Plasma Noradrenaline Levels in Regular Haemodialysis Patients

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Summary

Plasma concentrations of noradrenaline (NA), adrenaline (A) and renin (R) were measured in 29 regular haemodialysis patients (RHP) [13 normotensive, 10 hypertensive, 6 binephrectomised] and in 15 healthy control subjects (C) under various physiological conditions: supine—standing—walking. RHP had significant higher plasma levels of noradrenaline and adrenaline in the mean than C. All RHP responded to passive orthostasis with a significant increase in diastolic blood pressure, heart rate and plasma NA. In contrast to C, plasma NA did not drop after two hours of active orthostasis. Hypertensive RHP had significant higher plasma concentrations of R and A than normotensives. It is concluded that the sympathetic nervous system (SNS) plays a minor role in hypertensive blood pressure regulation of RHP. The adequate response to passive orthostasis in RHP with regard to diastolic blood pressure, heart rate and plasma NA indicates an intact function of the SNS under this condition. Hypertension in RHP not controllable by salt and volume depletion can be attributed to elevated levels of R, which in turn may stimulate adrenaline release from the adrenals. The mechanisms responsible for the elevated levels of circulating catecholamines remain unclear: an inhibition of re-uptake, disturbances in enzymatic metabolism or/and abolished renal clearance are suggested.

Introduction

In patients with chronic renal failure peripheral neuropathy is a common disorder. More recent studies demonstrated abnormal response to Valsalva manoeuvre (Goldberger et al, 1971), sweat dysfunction (Hennessy & Siemsen, 1968), non volume responding hypotension during haemodialysis (Kersh et al, 1974), reduced baroreceptor sensitivity (Lazarus et al, 1973) and noradrenaline depletion of adrenergic nerve terminals (Winkler et al, 1973) in patients with renal insufficiency.
These findings suggest that the autonomic nervous system may also be affected. This conception is supported by animal experiments describing various defects of sympathetic nervous system (SNS) in uraemic rats, such as inhibition of noradrenaline synthesis and re-uptake, an increased enzymatic metabolism and a depletion of the intraneuronal noradrenaline stores (Hennemann et al, 1973).

In the present study we investigated the SNS in patients on regular haemodialysis treatment under various physiological conditions. As a quantitative measure of sympathetic nervous activity we determined plasma catecholamines, of which noradrenaline especially has been proved to be a reliable index of overall sympathetic activity.

PATIENTS AND METHODS

Twenty-nine patients on regular haemodialysis treatment (RDT) and 15 healthy volunteers were studied (Table I). All patients underwent haemodialysis for three times nine hours weekly using a Kiil dialyser. They were divided into three subgroups: normotensive, hypertensive and binephrectomised.

To determine sympathetic nervous activity under various physiological conditions patients and healthy volunteers were subjected to a standardised test, which consisted of three phases: during phase 1 the proband rested for four hours (from 8.00 am to 12.00 am) in a supine position in order to establish basal conditions. The second phase was a seven minute standing period representing a strong physiological stimulus of SNS.

Phase 3 immediately following phase 2 consisted of two hours of walking (from 12.15 pm to 2.15 pm). After each of the test’s three phases blood pressure and heart rate were recorded and blood samples were taken for the determination of plasma catecholamines and plasma renin.

The test was performed under ambulatory conditions – 15-26 hours following the last haemodialysis. All drug treatment, especially the antihypertensive medication, was discontinued three days before the test.

Arterial blood pressure was measured by the auscultatory method. Heart volume was estimated radiologically using the formula of Rohrer and Kahlstorf (Reindell et al, 1960). The differential assay of noradrenaline and adrenaline in plasma was performed according to the fluorimetric method of Renzini et al (1970). Plasma renin concentration was determined by radioimmunoassay: exogenous sheep substrate (Skinner, 1967) and Dowex resin were added to the incubation mixture (pH 5.5). The generated angiotensin I was measured by means of a commercially available angiotensin I (125 J) radioimmunoassay kit, supplied by NEN Chemicals GmbH, West Germany.

