

## Progress report

# Renin-angiotensin-aldosterone system in cirrhosis

**SUMMARY** According to traditional concepts, ascites formation and portal hypertension in cirrhosis lead to a deficit in the 'effective' extracellular fluid (ECF) and blood volumes respectively. The renin-angiotensin-aldosterone (RAA) system is thus stimulated and the kidneys retain fluid as a homeostatic mechanism to restore the ECF and blood volumes. Recent studies, however, show that approximately two-thirds of patients with ascites *do not* have a stimulated RAA system and in those without clinical evidence of fluid retention the RAA system is actually suppressed. These findings are incompatible with the concepts of reduced effective ECF and blood volumes. Despite the fact that most patients retaining sodium and accumulating ascites have a normal plasma aldosterone concentration, other evidence strongly suggests a dominant role for aldosterone in the regulation of renal sodium excretion. There might therefore be an increased renal tubular sensitivity to aldosterone in cirrhosis. For the one-third of patients with ascites who do have a stimulated RAA system this may well be a response to reduced effective ECF and/or blood volumes in accord with traditional concepts.

In certain circumstances the renin-angiotensin-aldosterone (RAA) system is of major importance in the maintenance of the extracellular fluid (ECF) and blood volumes, and arterial blood pressure. This results from the sodium-retaining effect of aldosterone on the kidneys and the vasoconstrictor properties of angiotensin II. Angiotensin II may also have a direct renal sodium-retaining effect.<sup>1</sup> Reductions in the ECF or blood volumes, or in blood pressure, act as major stimuli to the RAA system. Conversely, it is suppressed by expansion of the ECF or blood volumes, or by hypertension. The RAA system also has an important effect on potassium balance, although this will not be further discussed in the present review.

The concept has developed, based on studies dating back to more than 25 years ago, that cirrhosis, especially when ascites is present, is a 'high renin-high aldosterone' state. Two interrelated mechanisms have been proposed to account for this: (1) loss of ECF into the peritoneal compartment as ascites leads to a reduction in the 'effective' ECF (that part of the ECF available to volume receptors), even though the total ECF may be markedly increased, and (2) sequestration of blood in the splanchnic circulation secondary to portal hypertension results in a deficit of the 'effective' blood volume. The stimulated RAA system is thus thought to act as a homeostatic mechanism to restore the effective ECF and/or blood volumes.

In many of these early studies, however, there appears to have been little control over sodium intake, body posture, or diuretic therapy, each of

which may profoundly affect the RAA system. Recent investigations in which these have been controlled have shown that only a minority of patients with cirrhosis have high values for the various components of the RAA system.

In the present review the available evidence concerning the RAA system in cirrhosis is critically evaluated with particular reference to mechanisms underlying volume and blood pressure homeostasis. The findings are considered for three clinical stages which often occur in sequence: (1) without fluid retention; (2) with fluid retention; and (3) with fluid retention and renal failure.

### **1 Cirrhosis without fluid retention**

Until recently, few studies had been carried out in patients with well-compensated cirrhosis who have never had clinical evidence of fluid retention. In a group of such patients we found both plasma renin activity<sup>2,3</sup> and measurements of aldosterone<sup>4</sup> to be *reduced* to approximately one-half of the values found in normal subjects under identical conditions of sodium intake and posture. Plasma renin activity (PRA) is a function of both the enzyme, renin, and its substrate, angiotensinogen. Since the latter is synthesised by the liver,<sup>5</sup> one explanation for low values for PRA could be impaired substrate production, but the latter were found to be normal and a reduction in renin secretion must therefore be implicated. Blood pressure was invariably normal and the suppression of renin secretion may have been the result of an expansion in the effective ECF and/or blood volumes. In keeping with this, others have found increased values for total exchangeable sodium,<sup>6</sup> ECF volume,<sup>6</sup> plasma volume,<sup>7</sup> and blood volume<sup>8</sup> at this stage of cirrhosis, even though these are not clinically detectable. A finding by Epstein<sup>9</sup> that three of four patients showed an exaggerated natriuretic response to acute volume expansion would also support the view that the effective ECF and/or blood volumes were already expanded. Additional evidence to support this conclusion comes from the work of Levy *et al.*<sup>10</sup> who have shown that the non-splanchnic (effective) blood volume is increased before ascites forms in dimethylnitrosamine-induced cirrhosis in the dog.

