ORTHOSTATIC CHANGES OF HAEMODYNAMICS, RENAL FUNCTION, PLASMA CATECHOLAMINES AND PLASMA RENIN CONCENTRATION IN NORMAL AND HYPERTENSIVE MAN

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SUMMARY

1. In eight normal subjects, ten patients with labile hypertension, six with advanced essential hypertension and six with renovascular hypertension, plasma renin concentration, cardiac output, mean arterial pressure, clearances of creatinine and p-aminohippurate (PAH), and sodium excretion were measured before and after 30 min of 45° upright tilting. Changes in plasma adrenaline and noradrenaline concentration were measured in addition in the normal subjects, and in plasma volume in normal subjects and patients with labile essential hypertension.

2. In patients with advanced essential hypertension, heart rate and calculated peripheral resistance increased significantly less than in normal subjects, and plasma renin increased by 15% in this group, in comparison to 37% in normal subjects, 48% in labile essential hypertension, and 57% in renovascular hypertension. There was a positive relationship between changes in renin and noradrenaline concentrations in normal subjects.

3. Apart from a negative correlation between the increases in plasma renin concentration and mean arterial pressure in patients with renovascular hypertension, there were no significant relationships between changes in plasma renin and haemodynamics.

4. A negative correlation between changes in plasma renin and filtration fraction and a positive relationship between changes in renin and sodium excretion were found in normal subjects and patients with labile hypertension. Plasma renin increase was directly related to changes in the tubular rejection fraction of sodium in patients with labile hypertension. In the same group there was a negative correlation between changes of sodium rejection fraction and filtration fraction.

5. The results suggest a role of the adrenergic system in orthostatic renin release, but the functional connection between renal haemodynamics, tubular sodium handling and renin release across orthostasis cannot fully be explained on the basis of our present knowledge of renin releasing mechanisms.

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The mechanisms by which renin release is stimulated are not established. The most important stimuli leading to an increase of renin in peripheral blood are sodium depletion, haemorrhage, decrease of renal arterial perfusion pressure, stimulation of renal nerves and infusion of noradrenaline (Vander, 1967; Page & McCubbin, 1968). Cohen, Rovner, Conn & Blough (1964, 1966) observed a rise of plasma renin activity after change from the supine to the upright posture. This has been confirmed by other groups measuring plasma renin activity (Gordon, Kuechel, Liddle & Island, 1967) or plasma renin concentration (Brown, Davies, Lever, McPherson & Robertson, 1966; Oelkers, 1968; Oelkers, Magnus & Samwer, 1970a).

The circulatory changes on assuming the upright posture are complex. Blood is pooled in the capacitance vessels of the lower body, cardiac output and renal blood flow decrease rapidly, and heart rate and vascular resistance rise because of a reflex increase of neuroadrenergic activity. Major changes of blood pressure normally do not occur (Tuckman & Shillingford, 1966; Frohlich, Tarazi, Ulrych, Dustan & Page, 1967). Since several of the factors that change in the upright position are potential stimuli of renin secretion, their relative importance for orthostatic renin release is of interest. An important observation was made by Winer, Chokshi, Yoon & Freedman (1969) who found that the orthostatic renin release in normal man could be inhibited by infusions of adrenergic receptor blocking agents. Kuechel, Fishman, Liddle & Michelakis (1967), Barth, Duesterdieck, Roscher, Wolff, Brown, Lever & Robertson (1968) and Oelkers et al. (1968, 1970a) found that the increase of plasma renin with posture is often diminished or absent in patients with essential hypertension. Kuechel et al. (1967) suggested that the failure of renin to rise in those patients might be due to a decreased activation of the neuroadrenergic system in the upright position. Haemodynamic studies (Frohlich et al., 1967) and measurements of plasma catecholamines (Hickler, Hamlin & Wells, 1959) led to the conclusion that in advanced essential hypertension the neuroadrenergic response to the fall of cardiac output on assuming the upright posture is blunted. This abnormality was also observed in patients with primary aldosteronism and with autonomic insufficiency, in which conditions renin has been found to be suppressed and usually not stimulated by orthostasis (Biglieri & McIlroy, 1966; Conn, Cohen & Rovner, 1964; Gordon et al., 1967).

