urinary sodium excretion and creatinine concentration were performed for the day and night separately. Sodium and creatinine in urine and serum was determined with a Technicon AutoAnalyzer. In order partly to diminish the influence of inadequate urine collection, the following criteria for exclusion were set up: creatinine excretion < 1000 mg/24 h, or excretion ratio day/night > 2 or night/day > 1.5. On the basis of these criteria, seven subjects in the reference group and normotensive group and one in the hypertensive group were excluded from analysis of variables requiring urine collection.

Statistical methods

Standard methods were used for calculation of mean values, SD and correlation coefficients. The hypothesis of no difference in mean value between two groups was tested with Student's $t$-test for approximately normally distributed variables. When the variables were not normally distributed or the
Results

Blood pressure and heart rate

Casual and resting blood pressure and heart rate are shown in Table 1 for the randomly selected half of the reference, normotensive and hypertensive groups in which the casual measurements were repeated after 1 h rest. In all three groups, systolic pressure, diastolic pressure and heart rate after rest were significantly lower than before (P<0.01). The hypertensive subjects had a significantly higher heart rate than the reference and normotensive groups before rest (P<0.05), but after rest there was no difference.

Urinary noradrenaline excretion

No differences were found in mean urinary noradrenaline excretion between the three groups and the distributions were roughly normal (Fig. 2). Means and standard deviations were higher for day excretion than for night excretion in all three groups. None in the hypertension group had a higher urinary noradrenaline excretion during the day than the highest value in the normotensive group.

Glomerular filtration rate and urinary sodium excretion

Mean glomerular filtration rate in the reference group was 100 ml/min (range 74–132); the corresponding figures in the normotensive group were 100 ml/min (78–125) and in the hypertensive group 96 ml/min (74–123); the differences were not statistically significant. Urinary sodium excretion during the day was 92 mmol (range 38–180) in the reference group, 101 mmol (53–180) in the normotensive group and 85 mmol (31–162) in the hypertensive group. Mean urinary sodium excretion during the 24 h in the reference group was 181 mmol (range 65–323); the corresponding figures in the normotensive group were 185 mmol (115–323), in the hypertensive group 167 (65–238). Again, the differences were not significant.

In the hypertension group glomerular filtration rate was negatively correlated to resting diastolic blood pressure and positively correlated to urinary sodium excretion during the day (Fig. 3). There was a tendency, although not statistically significant, towards a negative correlation between urinary sodium excretion during the day and resting diastolic blood pressure (r = -0.40). In the reference and normotensive groups no significant correlations were found between these three variables, r between glomerular filtration rate and resting diastolic blood pressure being 0.07 in the normotensive group and -0.03 in the reference group.

Relationships between noradrenaline excretion during the day and the other variables

The linear correlation coefficients were calculated
between urinary noradrenaline excretion during the day and blood pressure and heart rate before and after rest, relative body weight, urine volumes, creatinine concentrations and sodium excretions during the day and night and glomerular filtration rate. In the reference group heart rate after rest was positively correlated to urinary noradrenaline excretion during the day ($r = 0.42$, $P < 0.05$). The other variables were not significantly correlated to urinary noradrenaline excretion during the day in the reference or in the normotensive group.

In the hypertensive group systolic blood pressure
and diastolic blood pressure after rest were negatively correlated to urinary noradrenaline excretion during the day and heart rate tended to rise with rising urinary noradrenaline excretion during the day (Table 2; Fig. 4). No significant linear correlations were found between urinary noradrenaline excretion during the day and blood pressure or heart rate before rest or relative body weight.

There was no significant correlation between urinary noradrenaline excretion during the day and urine volume or creatinine concentration during the day or during the night (Table 3). Urinary sodium excretion during the day was positively correlated to urinary noradrenaline excretion during the day (Fig. 4). Urinary noradrenaline excretion during 24 h was also positively correlated to the urinary sodium excretion during the same time ($r = 0.44$, $P < 0.01$). Glomerular filtration rate was positively correlated to urinary noradrenaline excretion during the day.

**Discussion**

The present material has been drawn from the total male population in Göteborg. As most of the variables studied are age- and sex-dependent, we have chosen to study normotensive and hypertensive men of the same age. The reference group was drawn at random and the hypertensive group was selected
TABLE 3. Urine volume, creatinine concentration, urinary sodium excretion and glomerular filtration rate in tertiles of noradrenaline excretion during the day in the hypertensive group

The linear correlation coefficient (r) and the level of statistical significance (P) are given.

<table>
<thead>
<tr>
<th>Noradrenaline excretion</th>
<th>Linear correlation coefficient</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>(83–136 nmol/12 h)</td>
<td>(137–207 nmol/12 h)</td>
<td>(208–290 nmol/12 h)</td>
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<td></td>
<td>(n = 11)</td>
<td>(n = 11)</td>
<td>(n = 10)</td>
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<tr>
<td>Urine volume (l)</td>
<td></td>
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<td></td>
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<tr>
<td>Day</td>
<td>0.63</td>
<td>0.78</td>
<td>0.72</td>
<td>0.22</td>
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<tr>
<td>Night</td>
<td>0.75</td>
<td>0.69</td>
<td>0.67</td>
<td>-0.13</td>
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<tr>
<td>Creatinine concn. (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>12</td>
<td>10</td>
<td>13</td>
<td>0.09</td>
</tr>
<tr>
<td>Night</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>0.11</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/12 h)</td>
<td>58</td>
<td>100</td>
<td>99</td>
<td>0.47</td>
</tr>
<tr>
<td>Day</td>
<td>66</td>
<td>88</td>
<td>87</td>
<td>0.29</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml min⁻¹ 1.73 m⁻²)</td>
<td>85</td>
<td>101</td>
<td>105</td>
<td>0.67</td>
</tr>
</tbody>
</table>

so that subjects of different severity of hypertension had the same chance of being represented. The normotensive group was created by excluding possible ‘borderline’ hypertensive subjects from the reference group.

