SUMMARY The generally held views that plasma renin activity (PRA) is increased in cirrhosis and that this is secondary to reductions in the "effective" blood or extracellular fluid (ECF) volumes, consequent on the effects of portal hypertension, were re-examined in the present study. Measurements of PRA in 67 patients representing different clinical stages of cirrhosis showed that the mean value in 15 patients without ascites was significantly reduced. In 21 of 35 with ascites, PRA was either reduced or within the normal range. A low plasma renin substrate concentration was not the cause for the low PRA. These findings are not in keeping with the concepts of reduced "effective" blood or ECF volumes at least for the majority of patients at these stages of cirrhosis under the conditions of the present study. The only group showing a significantly increased PRA had evidence of renal impairment. In these 17 patients the underlying reduction in renal perfusion may have been the stimulus to the kidney that led to an increase in renin secretion.

KEY WORDS • plasma renin activity • cirrhosis • extracellular fluid volume • renin • renal impairment • blood volume • portal hypertension • ascites • renin substrate

A NUMBER of studies have reported plasma renin activity (PRA) to be increased in cirrhosis. This has usually been attributed to an increased renal release secondary to a deficit in either the "effective" blood volume (from splanchnic pooling consequent on portal hypertension) or "effective" extracellular fluid (ECF) volume (because of loss of the ECF into the peritoneal compartment as ascites), even though total blood, plasma and ECF volumes are usually increased. However, most of the above studies have been confined to patients with relatively advanced liver disease with ascites and/or renal failure and it has not always been clear whether they were being treated with diuretics, which are known to be a potent stimulus to renin secretion. Furthermore, little attention has been given to the values in patients with well-compensated disease.

Another important factor in the analysis of the renin-angiotensin system is the plasma concentration of the renin substrate, since PRA is a function of both this and its enzyme renin. In advanced liver disease, hepatic synthesis of substrate may be impaired the effect of which may limit the full activity of the renin secreted by the kidney.

In the present study we have determined PRA in 67 patients with cirrhosis at different stages of hepatic decompensation. The plasma concentration of renin substrate has also been determined.

Patients and Methods

The 67 patients in our series had histologically proven cirrhosis attributable to alcohol (44 cases), chronic active hepatitis (eight cases, five being HbAg positive), primary biliary cirrhosis (six cases). Nine cases were cryptogenic. Ages ranged from 33 to 68 years and 52 patients were men. They were divided into the following three groups:

Group A (Well-compensated). None of these 15 patients had ever had ascites, peripheral edema or hepatic encephalopathy. Radiological evidence of esophageal varices was present in 11. On the day of the investigation the glomerular filtration rate, as determined by inulin clearance, ranged from 80 to 254 ml/min. (Abnormally high values for glomerular filtration rate are well described in cirrhosis.)
Group B (Increasing ascites). These 35 patients were all in positive sodium balance with increasing body weight and ascites. None had encephalopathy. Esophageal varices were present in 34 of the 35 cases. The inulin clearance ranged from 40 to 249 ml/min.

Group C (Severe hepatic decompensation with renal failure). This group of 17 patients had evidence of more severe hepatic decompensation. In addition to the presence of esophageal varices and ascites all had renal failure, and all but two had encephalopathy, seven being deeply comatose. The values for inulin clearance (or in some cases creatinine clearance) varied between < 1 and 24 ml/min. Based on the biochemical findings in the urine, 13 of the 17 patients had “functional renal failure” (sodium concentration < 12 mmoles/liter, urine:plasma osmolality ratio > 1:10), whereas in the others the features were indicative of “acute tubular necrosis” (sodium concentration > 20 mmoles/liter urine:plasma osmolality ratio < 1:10).

The distribution of age, sex and cause of cirrhosis was similar in the three groups. None of the 67 patients had had a recent gastrointestinal hemorrhage. Diuretics, which had previously been administered to some of the patients in Groups B and C, were discontinued at least 2 weeks before the investigation. No patient was receiving corticosteroids or any other drug known to interfere with renal function or the renin-angiotensin system. All of the patients in Groups A and B received a controlled sodium intake of 40–50 mmoles/day for 5 days. In 11 of the Group C patients it was not possible to control the sodium intake for more than 2 days before study. The other six patients received the same intake as those of Groups A and B.