The present investigation was undertaken to elucidate further the relationship between orthostatic changes of cardiovascular and kidney function, blood volume, circulating catecholamines and plasma renin in normal and hypertensive subjects.

METHODS

Clinical subjects and normal controls

The experiments were carried out on thirty male subjects (eight normal, sixteen patients with essential hypertension and six with renovascular hypertension). The normal subjects (NS) were volunteer medical students. They were fully conversant with the nature of the study, the experimental procedure and possible dangers. Their mean age was 25 years (range 23–28 years). They were admitted to the ward one day before the experiment started. The hypertensive patients had been admitted for special diagnostic tests. The nature of the investigations had
been explained in detail to all of them, and all were willing to participate in those aspects of the study that were of no direct benefit to them. Apart from clinical examinations and daily blood pressure measurements the following screening tests were done: fundoscopy, chest X-ray, intravenous pyelogram, renal arteriography, and at least three measurements of serum potassium, sodium and creatinine. Vanillin mandelic acid was measured in ten patients with essential hypertension and found normal.

According to the results of the clinical tests, the patients were grouped in the following way.

**Labile essential hypertension (EH I).** In ten patients (19–37 years of age; mean age 30 years) kidney function was normal and other known causes of hypertension had been excluded as far as possible. Blood pressure had been found to be variable in the outpatient clinic. During their stay in the hospital for 8–10 days, recumbent blood pressure was found to be below 150/90 mmHg on at least two occasions, but above this value on other occasions. The highest blood pressure readings in this group did not exceed 200/110 mmHg. The fundi showed only slight narrowing of the retinal arteries in two cases and no hypertensive retinal lesions in the others. There was no evidence of left ventricular hypertrophy according to the electrocardiographic voltage criteria of Sokolow & Lyon (1949).

**Advanced essential hypertension (EH II).** In six patients recumbent diastolic blood pressure during their stay in the ward was always above 100 mmHg. The mean age of these patients was 47 years (range 37–56 years). Hypertensive retinal lesions (Keith, Wagener & Barker, 1939) were grade III and grade IV in one patient each and grades I or II in the remainder. There was evidence of left ventricular hypertrophy in the precordial leads of the electrocardiogram in all instances.

**Renovascular hypertension (RVH).** In six patients (39–55 years of age, mean age 47 years), renal angiograms showed unilateral renal artery stenosis. The mean longitudinal diameter of the poststenotic kidneys was 30% (range 20–35%) shorter than those of contralateral kidneys. At 90 min after the injection of 80 mg of frusemide, mean renin concentration was 70% (range 25–180%) higher in the venous blood of poststenotic kidneys compared with contralateral kidneys. Five of these patients were later operated on, four by aortorenal bypass and one by thromboendarterectomy and venous patch-graft. In four, blood pressure fell to less than 150/90 mmHg postoperatively. In one patient blood pressure fell from an average of 190/115 mmHg to 170/90 mmHg after operation. The postoperative blood pressure recordings refer to a mean observation time of 11 months (8–14 months).

**Experimental procedure and methods**

All experimental subjects had been supine for at least 10 h before the investigations began. Diuretics and antihypertensive drugs were withdrawn from the hypertensive patients at least 10 days before the experiment started. They received a standard hospital diet of normal sodium content for at least 4 days. The normal subjects had taken unrestricted home diets before they were given the standard hospital diet one day before the experiment. All experiments were performed under constant supervision, so that immediate return to the recumbent position was possible in case of any adverse reaction on tilting.

**Determination of blood volume before and after tilt.** This experiment, if included, was done on the day before the haemodynamic examination. The subjects were placed on a tilt table and 80 μCi of ⁵¹Cr-labelled erythrocytes and 5 μCi of ¹²⁵I-labelled human serum albumin
were injected into the brachial vein. After 20 min equilibration, three blood samples were drawn from the other arm at 10 min intervals. The subjects were then tilted to 45° and three additional blood samples were drawn after 20, 30 and 40 min. The radioactivities of the samples were counted in a well-type sodium iodide scintillation counter. Details of the method will be described elsewhere (Molzahn, Dissmann, Halim & Lohmann, 1972).