### **2 Cirrhosis with fluid retention**

For this group of patients there are the results of three recent reports to be considered. In each study sodium intake and posture were carefully controlled and no patient was receiving diuretics or other drugs known to influence the RAA system. In our own series we found PRA to be increased in only 14 of 35 patients<sup>2,3</sup> with the others having normal or reduced values. Epstein *et al.*<sup>11</sup> found an increased PRA in six of 16 patients, while in the series of Wernze *et al.*<sup>12</sup> only five of 23 patients had increased values. In the latter study plasma renin concentration was also determined, so circumventing any possible effect of a reduction in renin substrate, and the values were raised in only three of 22 patients. Measurements of aldosterone by each of these three groups were in agreement. We found 11 of 16 patients to have an increased plasma aldosterone concentration as did eight of 17 for its rate of renal excretion.<sup>4</sup> An increased plasma aldosterone concentration was found in only four of 16 patients by Epstein *et al.*<sup>11</sup> and six of 23 patients by Wernze *et al.*<sup>12</sup>

Taken together, these studies show that approximately two-thirds of

cirrhotic patients with ascites and positive sodium balance do not have a stimulated RAA system. The concept that many patients at this stage of cirrhosis have a deficit in their effective ECF and/or blood volumes cannot therefore be supported. Furthermore, if the effective ECF or blood volumes were reduced one would expect values for glomerular filtration rate and renal plasma flow to be reduced, yet a number of studies have shown these are often normal or even increased.<sup>2 13 14</sup>

For the one-third of patients who do have a stimulated RAA system the mechanism may well be a deficit in the effective ECF and/or blood volumes as discussed initially. Hypotension is another possible mechanism. Although blood pressure is usually normal in these patients, hypotension has been reported after infusion of the angiotensin II antagonist 1-sarcosine 8-alanine angiotensin II,<sup>15 16</sup> the fall in blood pressure being proportional to the pre-infusion PRA.<sup>16</sup> These findings implicate the stimulated RAA system as a mechanism for the maintenance of blood pressure. Previous hypotension may have been the stimulus to the system. Possible factors leading to a lowering of blood pressure include the reduced effective ECF and blood volumes, a 'distortion' of the normal vascular tree with the opening of arteriovenous shunts, and an increased blood flow to areas such as skin and muscle,<sup>17 18</sup> and endotoxaemia.<sup>19</sup>

The increased PRA has been shown to be related to two variables, an intrarenal redistribution of blood flow from outer cortical to juxtamedullary nephrons<sup>2</sup> and hyponatraemia,<sup>2</sup> both of which may be manifestations of either a deficit in the effective ECF and/or blood volumes or hypotension. With regard to the first, renin is secreted almost exclusively by the afferent glomerular arterioles of the outer cortical nephrons and, presumably, with a reduction in blood flow to this region of the kidney there is less 'stretch' of the afferent arteriolar renin-releasing baroreceptors. In experimental animals both volume depletion and hypotension result in such a change in intrarenal haemodynamics.<sup>20 21</sup> An alternative explanation—namely, that the changes in intrarenal blood flow distribution are the *result* of a stimulated renin-angiotensin system—seems unlikely, as suppression of renin by  $\beta$ -adrenergic blockade had no consistent effect on intrarenal haemodynamics.<sup>22</sup> Hyponatraemia probably acts by altering the sodium (or possibly chloride) load to the macula densa of the distal tubule,<sup>23</sup> and area immediately adjoining the renin-secreting cells of the afferent arterioles and histological studies have shown the height of the macula densa to be inversely related to the plasma sodium concentration in cirrhosis.<sup>24</sup> Volume depletion and hypotension also cause hyponatraemia, as a result of the release of anti-diuretic hormone<sup>25</sup> and an increased reabsorption of sodium by the proximal tubule of the nephron,<sup>26</sup> both of which give rise to an impaired renal capacity to excrete water. Alternatively, hyponatraemia could be the *result* of a stimulated renin-angiotensin system, as the latter may induce thirst,<sup>27</sup> and presumably a dilutional hyponatraemia.