For statistical analysis we used the paired and unpaired Student t-test.
### TABLE I. Clinical Data of the Investigated Groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls n = 15</th>
<th>Regular normotensive n = 13</th>
<th>Haemodialysis hypertensive n = 10</th>
<th>Patients binephrectomized n = 9</th>
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<tr>
<td><strong>Diagnosis</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>--</td>
<td>3</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>--</td>
<td>7</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Polycystic Kidney</td>
<td>--</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>--</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>32</td>
<td>44</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>years (28 - 36)</td>
<td></td>
<td>(33 - 70)</td>
<td>(34 - 54)</td>
<td>(21 - 48)</td>
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<tr>
<td><strong>Sex</strong></td>
<td>12♂ 3♀</td>
<td>4♂ 9♀</td>
<td>8♂ 2♀</td>
<td>5♂ 1♀</td>
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<tr>
<td><strong>Average Blood Pressure</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- 4 h supine- mmHg</td>
<td>116/80</td>
<td>110/75</td>
<td>158/103</td>
<td>112/73</td>
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<tr>
<td><strong>Mean Heart Rate</strong></td>
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<td></td>
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<tr>
<td>- 4 h supine- b/min</td>
<td>67</td>
<td>72</td>
<td>81</td>
<td>79</td>
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<tr>
<td><strong>Mean Duration</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>of R. D. T. months</td>
<td>--</td>
<td>50</td>
<td>40</td>
<td>52</td>
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<tr>
<td>(30 - 81)</td>
<td></td>
<td>(32 - 78)</td>
<td>(26 - 106)</td>
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<tr>
<td><strong>Mean Heart Volume</strong></td>
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<td></td>
<td></td>
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<tr>
<td>ml/1.73 m²</td>
<td>700</td>
<td>750</td>
<td>1067</td>
<td>1102</td>
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<tr>
<td><strong>Mean Haematocrit</strong></td>
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<tr>
<td>%</td>
<td>45</td>
<td>29</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>(42 - 48)</td>
<td></td>
<td>(21 - 41)</td>
<td>(22 - 45)</td>
<td>(17 - 25)</td>
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</table>

### RESULTS

**Blood Pressure and Heart Rate (Figure 1)**

Healthy subjects responded to change in posture from supine to standing by an increase in diastolic blood pressure and heart rate. All three groups of
Figure 1. Mean values of systolic and diastolic blood pressure and heart rate in control subjects and haemodialysis patients under various physiological conditions.
patients showed the same pattern of response and all tolerated the seven minutes of passive orthostasis remarkably well. After two hours of walking diastolic blood pressure fell again in all but the binephrectomised group. Heart rate after two hours of walking paralleled diastolic blood pressure in control subjects showing a significant decrease from standing to walking, whereas in haemodialysis patients, heart rate did not change significantly under the same conditions.

**Plasma Noradrenaline (PNA) (Figure 2)**

In control subjects the mean PNA level was $135 \pm 15.1\text{ng/L (SEM)}$ under basal conditions; passive orthostasis led to a significant increase up to a mean level of $373 \pm 24.1\text{ng/L}$. Under walking conditions PNA dropped again significantly to a mean of $234 \pm 22.1\text{ng/L}$, a level still higher than under supine conditions.

Haemodialysis patients already under basal conditions exhibited significant higher PNA levels than normals regardless of whether their blood pressure was high or normal. When exposed to passive orthostasis all haemodialysis patients responded by a significant increase in PNA. This increase again occurred, regardless of whether the patient was normotensive, hypertensive or binephrectomised. The absolute amount of PNA increase was similar to the increase found in control subjects; the percentage increase, however, was less. After two hours of walking in haemodialysis patients the PNA levels did not drop again below the levels measured after seven minutes of standing. In comparison to the normotensive group of patients, the hypertensive group showed a slight but not significant tendency to lower levels of PNA under all test conditions.

**Plasma Adrenaline (PA (Figure 3))**

In haemodialysis patients the mean values of PA were significantly higher than in control subjects under all test conditions; the hypertensive group of patients, however, had PA levels even significantly higher than the normotensive group. In contrast to PNA in all four groups investigated, PA did not change significantly after orthostatic stimulation.