**Haemodynamics and renal function.** On the next day a Seldinger cannula was introduced into the brachial artery, a central venous catheter through the antecubital vein of the other arm, and an indwelling balloon catheter into the urinary bladder. All these operations were performed after local anaesthesia, the subjects being supine on the tilt table. A priming dose of sodium p-aminomippurate (PAH, Nephrotest) was then injected intravenously and a plasma concentration of PAH between 1.5 and 2.5 mg/100 ml was maintained by infusion of PAH with a motor-driven infusion pump (Braun-Melsungen). The experiment was started after 45 min of infusion with two supine clearance periods of 15 min. The patients were then tilted to 45° for 30 min (two clearance periods). The plasma concentrations of PAH and creatinine were calculated from two measurements at the beginning and end of each clearance period. Sodium and potassium concentrations were measured in all plasma and urine samples. Systolic, diastolic and mean arterial pressures were measured directly during the second clearance periods in the supine and upright position by using a Statham transducer and an electronic amplifier (Hewlett-Packard) and recorder (Schwartz). After recording blood pressure at the end of the second clearance period, cardiac output was measured by a dye-dilution technique as follows: 5 mg of Cardio Green was rapidly injected into the central venous catheter and arterial blood was automatically drawn via the Seldinger cannula. Indocyanine Green concentrations were continuously measured by Atlas densitometer and an amplifier-recorder unit (Atlas Cardiognost R). The dye-dilution curves were evaluated by the triangle method using correction factors as given by Schröder, Dissman, Kauder & Schüren (1966). All results are means of at least two measurements. The peripheral arterial resistance index is the ratio of mean arterial pressure and cardiac index. Heart rate was recorded by ECG. Venous blood for the determination of plasma renin and catecholamine concentration was withdrawn after cardiac output measurements at the end of the second clearance periods in the supine and upright position.

Sodium and potassium concentrations in plasma and urine were measured by using an Eppendorf flame photometer. Creatinine was measured as described by Popper, Mandel & Mayer (1937) and PAH as described by Czok, Kreienberg & Mertz (1952). The control values of clearances and sodium excretion are the means of two supine clearance periods. They are compared with the second clearance period in the upright position. The tubular rejection fraction of sodium (percentage of filtered sodium which is excreted) was calculated according to the formula:

\[
RF_{Na} = \frac{U_{Na}V \times 100}{C_{\text{creat.}} \times (\text{Na})_{\text{plasma}}}
\]

Plasma renin concentration was measured as described by Brown, Davies, Lever, Robertson & Tree (1964), and catecholamines by a spectrofluorimetric method (Haeggendal, 1963). The mean difference between ten duplicate measurements of plasma renin was 10±6% (SD) of their mean, those of plasma noradrenaline and adrenaline \((n = 17)\) were 8±6% (SD) and 40±36% (SD) respectively. A difference in any pair of renin or noradrenaline measurements
<table>
<thead>
<tr>
<th></th>
<th>Cardiac index (l/min(^{-1}) m(^2))</th>
<th>Heart rate (beats/min)</th>
<th>Stroke volume (ml/m(^2))</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Peripheral resistance</th>
<th>Plasma volume (ml/m(^2))</th>
<th>Mean body haematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS</strong> n = 8</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age: 25 ± 1.6 years</td>
<td>4.1 ± 0.9</td>
<td>66 ± 16</td>
<td>61.3 ± 22.3</td>
<td>21.4 ± 6.6</td>
<td>1705 ± 117</td>
<td>38.5 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>BSA: 1.95 ± 0.05 m(^2)</td>
<td>±0.5 ± 0.4</td>
<td>±5 ± 7</td>
<td>±7.2 ± 8.4</td>
<td>±2.9 ± 3.3</td>
<td>±195 ± 60</td>
<td>±1 ± 1 ± 0.9</td>
<td></td>
</tr>
<tr>
<td><strong>EH I</strong> n = 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 30 ± 4.7 years</td>
<td>4.9 ± 1.1</td>
<td>76 ± 14</td>
<td>65.7 ± 22.2</td>
<td>21.8 ± 7.5</td>
<td>1390 ± 105</td>
<td>41.0 ± 1.3</td>
<td></td>
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<tr>
<td>BSA: 1.94 ± 0.1 m(^2)</td>
<td>±0.7 ± 0.7</td>
<td>±10 ± 8</td>
<td>±9.9 ± 11.9</td>
<td>±9.9 ± 4.5</td>
<td>±223 ± 67</td>
<td>±2 ± 1.9</td>
<td></td>
</tr>
<tr>
<td><strong>RVH</strong> n = 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 47 ± 5.1 years</td>
<td>3.8 ± 0.9</td>
<td>79 ± 11</td>
<td>48.7 ± 16</td>
<td>148 ± 10</td>
<td>39.9 ± 10.2</td>
<td>24.0 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>BSA: 1.86 ± 0.18 m(^2)</td>
<td>±0.6 ± 0.4</td>
<td>±14 ± 5</td>
<td>±4.8 ± 2.8</td>
<td>±17 ± 11</td>
<td>±87 ± 9.5</td>
<td>±21 ± 2.4</td>
<td></td>
</tr>
</tbody>
</table>

