Hepatic elimination of renin in man

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Summary

1. Hepatic elimination of renin was measured in 10 well-compensated cardiac patients with normal liver function during a control period and during a period of reduced hepatic plasma flow, induced by physical exercise (seven patients) or intravenous infusion of lysine vasopressin (three patients).

2. Hepatic renin elimination rate (hepatic plasma flow × arterial–hepatic vein difference of plasma renin activity) was found to be linearly correlated with arterial plasma renin activity ($r = 0.986, P < 0.001$).

3. When hepatic plasma flow fell by 45% the hepatic extraction ratio of renin (arterial–hepatic vein plasma renin activity difference/arterial plasma renin activity) increased by 75%. Hepatic renin clearance (hepatic plasma flow × extraction ratio) remained constant.

4. The results indicate that changes in the hepatic elimination rate of renin do not contribute to changes in plasma renin activity during these events.

Key words: antidiuretic hormone, exercise, hepatic clearance, liver plasma flow, lysine vasopressin, renin.

Abbreviations: HPF, hepatic plasma flow; PRA, plasma renin activity; $PRA_a$, arterial PRA (pmol h$^{-1}$ ml$^{-1}$); $PRA_{hv}$, hepatic vein PRA (pmol h$^{-1}$ ml$^{-1}$); $PRA_{a-hv}$, arterial–hepatic vein PRA difference (pmol h$^{-1}$ ml$^{-1}$); $PRA_{a-hv/a}$, renin extraction ratio of the liver; $PRA_{a-hv} \times$ HPF, hepatic renin elimination rate (pmol h$^{-1}$ min$^{-1}$); $C_{PRA}$, hepatic renin clearance, calculated as $PRA_{a-hv/a} \times$ HPF (from indocyanine green values) (ml/min).

Patients

Ten patients (four women and six men, aged 26–67 years), who were referred for haemodynamic investigation, were studied. Five had mitral valvular disease, two aortic valvular disease, one pulmonary valvular disease and benign essential hypertension, one cardiomyopathy, and one an
innocent cardiac murmur. Seven were on maintenance treatment with diuretics and potassium supplementation: four patients (nos. 1, 7, 8 and 10) received bumetanide (2 mg daily); patient no. 2 received frusemide (240 mg) and triamterene (100 mg) daily; two patients (nos. 3 and 5) received bendroflumethiazide (10 mg) daily. Six patients (nos. 1, 2, 5, 6, 8 and 10) were on digitalis. Two patients (nos. 4 and 9) had no medication. None of the patients had clinical signs of overt heart failure or liver disease, all had normal plasma albumin concentration and the pressure gradient from the wedged to free position in the hepatic veins was 3 mmHg or less. All were on liberal salt and water intake.

Informed consent was obtained in each case. The project was approved by the heads of the two Divisions of the hospital and the medical director of the Department of Medicine regarding the scientific approach and the ethical problems.

Methods

A Cournand catheter (no. 7) was advanced from an antecubital vein into the major right hepatic vein. The catheter was wedged and then drawn back just enough for easy withdrawal of blood samples. A 20 cm polyethylene catheter was introduced into the brachial artery by the Seldinger technique. Pressures were measured with capacitance transducers (Hansen, 1949). Expired air was collected into Douglas bags for 5 min at rest and for 3 min during exercise, oxygen concentration being measured by Haldane analysis and expired volume by a gasometer. Blood oxygen saturation was determined by an oximeter (Siemens–Elema, Sweden) and haemoglobin concentration with a photoelectric haemoglobinometer (Haemotest, Testa Laboratories, Denmark). Indocyanine green (1 mg/ml) in sodium chloride solution (154 mmol/l: saline) was administered by an infusion pump (1 ml/min) through a small indwelling needle placed in an antecubital vein of the opposite arm. After an equilibration for 15 min blood samples for determination of indocyanine green were drawn simultaneously from the hepatic vein and brachial artery. The plasma was separated immediately by centrifugation for 20 min and analysed in a Zeiss spectrophotometer at 800 and 900 nm for turbidity correction (Nielsen, 1963). PRA was measured by a radioimmunoassay (Haber, Koerner, Page, Kliman & Purnode, 1969) with the angiotensin I \( I^{125} \) kit of NEN New England Nuclear, and with incubation at pH 6-0. Each plasma sample from one patient was measured in duplicate, the coefficient of variation of samples run within the same analysis being 3-3%. The normal range of PRA by this method is 0-52–2-2 pmol of angiotensin I h\(^{-1}\) ml\(^{-1}\).