The increased PRA would be expected to result in an increased aldosterone secretion and statistically significant correlations between PRA or angiotensin II on the one hand and plasma aldosterone on the other have been reported.<sup>12</sup> Other as yet unidentified are also likely to be involved in the increased aldosterone secretion, as, when PRA was suppressed with  $\beta$ -adrenergic blocking drugs, values for aldosterone 18-glucuronide excretion—a measurement which correlates closely with aldosterone secretion rate in

cirrhosis—showed no consistent change.<sup>22</sup> Similarly, the plasma aldosterone concentration showed no consistent change after infusion of the competitive angiotensin II antagonist, l-sarcosine 8-isoleucine angiotensin II.<sup>28</sup> Impaired hepatic metabolism is undoubtedly another factor contributing to an increased plasma aldosterone concentration.<sup>29</sup>

### 3 Cirrhosis with fluid retention and renal failure

Up to 85% of patients with advanced cirrhosis have evidence of renal impairment and at this stage there is almost invariably ascites.<sup>30</sup> In many cases the renal failure occurs without biochemical or histological evidence of tubular necrosis<sup>31</sup> and is probably due to a profound generalised renal vasoconstriction.<sup>32</sup> It has often been suggested that the renal vasoconstriction is secondary to a marked deficit in the effective ECF or blood volumes. Although this may be so when the renal failure has been precipitated by diuretics,<sup>33</sup> it is unlikely to account for those instances in which renal failure develops spontaneously, as plasma infusion<sup>34</sup> and ascites reinfusion<sup>35 36</sup> do not correct the reduction in glomerular filtration rate.

In this group values for PRA (and presumably angiotensin II), and the plasma concentrations of renin are almost invariably raised<sup>3 37</sup> and it has been suggested that high circulating levels of angiotensin II might be the explanation for the profound vasoconstriction already referred to<sup>38</sup> but several findings argue against this. Firstly, the renal circulation in cirrhosis is often refractory to the effects of angiotensin II.<sup>39 40</sup> Secondly, infusions of angiotensin II in cirrhosis usually result in a natriuresis,<sup>39 40</sup> whereas the renal failure in these patients is characterised by profound renal sodium retention. Finally, administration of the angiotensin II antagonist, l-sarcosine 8-alanine angiotensin II was not followed by an improvement in renal function (unpublished observations), although this substance does have partial agonist properties.<sup>38</sup> We would support the view proposed by Barnardo *et al.*<sup>41</sup> that the renin-angiotensin system is stimulated as a *result* of the reduction in renal blood flow. This group found that a raised PRA associated with a reduced renal plasma flow could be corrected when the latter was improved by dopamine. Although the mechanism for renal vasoconstriction remains uncertain, in several studies endotoxaemia has been implicated.<sup>42–44</sup>

### Particular role for aldosterone in regulation of renal sodium excretion

The finding of normal values for aldosterone in some two-thirds of the patients with cirrhosis who are in positive sodium balance—that is, accumulating ascites—together with the reduced levels shown for patients in sodium equilibrium, could raise serious doubts as to the importance of aldosterone in the overall regulation of renal sodium excretion in cirrhosis. Other findings do, however, point to a major role—for example, (1) whatever the state of sodium balance the rate of renal sodium excretion is closely related to both the plasma concentration<sup>4 45</sup> and the renal excretion of aldosterone<sup>4 46</sup>; (2) the aldosterone antagonist spironolactone will almost invariably reverse the sodium retention providing renal failure is not already present.<sup>4 47 48</sup> Adrenalectomy has a similar effect<sup>49–51</sup>; (3) in an investigation into the effects of  $\beta$ -adrenergic blockade the renal sodium excretion, which ranged

widely, was found to increase or decrease exactly as predicted by the changes in aldosterone.<sup>22</sup> With regard to (1) the aldosterone/sodium excretion relationship is clearly abnormal in cirrhosis in that for a given sodium excretion the plasma aldosterone concentration was found to be only about one-third of that found for healthy control subjects.<sup>4</sup> This could be explained if the cirrhotic patient had either a deficiency of a natriuretic factor or an increased renal tubular sensitivity to aldosterone. We would emphasise, however, that there is no direct evidence to support either of these concepts, although the latter has been described for dogs with constriction of the thoracic segment of the inferior vena cava,<sup>52</sup> a model with many similarities to cirrhosis with ascites.