**Statistical methods:** changes across orthostasis within one group are regarded as significant (zero hypothesis Δ≈0) if \(P = a < 0.05\). Difference of means in different groups (e.g. NS→EH I) are significant if \(P = 2a < 0.05\). \(P > 0.05\) = not significant (n.s.).
greater than 22% and 20% respectively was regarded as significant (mean difference between duplicates + 2 SD).

RESULTS

The tables show the mean of control values, absolute and percentage changes in the upright position, and their statistical characteristics. Results of haemodynamic and blood volume determinations are shown in Table 1, those of renal function measurements, renin and catecholamines in Table 2. A table containing the individual measurements is deposited with the Librarian of the Royal Society of Medicine and is available on request (deposited as Clinical Science Table 42/1).

Differences of age

The mean ages of the patients in groups EH I, EH II and RVH were 5 years ($P<0.05$), 21 years ($P<0.001$) and 22 years ($P<0.001$) greater than that of the control group. The mean difference of age between EH I and EH II was 16 years ($P<0.001$). No significant correlations were found between any of the measurements or their orthostatic changes on one hand and

| Table 2. Renal function, renin and catecholamines. For explanation see legend to Table 1. |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| C_{Creatinine} (ml min^{-1} 1.73 m^{-2}) | C_{PAH} (ml min^{-1} 1.73 m^{-1}) | Filtration fraction |
| C | A | A% | C | A | A% | C | A | A% |
| NS | M | 133 | -40 | -27 | 686 | -286 | -38 | 0.20 | +0.03 | 0.30 | -0.15 | -45 |
| SD | ±20 | ±42 | ±27 | ±102 | ±214 | ±27 | ±0.01 | ±0.03 | ±0.29 | ±0.16 | ±15 |
| Δ→0.1, $P<$ | 0.01 | 0.01 | 0.005 | 0.005 | 0.005 | 0.01 | 0.001 |
| EH I | M | 146 | -35 | -24 | 726 | -129 | -16 | 0.20 | -0.01 | 0.28 | -0.11 | -33 |
| SD | ±37 | ±39 | ±28 | ±186 | ±194 | ±35 | ±0.04 | ±0.03 | ±0.10 | ±0.13 | ±47 |
| Δ→0.1, $P<$ | 0.005 | 0.05 | 0.05 | n.s. | n.s. | n.s. | 0.01 | 0.005 |
| EH II | M | 112 | -35 | -34 | 619 | -215 | -35 | 0.21 | +0.01 | 0.36 | -0.22 | -57 |
| SD | ±31 | ±18 | +16 | ±256 | ±173 | ±22 | ±0.07 | ±0.02 | ±0.17 | ±0.14 | ±15 |
| Δ→0.1, $P<$ | 0.001 | 0.001 | 0.01 | 0.01 | n.s. | 0.005 | 0.001 |
| RVH | M | 100 | -26 | -26 | 506 | -145 | -29 | 0.21 | +0.01 | 0.29 | -0.16 | -56 |
| SD | ±12 | ±13 | ±14 | ±135 | ±46 | ±6 | ±0.04 | ±0.03 | ±0.08 | ±0.04 | ±10 |
| Δ→0.1, $P<$ | 0.001 | 0.001 | 0.001 | 0.001 | n.s. | 0.001 | 0.001 |
| NS→EH I, $P<$ | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| NS→EH II, $P<$ | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| NS→RVH, $P<$ | 0.005 | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| EH I→EH II, $P<$ | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| EH I→RVH, $P<$ | 0.05 | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| EH II→RVH, $P<$ | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
age on the other hand, when calculated for each group separately, for all groups together or for groups EH I and EH II combined.