**Plasma Renin (PR)**

Under resting conditions the hypertensive group of patients had significantly higher PR concentrations than the normotensive group ($20.7 \pm 4.55$ vs $4.44 \pm 0.66\text{ng Ag I/ml/h (SEM)}$; $p < 0.01$). After two hours of walking PR increased in both groups to $33.6 \pm 6.38 \text{ng Ag I/ml/h (p<0.05)}$ in the hypertensive and to $6.87 \pm 1.00 \text{ng Ag I/ml/h (p<0.001)}$ in the normotensive patients. The difference of PR after two hours of walking between the two groups again was significant ($p<0.01$). The mean PR concentrations under
Figure 2. Plasma concentrations of noradrenaline in control subjects and haemodialysis patients under various physiological conditions. (SU=supine; ST=standing; WA=walking)
**Figure 3.** Plasma concentrations of adrenaline in control subjects and haemodialysis patients under various physiological conditions. (SU=supine; ST=standing; WA=walking)
both resting and orthostatic conditions in the normotensive group of patients did not differ significantly from the values found in the control subjects under the same conditions (4.82 ± 0.50 supine and 8.70 ± 1.18 ng Ag I/ml/h walking).

**DISCUSSION**

The majority of reports on autonomic dysfunction in uraemic patients describe disturbances of the parasympathetic part of the autonomous nervous system (Hennessy & Siemsen, 1968; Goldberger et al, 1971; Lazarus et al, 1973). Only few studies (Winkler et al, 1973; Kersh et al, 1974) are available concerning the function of the sympathetic adrenergic nervous system. Kersh et al described non volume responding hypotension during haemodialysis, which he ascribed to sympathetic insufficiency because blood pressure could be raised by noradrenaline administration. However the ineffectiveness of volume treatment and the good response to noradrenaline could have been due to the fall of plasma noradrenaline levels which occurs during haemodialysis (own unpublished observation).

Lesions of the SNS usually result in orthostatic or postural hypotension characterised by a fall in blood pressure without significant rise in heart rate (Hickler et al, 1960). In patients with postural hypotension blood levels and excretion of catecholamines are decreased and it was postulated that the compensatory orthostatic reflexes are mediated by noradrenaline (Hickler et al, 1959).

In all 29 haemodialysis patients investigated the function of the SNS seemed to be intact at least when the patients were subjected to orthostasis: PNA increased significantly as well as diastolic blood pressure and heart rate and patients showed a remarkable good tolerance to orthostasis. Increased levels of circulating noradrenaline under resting and under orthostatic conditions did not correlate with arterial blood pressure as found in patients with essential hypertension (Brecht et al, 1974). Hypertensive haemodialysis patients do not have higher plasma noradrenaline concentrations than normotensive or binephrectomised patients. This finding suggests that SNS plays a minor role in hypertensive blood pressure regulation in haemodialysis patients. The fact that hypertensive patients have significant higher plasma renin concentrations points to a causal role of the renin angiotensin system in elevation of blood pressure. The concomitant high levels of circulating adrenaline in these patients can partly be explained by the stimulated renin angiotensin system, which leads to an augmented release of adrenaline from the adrenals (Feldberg & Lewis, 1964; Cession & Cession-Fossion, 1966; Robinson, 1967). The mechanisms responsible for the elevated levels of plasma catecholamines in haemodialysis patients are not clear. An increased release of noradrenaline by the sympathetic nerve endings seems to be
unlikely since the increase in plasma noradrenaline in response to upright posture is not higher than in control subjects. The lack of renal clearance of catecholamines in haemodialysis patients may contribute to some extent to their elevated plasma levels.

Other factors such as inhibition of re-uptake and/or an altered enzymatic metabolism because of only partially corrected uraemic intoxication may be involved.

References


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Open Discussion

DORHOUT MEES (Utrecht) Did you find any correlation between levels of plasma renin activity and catecholamines within the group of hypertensive patients?

BRECHT No.

MASSRY (Los Angeles) There are data suggesting a relationship between blood catecholamines and body sodium. Have you measured total body sodium in your patients? Do haemodialysis and ultrafiltration affect the blood levels of catecholamines?

BRECHT First, we did not measure sodium spaces and total exchangeable sodium in our patients. Second, we measured the plasma catecholamine levels during haemodialysis treatment, and we found that they continuously decreased during treatment. There was no increase due to ultrafiltration.