The importance of aldosterone has been questioned by others. Epstein *et al.*<sup>11</sup> subjected cirrhotic patients to central volume expansion using the technique of isothermic head-out water immersion. This resulted in a suppression of the plasma aldosterone concentration, but sodium excretion was said to have increased in only one-half of their patients (those with the lowest aldosterone levels). Chonko *et al.*<sup>53</sup> suppressed aldosterone levels by dietary sodium loading, but the resulting natriuresis was inappropriately low. Both of these groups argued that the failure to increase sodium excretion appropriately was evidence against a major involvement of aldosterone in the regulation of sodium excretion. However, the normal aldosterone/sodium excretion relationship has the form of a rectangular hyperbole so the large changes in aldosterone need not necessarily result in detectable changes in sodium excretion. The importance of taking this into account has been shown in our own studies with  $\beta$ -adrenergic blockade.<sup>22</sup> We have plotted Epstein's data for the given mean values of the plasma aldosterone concentration and sodium excretion before immersion, at one, two, three, and four hours of immersion, and after recovery, and found the plasma aldosterone concentration and sodium excretion to be closely related ( $r = -0.952$ ;  $p < 0.001$ ). Although in the study of Chonko *et al.* aldosterone levels were reported to have fallen to values similar to those found in control subjects, as already pointed out, the aldosterone/sodium relationship is abnormal in cirrhosis in such a way that sodium retention is to be expected with a plasma aldosterone concentration within the normal range.

Another point to consider is the mineralocorticoid 'escape'. When mineralocorticoids are given to normal subjects, there is, after a period of sodium retention, an escape from the sodium-retaining effect.<sup>54</sup> In cirrhotic patients with ascites and increased aldosterone levels, the latter is presumably a secondary homeostatic response to effective volume depletion and/or hypotension so that one need not imply a deranged escape mechanism. For the other ascitic patients without evidence of effective volume depletion, the failure to show the normal mineralocorticoid escape must be explained if the view that aldosterone is a major mechanism for the retention of sodium is to be sustained. Of interest, two groups have shown that many cirrhotic patients are unable to escape from the sodium-retaining effect of exogenously administered mineralocorticoids.<sup>55 56</sup> In each study  $9\alpha$  fluorohydrocortisone was given to patients without clinical evidence of fluid retention and a number continued to retain sodium with development of ascites. One possible explanation is that, because of the ascites formation, expansion of the effective ECF does not occur, but we could not confirm this in that changes in PRA and inulin clearance, used as indirect markers of changes

in the effective ECF, showed changes that were similar in those patients who continued to retain sodium<sup>56</sup> to the changes observed in those in whom there was an escape. However, in the former group, there was no increase in the renal excretion of a substance that is natriuretic (?natriuretic hormone) when injected into conscious rats, whereas a natriuresis was induced in the rats with the urine extract from those showing the escape phenomenon,<sup>57</sup> Some patients with cirrhosis may therefore have an intrinsic inability to produce a natriuretic hormone and there is evidence that this may be synthesised in the liver.<sup>58 59</sup>

Finally, one must consider the role of aldosterone in mediating the almost complete renal tubular sodium retention characteristic of the group of patients with renal failure. Although the plasma aldosterone level is almost invariably raised at this stage, this may be of minor importance, as the sodium retention can almost certainly be explained on the basis of the reduced perfusion alone.<sup>60</sup>

#### **Unifying concept and unresolved problems**

With the exception of cirrhotic patients with renal failure, the abnormality in the aldosterone/sodium excretion relationship which has been defined—namely, that for a given level of aldosterone renal sodium excretion is abnormally low in cirrhosis—may be an adequate explanation for many of the changes found in the RAA system. In patients without clinical evidence of fluid retention, because of the abnormal aldosterone/sodium excretion relationship, sodium (and water) retention occurs with some expansion of the effective ECF volume. The measured increases in total exchangeable sodium,<sup>6</sup> ECF volume,<sup>6</sup> plasma,<sup>7</sup> and blood volumes<sup>8</sup> described by others at this stage of cirrhosis are in keeping with this. Although not clinically detectable, the retained fluid results in suppression of the RAA system with a return of sodium balance at a higher level of total body sodium.