**Plasma renin concentration (PRC)**

Recumbent PRC was significantly higher in group EH I (7.4 ± 3.5 units/l) than in normal subjects (4.6 ± 1.0 units/l, P < 0.05). Mean recumbent PRC was still higher in RVH (9.7 ± 7.8 units/l), but the difference from the other groups was not statistically significant because of a relatively wide scatter of individual measurements.

After 30 min of tilting PRC was increased in all normal subjects and in most of the hypertensive patients. PRC did not increase significantly in two normal subjects, in two subjects each of group EH I and EH II and in one patient of group RVH. The mean increase of PRC was 37% in normal subjects, 48% and 15% in groups EH I and EH II respectively and 57% in groups RVH. Since the changes of PRC were not uniform within the separate groups, the mean increases of PRC did not differ significantly in the four groups. In contrast with normal subjects and patients with labile essential and renovascular hypertension, PRC increased in none of the patients of group EH II by more than 35%. It decreased significantly in one patient of this group (Fig. 1).

<table>
<thead>
<tr>
<th>RF&lt;sub&gt;Na&lt;/sub&gt;</th>
<th>UrV&lt;sub&gt;UKV&lt;/sub&gt; (mEq/min)</th>
<th>Plasma renin (units/l)</th>
<th>Plasma noradrenaline (µg/l)</th>
<th>Plasma adrenaline (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Δ</td>
<td>C</td>
<td>Δ</td>
<td>Δ%</td>
</tr>
<tr>
<td>1.60 ± 0.38</td>
<td>0.10 ± 0.03</td>
<td>4.6 ± 1.7</td>
<td>+37</td>
<td>0.254 ± 0.074</td>
</tr>
<tr>
<td>± 1.02 ± 0.44</td>
<td>± 0.03 ± 0.03</td>
<td>± 1.0 ± 1.2</td>
<td>± 24</td>
<td>± 0.139 ± 0.084</td>
</tr>
<tr>
<td>0.05</td>
<td>± 0.005 ± 0.005</td>
<td>0.001 ± 0.008</td>
<td>0.01 ± 0.05</td>
<td>n.s.</td>
</tr>
<tr>
<td>1.40 ± 0.29</td>
<td>0.10 ± 0.04</td>
<td>7.4 ± 2.9</td>
<td>+48</td>
<td>0.075 ± 0.006</td>
</tr>
<tr>
<td>± 0.47 ± 0.53</td>
<td>± 0.03 ± 0.03</td>
<td>± 3.5 ± 2.8</td>
<td>± 44</td>
<td>± 0.042 ± 0.06</td>
</tr>
<tr>
<td>0.05</td>
<td>± 0.001 ± 0.001</td>
<td>± 0.005 ± 0.005</td>
<td></td>
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<tr>
<td>2.93 ± 1.12</td>
<td>0.08 ± 0.02</td>
<td>5.0 ± 0.9</td>
<td>+15</td>
<td>0.05 ± 0.05</td>
</tr>
<tr>
<td>± 2.77 ± 1.3</td>
<td>± 0.02 ± 0.02</td>
<td>± 3.1 ± 1.3</td>
<td>± 25</td>
<td>n.s.</td>
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<tr>
<td>0.05</td>
<td>± 0.05 ± n.s.</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>1.93 ± 0.66</td>
<td>0.11 ± 0.04</td>
<td>9.7 ± 5.2</td>
<td>+57</td>
<td>0.001 ± 0.001</td>
</tr>
<tr>
<td>± 0.38 ± 0.25</td>
<td>± 0.08 ± 0.03</td>
<td>± 7.8 ± 4.4</td>
<td>± 39</td>
<td>± 0.001 ± 0.005</td>
</tr>
<tr>
<td>0.001</td>
<td>± 0.01 ± n.s.</td>
<td>n.s.</td>
<td></td>
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</table>

n.s. n.s. n.s. n.s. n.s. 0.05 n.s. n.s. n.s. n.s. n.s. 0.05 0.05
**Haemodynamics**