Synthetic lysine vasopressin (Vasopressin, Sandoz), dissolved in saline, was infused intravenously at a rate of 0-25 unit/min after a priming dose of 1 unit during the first minute. The activity of this vasopressin is controlled by a bioassay (U.S.P. XVII), the reference substance being the third international standard of oxytocic, vasopressor and antidiuretic substances.
Calculations and statistics

Hepatic plasma flow (the term conventionally used instead of the more correct term 'splanchnic plasma flow') was calculated for each sampling period as:

\[
\text{HPF} = \frac{\text{infusion rate of indocyanine green} - (\Delta A \times V)}{A - hV}
\]

where \(\Delta A\) is the change in the arterial concentration of dye, \(V\) the volume of distribution of dye, which is assumed to be plasma volume (in litres = 0.05 \times body weight in kg), \(A\) and \(hV\) the mean concentrations of indocyanine green in arterial and hepatic vein plasma. The individual HPF values of the control, exercise, and lysine vasopressin infusion periods (Tables 1 and 2) are mean values of six (control), three or four (exercise) and two or three (LVP) sampling intervals. The calculation of HPF depends upon stable plasma concentrations of the test substance (Bradley, Ingelfinger, Bradley & Curry, 1945), so that the validity of the method may be questioned when rapid fluctuations of plasma concentration occur. Such fluctuations must occur during brief periods of HPF reduction, the arterial concentration of indocyanine green rising when HPF falls and decreasing as flow returns to the control rate. In case of rapid changes of dye concentration, the volume of distribution may be overestimated, since the dye is not evenly distributed during such brief periods. The rather rough estimate of plasma volume represents another source of error, the correct factor probably being between 0.03 and 0.06 \times body weight. However, since the arterial dye concentration largely stabilized within the exercise and lysine vasopressin infusion periods both errors are probably of limited importance. HPF values during exercise and during LVP infusion were also calculated from the relative changes in arterial–hepatic vein oxygen difference multiplied by values of HPF during the control study, on the assumption that the oxygen uptake of the liver remains constant (Jacobsen et al., 1969; Rowell, Blackmon & Bruce, 1964).

The results have been evaluated statistically with linear regression analysis and by the Wilcoxon test for paired comparison (Keeping, 1962).

Results

Arterial pressures, heart rate and oxygen uptake increased during exercise (\(P < 0.02\), Table 1), whereas HPF fell, on average to 61% (range 33–98%) of the control value in patients nos. 1–6, calculated by indocyanine green, and by 57% (range 38–66%), calculated by the changes in oxygen extraction of the liver. In patient no. 7 the HPF values calculated by dye became negative during exercise.

In all patients the arterial–hepatic vein PRA difference (\(\text{PRA}_{a-hv}\)) was positive. Arterial PRA (\(\text{PRA}_a\)), hepatic vein PRA (\(\text{PRA}_{hv}\)), \(\text{PRA}_{a-hv}\) and the hepatic renin extraction ratio (\(\text{PRA}_{a-hv/}\)) all increased during exercise (\(P < 0.02\), Table 1).