Plasma Renin Activity and Renin Substrate

The blood sample was taken on the morning of the final day of controlled dietary sodium intake after the patient had been supine for at least 1 hour. Both PRA and renin substrate were determined by radio-immunoassay for angiotensin I generation, with excess renin added for the substrate measurements as previously described. Normal values established for healthy control subjects under identical conditions of sodium intake and posture were 0.92 to 2.96 mmoles/liter/hr (mean 1.82 ± SD 0.57, n = 20), and 0.57 to 0.94 mmoles/liter (mean 0.78 ± SD 0.10, n = 13), respectively.

Statistical Methods

Renin substrate values were compared using Student's t test. The distributions of points for PRA were non-parametric for Groups B and C and therefore Wilcoxon's rank sum test for unpaired data was used for group comparisons.

Results

With one exception, PRA was either in the normal range or reduced in the group of patients without ascites (fig. 1). The mean value was approximately one half of that for the control subjects (0.91 mmoles/liter/hr, 1.82 mmoles/liter/hr, respectively, p < 0.01). The low values were not due to substrate depletion since measurements for this were almost identical to the control values (means of 0.83 mmoles/liter ± SD 0.20, and 0.78 mmoles/liter ± SD 0.10, respectively, p not significant; fig. 2).

In the Group B patients with increasing ascites, the mean value for PRA was approximately twice that for the controls, but the difference did not achieve statistical significance (3.99 mmoles/liter/hr and 1.82 mmoles/liter/hr, respectively). In five of the 35 patients it was reduced, in 16 it was within the normal range, and increased up to 17.92 mmoles/liter/hr in the others. Renin substrate was determined in 17 patients of this group, and although the mean value was significantly lower than for the control subjects (0.64 mmoles/liter ± SD 0.27 and 0.78 mmoles/liter ± 0.10, respectively, p < 0.05), substrate depletion could not account for the low values of PRA found in four patients with a reduced PRA in whom substrate was determined; a low value for the latter was found in only one case. Of the patients with a normal PRA, substrate was normal or increased in four of eight cases, but was reduced in four of five cases with an increased PRA.

In the Group C patients with the most severe hepatic decompensation and renal failure, PRA was significantly increased compared with control subjects (means of 9.50 mmoles/liter/hr and 1.82 mmoles/liter/hr, respectively, p < 0.01), the highest value being 21.77 mmoles/liter/hr. Two of the 17 patients had a normal PRA and there was no difference in the values between those with functional renal failure and the smaller group with acute tubular necrosis (means of 9.80 mmoles/liter/hr and 9.50 mmoles/liter/hr, respectively). Renin substrate concentration was significantly lower than for controls (means of 0.48 mmoles/liter ± SD 0.15 and 0.78 mmoles/liter ± SD 0.10, respectively, p < 0.001), but was not determined in the two patients with a normal PRA.

Discussion

The high values for PRA and the reduced renin substrate concentration in the patients with the most severe hepatocellular impairment (Group C) are in agreement with the results reported in other studies. Although normal values for PRA and plasma renin concentration have been reported in some patients with ascites, the abnormally low values, as found in our patients without ascites (Group A) and in some of those accumulating ascites (Group B), have not been reported. Hepatic synthesis of renin substrate is often presumed to be reduced in cirrhosis and might
Figure 1. Plasma renin activity in the three patient groups (shaded area indicates normal range).

Figure 2. Renin substrate values in the three patient groups (shaded area indicates normal range).
therefore be expected to result in abnormally low values for PRA. However, in the present study of 11 patients with a low PRA, in whom substrate was determined (seven from Group A, four from Group B), an abnormally low value for the latter was found in only one instance. Clearly, factors other than a reduced substrate must have been responsible for the low PRA. Also, because of reduced substrate, PRA might have been inappropriately low in those patients with a normal PRA, but of 11 such patients with substrate determinations (three in Group A, eight in Group B) low values for the latter were found in only five. In fact, in the complete series there was a statistically significant inverse relationship between PRA and substrate ($r = -0.51$, $p < 0.01$), suggesting that consumption of substrate, secondary to an increased plasma renin concentration, is an important factor determining substrate levels in cirrhosis, in addition to any presumed reduction in hepatic synthesis.