In all groups cardiac index decreased significantly on 45° tilting due to a fall of stroke volume which was only in part compensated for by an increase of heart rate. Heart rate increased by 11–16 beats/min (+15 to +24%) in normal subjects, and groups EH I and RVH, but significantly less in group EH II (+4 beats/min, +5%). Supine cardiac index was significantly higher in group EH I than in normal subjects, but significantly lower in EH II. Mean arterial pressure (MAP) increased in normal subjects and in group EH I by 3 mmHg (+4%) and 6 mmHg (+6%) respectively. It fell in groups EH II and RVH significantly by 12 mmHg (−8%) and 10 mmHg (−7%) respectively. Calculated peripheral resistance increased in all groups, but in group EH II significantly less than in other groups.

**Plasma volume and mean body haematocrit**

Plasma volume changes across tilting were measured only in normal subjects and in six patients of group EH I. Supine plasma volume per square metre of body surface area was significantly lower in group EH I than in normal subjects (P<0.001), but the decrease on tilting did not differ significantly in the two groups (8% in group EH I, 7% in normal subjects). Mean body haematocrit increased by 1% in normal subjects and by 1.3% in group EH I.

**Renal function**

Clearances of creatinine (C\textsubscript{crea}) and PAH (C\textsubscript{PAH}) decreased significantly in all groups during upright tilting. In normal subjects mean filtration fraction (FF) increased significantly since C\textsubscript{PAH} decreased more than C\textsubscript{crea}. In the other groups filtration fraction did not change significantly since the decrease of C\textsubscript{PAH} was not consistently larger than the decrease of C\textsubscript{crea} in individual patients. The excretion of sodium and potassium decreased consistently in all groups during tilting. Since sodium excretion fell more than C\textsubscript{crea}, the calculated sodium rejection fraction (RF\textsubscript{Na}) decreased in all groups during tilting. Mean sodium rejection was higher in group EH II than in the other groups. This was due to two patients with high RF\textsubscript{Na} values (2.9% and 8.9%). In both patients sodium rejection fraction fell
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considerably after tilting but these were the only subjects of all groups in whom heart rate decreased slightly in the upright position.

**Plasma catecholamines**

Plasma catecholamines were measured only in normal subjects. A small increase of plasma adrenaline concentration after tilt was not statistically significant. Plasma noradrenaline (PNC), however, increased significantly by about 30%.

**Correlations between measurements**

The relationship between ΔPRC and changes of cardiac index, mean blood pressure, peripheral resistance, plasma volume and mean body haematocrit, were not significant except in group RVH, where the negative correlation between ΔMAP and ΔPRC was significant ($r = -0.84; P<0.05$).

A positive correlation of borderline significance was found between ΔPRC and ΔPNC in normal subjects ($r = 0.69, 0.1 > P > 0.05$) (Fig. 2). There was a positive correlation between

\[ r = 0.69 \]

\[ 0.1 > P > 0.05 \]

\[ C_{PAH} \] and PRC in the recumbent position in group EH I ($r = 0.68; P<0.05$), and the relationship between Δ%$C_{PAH}$ and Δ%PRC was also significantly positive ($r = 0.74, P<0.05$) in group EH I. In the other groups the inconsistent relations between the increase in PRC and changes of both clearances were not significant. There was, however, a significantly negative correlation between the percentage increase in PRC and the orthostatic change of filtration fraction in normal subjects ($r = -0.85, P<0.05$) and in group EH I ($r = -0.89, P<0.01$). In groups EH II and RVH, the negative correlation was not significant.