Noradrenaline, the sympathetic neurotransmitter, leaks out from the sympathetic nerve endings into the blood stream. A small amount is excreted into the urine. This urinary noradrenaline excretion reflects sympathetic nervous activity, as demonstrated by the fact that urinary noradrenaline excretion increases in the standing position, at work and during stress and decreases after sympathectomy and ganglion blockade (von Euler, 1956). Urinary noradrenaline has been shown to be a better indicator of sympathetic nervous system activity than urinary excretion of other catecholamines (de Quattro & Miura, 1973). We therefore chose urinary noradrenaline excretion for measurement of sympathetic activity. However, small changes in the tonic sympathetic activity cause great changes in the lumen of resistance and capacitance vessels and hence in blood pressure and heart rate (Folkow & Hamberger, 1956; Mellander, 1960). The noradrenaline excreted in the urine is probably a very rough measure of average overall sympathetic activity during the time of collection. The correlation found between noradrenaline and heart rate at rest indicates, however, that urinary noradrenaline mirrors sympathetic nervous system activity at rest.

The fact that urinary noradrenaline excretion was not absolutely increased in any of the hypertensive subjects is in contrast to other studies, in which increased urinary noradrenaline excretion has been found in up to 25% of the hypertensive subjects studied (Nestel & Doyle, 1968; Nestel & Esler, 1970; Esler & Nestel, 1973). These studies, however, were performed in selected hospital series and the groups of normal and hypertensive subjects compared were not homogeneous for age and sex. This might partly explain the discrepancies between our results and the results of these studies.

The negative correlation between resting blood pressure and urinary noradrenaline excretion during the day in the hypertensive group indicates that some factor other than sympathetic activity is the ultimate determinant of blood pressure in hypertensive subjects of the kind studied. The tendency to a negative correlation between urinary sodium excretion and resting blood pressure, and the positive correlation between urinary sodium excretion and urinary noradrenaline excretion, might indicate that factors determining excretion and intake of sodium override sympathetic nervous system activity in the long-
term blood pressure regulation of these hypertensive subjects, as has been proposed by Guyton, Coleman, Cowley, Manning, Norman & Ferguson (1974). This interpretation is contradictory to the findings of a previous study (Esler & Nestel, 1973) showing a positive correlation between urinary noradrenaline corrected for glomerular filtration rate and resting blood pressure in a combined group of borderline and established hypertensive subjects. The correlation, in our study, between glomerular filtration rate and urinary noradrenaline excretion during the day might have been caused by a decreased urinary excretion of noradrenaline resulting from either (a) a lower filtration rate of noradrenaline or (b) an altered noradrenaline metabolism in hypertensives with consequently decreased urinary excretion.

These interpretations seem unlikely since no significant positive correlation between glomerular filtration rate and urinary noradrenaline excretion during the day could be found in the reference group or normotensive group, despite the fact that the ranges were quite similar and previous studies have not given evidence of an altered noradrenaline metabolism in hypertensive subjects (de Quattro & Miura, 1973). Furthermore, in the hypertensive group, a significant negative correlation was found between blood pressure after rest and glomerular filtration rate. Thus, if correction for glomerular filtration rate is made, there is no possibility of detecting a change in the activity of the sympathetic nervous system with increasing severity of the hypertensive disease.

Thus our results indicate that severely hypertensive subjects with persistent high blood pressure at rest and with reduced glomerular filtration rate are characterized by decreased sympathetic nervous system activity.

Sympathetic activity was also shown to be related to the excretion of salt and water (Table 3). Hypertensive subjects with low sympathetic activity were characterized by lower urinary sodium excretion during the day and during the 24 h and a reversed diurnal pattern of urine excretion, indicating high renal resistance in these subjects (Brod, 1973). Assuming steady-state conditions the lower urinary sodium excretion in these hypertensive subjects mirrors a lower sodium intake. The relationships were not found in the reference group and were thus related to the hypertensive state.

A possible physiological background to these findings is that as the hypertensive disease progresses into an established phase with persistent high blood pressure at rest, adaptive changes develop in the renal vascular bed leading to a high renal resistance, a reduced glomerular filtration rate and a low urinary sodium excretion. Animal studies have shown that sodium losses increase sodium appetite and sodium loading decreases (Stricker, 1973). A possible explanation for the low sodium excretion in the established phase of hypertension would thus be a decreased salt appetite and intake. These hypertensive subjects also have decreased sympathetic activity and hence decreased urinary noradrenaline excretion. A possible explanation is that the higher blood pressure in these subjects causes inhibition of sympathetic activity via the baroreceptors (Koch-Weser, 1973).

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