Systolic arterial pressure increased during in-

<table>
<thead>
<tr>
<th>Table 1. Experiments involving exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>1 Control</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>2 Control</td>
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<tr>
<td>Exercise</td>
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<tr>
<td>3 Control</td>
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<tr>
<td>Exercise</td>
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<td>4 Control</td>
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<td>6 Control</td>
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<tr>
<td>Exercise</td>
</tr>
<tr>
<td>7 Control</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
</tbody>
</table>

* Hepatic plasma flow, calculated from indocyanine green (ICG) values.
† Hepatic plasma flow, calculated by control indocyanine green value and \(O_2\) changes during exercise.
TABLE 2. Experiments with infusion of lysine vasopressin (LVP)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Arterial pressure (mmHg)</th>
<th>Heart rate (min⁻¹)</th>
<th>HPF (ml/min)</th>
<th>ICG*</th>
<th>O₂†</th>
<th>PRA (pmol h⁻¹ ml⁻¹)</th>
<th>PRAa-hv</th>
<th>PRAa-hv/a</th>
<th>C_PRA (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Control</td>
<td>148/57</td>
<td>60</td>
<td>450</td>
<td>—</td>
<td>—</td>
<td>6.9</td>
<td>6.3</td>
<td>0.65</td>
<td>0.09</td>
</tr>
<tr>
<td>LVP</td>
<td>178/55</td>
<td>60</td>
<td>141</td>
<td>240</td>
<td>—</td>
<td>8.3</td>
<td>5.9</td>
<td>2.4</td>
<td>0.30</td>
</tr>
<tr>
<td>9 Control</td>
<td>119/62</td>
<td>72</td>
<td>911</td>
<td>—</td>
<td>—</td>
<td>0.59</td>
<td>0.47</td>
<td>0.12</td>
<td>0.21</td>
</tr>
<tr>
<td>LVP</td>
<td>140/67</td>
<td>72</td>
<td>599</td>
<td>696</td>
<td>—</td>
<td>0.65</td>
<td>0.37</td>
<td>0.28</td>
<td>0.43</td>
</tr>
<tr>
<td>10 Control</td>
<td>115/50</td>
<td>84</td>
<td>560</td>
<td>—</td>
<td>—</td>
<td>1.92</td>
<td>1.71</td>
<td>0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>LVP</td>
<td>145/57</td>
<td>84</td>
<td>326</td>
<td>324</td>
<td>—</td>
<td>1.78</td>
<td>1.52</td>
<td>0.26</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Hepatic plasma flow, calculated from indocyanine green (ICG) values.
† Hepatic plasma flow, calculated by control indocyanine green value and O₂ changes.

Fusion of lysine vasopressin and heart rate was unchanged (Table 2). HPF during the infusion, as calculated with indocyanine green, fell to 31, 65 and 58% respectively of the control value, and to 53, 77 and 58% respectively of the control value as calculated by the changes in the oxygen extraction. PRAa-hv was positive in all three patients. PRAa was unchanged during lysine vasopressin infusion. PRAhv decreased, PRAa-hv and PRAa-hv/a increased in all three patients (Table 2).

HPF during exercise or infusion of lysine vasopressin, as calculated by indocyanine green, was correlated with that measured by the relative changes in oxygen extraction of the liver (Fig. 1, \(r = 0.88, P < 0.01\) if the negative value of patient no. 7 is omitted; if it is included, \(r = 0.83, P < 0.01\)).

The hepatic elimination rate of renin was closely correlated with PRAa, both in the control period and during exercise and infusion of lysine vasopressin [Fig. 2, which is a double logarithmic plot to show the very wide range of values: the correlation is linear \((r = 0.986, P < 0.001)\)]. Both scales are logarithmic, adopted to show the linear correlation within the wide range of PRA values. \(n = 19\); \(r = 0.986; P < 0.001\).