Changes in sodium excretion and percentage changes of PRC were positively related in normal subjects ($r = 0.76, P<0.05$) and in group EH I ($r = 0.75, P<0.05$). The positive

![Fig. 2. Correlation between the orthostatic percentage increase of plasma renin concentration (ΔPRC) and of plasma noradrenaline concentration (ΔPNC) in eight normal subjects. 0.1 > P > 0.05.](image-url)
correlation between $\Delta$PRC and $\Delta$RF$_{Na}$ was also highly significant in EH I ($r = 0.92, P<0.01$), but not in normal subjects ($r = 0.34, P>0.1$).

The relationship between $\Delta$FF and $\Delta$U$_{Na}V$ was significantly negative in normal subjects ($r = -0.75, P<0.05$), and the correlation between $\Delta$FF and $\Delta$RF$_{Na}$ was significantly negative in group EH I ($r = -0.91, P<0.01$). Relationships between $\Delta$PRC and changes in other measurements not mentioned were not significant.

**DISCUSSION**

Since the number of subjects in all four groups of this study was relatively small and since the methods employed are subject to error, statistically insignificant relationships between two variables do not prove their independence. Significant relations, however, should indicate a high degree of interdependence. In group EH I, changes of PRC were very small. Since measured changes of plasma renin less than 22% were not regarded as significant, it is not surprising that none of the relationships between $\Delta$PRC and orthostatic changes of other variables was statistically significant in this group.

**Haemodynamics**

The normal response to 45° upright tilting for 30 min is a decrease of cardiac index and an increase in heart rate and peripheral resistance. The latter changes are mediated by baro-receptor mechanisms and by an increase in sympathetic nervous activity. Their effect is to prevent arterial pressure falling (see also Tuckman & Shillingford, 1966; Frohlich et al., 1967).

Important haemodynamic features of groups EH I and EH II which were classified merely by clinical differences, are the significantly increased mean cardiac index in group EH I and the significantly decreased cardiac index in group EH II, there being no overlap between the two groups. In the patients with renovascular hypertension whose mean age was comparable with that of group EH II, cardiac index was not significantly different from normal (for discussion of different haemodynamic states in arterial hypertension see Dissmann, Gotzen, Lohmann & Molzahn, 1970). Mean arterial pressure increased slightly in normal subjects and in group EH I, but it decreased significantly by 8% and 7% in groups EH II and RVH respectively. The fall of mean arterial pressure was caused by a significantly diminished rise in heart rate and peripheral resistance in group EH II, whereas in RVH the combined effects of a slightly increased fall of cardiac index and a smaller increase of heart rate and peripheral resistance accounts for this abnormal behaviour.

**Relationship between renin, haemodynamics and sympathetic output**

Recumbent PRC and cardiac index were significantly higher in patients with labile essential hypertension than in normal subjects. This finding is in agreement with positive correlations between recumbent plasma renin and cardiac output (Dustan, Tarazi & Frohlich, 1970). Schalekamp, Schalekamp-Kuyken & Birkenhäuser (1970) also reported a positive correlation between recumbent PRC and variability of blood pressure in essential hypertension.

It is noteworthy that PRC exhibited the least mean increase in group EH II in which the neuroadrenergic response appeared to be impaired as suggested by the postural hypotension and by the relatively small change of heart rate and total peripheral resistance on tilting. These findings are in keeping with the observations of Frohlich et al. (1967), that orthostatic
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Hypotension with diminished increase of orthostatic peripheral resistance occurs more often in patients with advanced hypertension. Moreover, Kaneko, Ikeda, Takeda, Inoue, Tagawa & Ueda (1968) observed a diminished response of renin release to lowering of blood pressure by sodium nitroprusside in patients with more longstanding hypertension. These observations together suggest an influence of duration of hypertension on orthostatic sympathetic response and renin release. An influence of age per se, though less likely, cannot be excluded.