Major determinants of PRA are known to be the “effective” blood and ECF volumes, the components of these volumes available to volume receptors. Because of splanchnic pooling of blood consequent to portal hypertension, and loss of the ECF into the peritoneal compartment as ascites, the “effective” blood and ECF volumes are often thought to be reduced in cirrhosis. The present finding of a reduced PRA for Group A patients does not support this concept, at least under the conditions of the present study, since most of these patients had esophageal varices and, by inference, portal hypertension. Similarly, the finding that PRA was normal or reduced in more than half of the patients comprising Group B would also argue against deficits in either the “effective” blood or ECF volumes. These findings suggest that the measured increases in total blood, plasma and ECF volumes reported by others are, at least in those patients with a reduced PRA, “effective” and not merely a reflection of sequestered pools in the splanchnic circulation and peritoneal compartment. In support of this interpretation the non-splanchnic component of the total blood volume has been found to be increased in dogs with dimethylnitrosamine-induced cirrhosis, whether or not ascites is present.

A number of other factors are also known to result in a reduced PRA including hyperkalemia, hypokalemia, an increased renal perfusion pressure and a decreased renal sympathetic nervous activity. The first two of these factors could be excluded in the present cases and no patient had hypertension to account for an increased renal perfusion pressure. There is evidence for a reduced activity of the sympathetic nervous system in cirrhosis, but we have found no differences for the renal excretion of the metabolite of catecholamines, vanillylmandelic acid (VMA), among patients with low, normal or high PRA (unpublished data), although we have no evidence that VMA excretion specifically relates to renal sympathetic activity. Increasing age is also associated with a reduced PRA, but in the present series no relationship between age and PRA was found ($r = -0.05$).

The present findings are in keeping with a mechanism proposed by Lieberman et al. in which the renal retention of sodium and water is a primary abnormality. This results in an expansion of the blood and ECF volumes and would be expected to suppress PRA. Retained fluid “overflows” to the peritoneal compartment as ascites if localizing physical factors (portal hypertension, reduced plasma oncotic pressure and impaired hepatic lymph drainage) favor this. Such a mechanism would explain why a reduction in PRA may be found in patients who have not yet developed ascites. In those with ascites, PRA would be expected to be normal if the amount of fluid that had “overflowed” as ascites balanced the amount retained by the kidney, or reduced if the latter exceeded the former. The mechanism for the primary renal retention of sodium is uncertain but an increased renal tubular sensitivity to aldosterone has been proposed.

Some of the patients forming ascites in the present series (Group B), however, did have strikingly high values for PRA. Although a reduction in “effective” blood or ECF volumes could be one reason for this, there are other possibilities. Thus, an increased PRA in cirrhosis has been shown to correlate with both hyperkalemia and a redistribution of plasma flow within the kidney from the renin secreting outer cortical to juxtamedullary nephrons, both potent stimuli to renin release. In the present study, 11 patients in Group B had hyperkalemia (plasma sodium concentration 119 to 129 mmol/liter) and PRA was higher for these patients than for the 24 with a normal plasma sodium concentration (mean values of 8.26 mmol/liter/hr and 2.03 mmol/liter/hr, respectively, $p < 0.001$).

The increased PRA in the patients with renal failure (Group C) may be largely a consequence of the reduced renal perfusion responsible for the development of the renal failure. In keeping with this, Barndardo et al. found that increasing renal blood flow with dopamine was followed by a reduction in a raised PRA. However, the plasma angiotensin II concentration correlates closely with PRA in cirrhosis, and it has been suggested that the high circulating levels of angiotensin II could be the cause for the renal failure since it is a powerful renal vasoconstrictor. If this were so, other mechanisms (such as reduced “effective” ECF volume and hyperkalemia) would have to be responsible for the initial stimulation of the renin-angiotensin system. It must also be emphasized that many patients with cirrhosis are refractory to the renal vasoconstrictor effects of angiotensin II. A further possible mechanism for an increased PRA is reduced hepatic inactivation.

Acknowledgments

We are grateful to Mrs. J. Richardson for technical assistance, to Dr. S. Lader of Wellcome Reagents for supplying the angiotensin I antibody, and to Linda Rimmer for editorial assistance.
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Hypertension. 1979;1:125-129
doi: 10.1161/01.HYP.1.2.125

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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