In patients with clinical evidence of fluid retention the traditional concept linking ascites formation, the RAA system, and renal sodium excretions cannot be implicated in the two-thirds of patients in whom the RAA system is not stimulated. An alternative mechanism has been proposed and is known as the 'overflow theory'.<sup>61</sup> According to this concept the renal retention of sodium is the primary abnormality, the ECF expands and, if certain localising factors (portal hypertension, reduced plasma oncotic pressure, impaired hepatic lymph drainage) are sufficiently altered, there is an overflow of the expanded ECF into the peritoneal cavity as ascites. Current findings fit well with this concept. As in patients without clinical evidence of ascites or oedema, the abnormal aldosterone/sodium excretion relationship leads to fluid retention. At this more advanced stage of cirrhosis, however, the localising factors are such that this fluid cannot remain within the effective ECF and as a consequence ascites forms. The net result is that the effective ECF is not expanded, the renin-angiotensin-aldosterone system is not suppressed and fluid retention continues at normal levels of PRA and aldosterone (Figure).

In the one-third of patients with ascites who are found to have a stimulated RAA system this may well represent a homeostatic response to reduced effective ECF and/or blood volumes, or to hypotension (Figure). What relationship there is between the changes in this group and those described

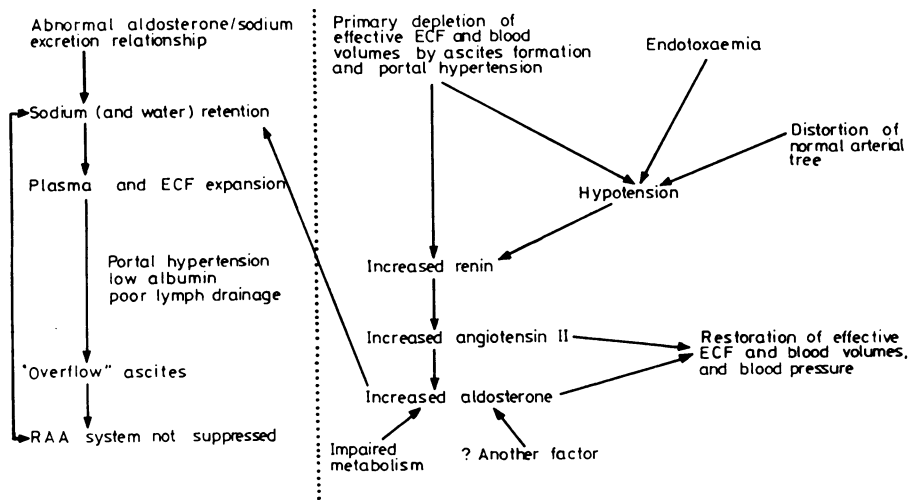


Figure Proposed interrelationship between the renin-angiotensin-aldosterone (RAA) system, ascites formation, and volume and blood pressure homeostasis. Changes on the left side refer to the two-thirds of patients without a simulated RAA system, those to the right for the remaining one-third in whom this is stimulated.

above which might represent an 'earlier' stage of the disease and what determines the transition is uncertain.

For the group with renal failure the markedly reduced renal perfusion is probably of overriding importance in both stimulating the RAA system and promoting sodium retention. Localising factors for ascites formation are likely to be as important as in the other groups.

Other unresolved and important problems concerning the RAA system and sodium excretion in cirrhosis include the cause for the abnormal aldosterone/sodium excretion relationship, the mechanism responsible for failure to show the mineralocorticoid escape, and the possible role for natriuretic hormone, and, finally, the nature of the control system other than the renin-angiotensin system which leads to hypersecretion of aldosterone.

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