In our patients with essential hypertension, however, there was no significant correlation between the percentage change of PRC and Δ heart rate, Δ mean arterial pressure or the change of other haemodynamic measurements. In patients with RVH there was a borderline significant negative correlation between ΔPRC and ΔMAP. In these patients the mean increase of PRC was larger than in other groups, though the haemodynamic changes were similar to those in group EH II in which PRC did not increase significantly. This difference may be due to the peculiar circulatory changes in the kidney supplied by the diseased artery. It has been shown by many groups that renin activity or concentration is often raised in the vein of the diseased kidney in RVH and that in most cases the calculated renin output by this kidney is also increased (Woods & Michelakis, 1968; Oelkers, Dissmann, Lohmann & Bachmann, 1970b). The slight orthostatic decrease in blood pressure may be more effective in the kidney supplied by a stenosed artery and may stimulate renin release more or less independent of mechanisms that provoke orthostatic renin release in normal man. When the diseased kidney is removed, the enhanced orthostatic increase of plasma renin (Conn, Rovner & Cohen, 1965; Weidmann, Siegenthaler, Moehring, Wirz, Scheitlin & Roesler, 1967) is abolished (Oelkers et al., 1970b).

A finding that favours the role of the adrenergic system in the orthostatic stimulation of renin release is the positive relationship between changes of plasma noradrenaline and renin concentration in normal subjects. Though the significance of the correlation is not yet proved, circulating catecholamines could be involved in the control of orthostatic renin release. Wathen, Kingsbury, Stouder, Schneider & Rostorfer (1965), Vander (1965) and Ueda, Yasuda, Takabatake, Iiuzuka, Ihori & Sakamoto (1970) observed the stimulation of renin release by infusions of noradrenaline in dogs and Gordon et al. (1967) confirmed this finding in man. Winer et al. (1969) found blunting of the orthostatic increase of renin activity in man by intravenous infusion of α- or β-receptor blocking agents, and Greene, Vander & Kowalczyk (1968) showed that plasma renin activity increases in the upright position in man with a transplanted kidney. The observations of Winer et al. (1969) do not distinguish the effect of circulating catecholamines from those of renal nerves, but both observations together are in favour of the ability of physiological increases of catecholamines to stimulate renin release, since the transplanted kidney is probably denervated for some time. A converse causal relationship, the stimulation of catecholamine release by angiotensin (Feldberg & Lewis, 1965), is less probable since propranolol and phentolamine blunt the orthostatic increase of plasma renin activity (Winer et al., 1969). However, the positive correlation between ΔPRC and ΔPNC could also be explained by a general increase of sympathetic discharge without one of these factors being the direct cause of the other.

Relationships between kidney function and plasma renin

To explain the relationships between orthostatic changes of PRC and those of renal function in normal subjects and in patients with labile essential hypertension is also difficult. The
most significant (negative) correlation is that between ΔPRC and ΔAFF in both groups. Changes of filtration fraction indicate an altered relation between C\text{crea}, and C\text{PAH} and it is commonly believed that this ratio reflects the pressure by which plasma is filtered in the glomeruli. In an independent study of a design similar to ours Schalekamp et al. (1970) found a significant negative correlation between resting plasma renin concentration and filtration fraction in hypertensive subjects on a low sodium diet. They considered the possibility that in cases with a high filtration fraction, when the glomerular capillary pressure is comparatively high, the pressure in the afferent arterioles is also increased, and they interpreted the results on the basis of a pressure feedback control mechanism of renin release.

The significant negative correlation between AFF and ΔRF_{Na} in group EH I and the positive correlations between ΔPRC and ΔRF_{Na} or ΔU_{Na},V in normal subjects and group EH I indicate that there exists a more complicated interrelationship between orthostatic changes of intrarenal haemodynamics, tubular sodium handling and renin release. The observation of a positive correlation between changes in sodium output or sodium rejection and renin response is remarkable since under many experimental conditions in dog (Vander, 1967) and in man taking different diets (de Champlain, Genest, Veyrat & Boucher, 1966) plasma renin and sodium output are inversely related. Vander's (1967) macula densa hypothesis of renin release is based on this negative correlation.

It is difficult to assess the role of sympatho-adrenergic impulses as mediators of the orthostatic changes in kidney function observed. Sodium excretion, for instance, will fall as a consequence of direct intrarenal vasoconstriction, but the prevention of orthostatic hypotension by an adequate increase of heart rate and peripheral resistance will oppose the fall of sodium output.

It is evident that more work has still to be done to elucidate the relative importance of circulating catecholamines, sympathetic nervous activity and of renal haemodynamic changes that are independent of the adrenergic system for orthostatic changes of renin secretion.

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