Fig. 3. Mean values of hepatic plasma flow (HPF), hepatic renin extraction ratio \((PRAa-hv/a)\) and hepatic renin clearance \((C_PRA)\); bars indicate 1 SEM. Open columns: control periods; stippled columns: exercise and lysine vasopressin periods. \(n = 9\).
Fig. 3 shows that mean $C_{PRA}$ was unchanged when HPF fell to 45%, owing to a concurrent increase in the extraction ratio of PRA from 0.16 to 0.28.

Discussion

We have found a mean hepatic renin extraction ratio of 0.16 (range 0.05-0.35) in the control state, slightly lower than that previously reported in man (Christlieb et al., 1968: 0.26; Kokot et al., 1968: 0.29). But it should be pointed out that there were very wide limits in the individual extraction ratios reported in those two studies, ranging from -0.26 to 0.59 and 0.0 to 0.59 respectively. Thus all the extraction ratio values of the present study are well within these limits. The mean values reported in dogs (Heacox et al., 1967: 0.28; Johnson et al., 1971: 0.25; Tapia, Kuster, Woods & Strong, 1973: 0.38) and rats (Horky, Rojo-Ortega, Rodriguez & Genest, 1970: 0.28) are also somewhat higher than that of the present study.

However, as the extraction ratio in an individual (dog or man) varies according to his hepatic blood flow at the time of measurement (Johnson et al., 1971, and this study) the ratio is highly dependent on the experimental design. Since HPF is reduced by anaesthesia (Deutsch, 1967), exercise and cardiac disease (Wade & Bishop, 1962) the lowest extraction ratios are to be expected in normal, resting, conscious individuals. In the present patients the rather low extraction ratio of renin can therefore not be attributed to the cardiac diseases.

The hepatic clearance of substances excreted by the liver with an extraction ratio of less than 0.30 (like renin) is expected to be independent of changes in HPF (Wilkinson & Shand, 1975). This was confirmed by our finding of a constant hepatic $C_{PRA}$, despite a marked decrease of HPF. The constant $C_{PRA}$ means that the renin elimination rate was independent of variations in HPF. Changes in HPF do not therefore contribute to the acute alterations in PRA during procedures which influence both renin release and HPF.

Our findings that $C_{PRA}$ was constant during reduction of HPF, and of a linear correlation between the hepatic elimination rate of renin and $PRA_r$ (Fig. 2) differ from the observations of Schneider, Davis, Baumber & Johnson (1970) and the study of Johnson et al. (1971), who found that reduction of HPF after constriction of the hepatic artery and portal vein in anaesthetized dogs did not alter the hepatic extraction ratio of renin (Schneider et al., 1970). Furthermore, a reduction in HPF by haemorrhage of 30 ml/kg had no significant influence on the hepatic extraction ratio (Johnson et al., 1971), leading to the conclusion that changes in $C_{PRA}$ may contribute to changes in peripheral PRA during procedures influencing HPF.

This discrepancy may be due to: differences between man and dog, and different experimental designs (haemorrhage vs exercise and infusion of lysine vasopressin), and also from a lack of steady state in renin release after a haemorrhage, where up to tenfold increases in peripheral PRA were observed (Johnson et al., 1971).

The reliability of the HPF values during brief periods of flow reduction may be questioned in the light of the increasing arterial concentration of indocyanine green. This increase may induce some error in the HPF calculation, which can be seen in the negative values of HPF calculated for patient no. 7 during exercise. In this patient the arterial dye concentration rose very rapidly (cf. the Methods section, 'Calculations and statistics'). However, the fairly strong correlation between HPF calculated by indocyanine green and by the changes in oxygen extraction supports the reliability of the HPF values.

We conclude that the hepatic elimination rate of renin is a linear function of the peripheral PRA, and that $C_{PRA}$ is independent of HPF under physiological circumstances in man. An increase in renin release causes an increase in peripheral PRA, which, in turn, is followed by a rise in the hepatic elimination rate of renin, and a new steady state develops. Acute changes in PRA cannot be attributed to changes in the elimination rate of renin in man.

Acknowledgments

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References


