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## Review

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# Blood pressure in haemodialysis patients: The importance of the relationship between the renin-angiotensin-aldosterone system, salt intake and extracellular volume

Timothy WR Doulton, Graham A MacGregor

## Abstract

This review outlines the major mechanisms for control of blood pressure (BP) in individuals with renal failure on haemodialysis. Dietary salt stimulates thirst and, thereby, greater fluid intake with excessive fluid gain between dialysis sessions and chronic expansion of extracellular volume. At the same time, this volume expansion often fails to suppress the renin-angiotensin system (RAS) appropriately and this inevitably leads to high BP in the majority of individuals on haemodialysis.

A greater understanding of the mechanisms involved leads to more rational treatment and better BP control. This can be achieved by careful measurement of BP before and after dialysis, allowing time for the equilibration of extracellular fluid shifts that occur after dialysis, combined with measurements of plasma renin activity. It is relatively easy to then decide how the high BP should be treated, either by removal of excess volume by gradual ultrafiltration combined with restriction of salt intake to help prevent thirst and excessive fluid gain between dialyses, or by inhibition of the RAS, or by a combination of both.

In those individuals who are unable to adequately reduce their dietary salt intake and still continue to gain large amounts of weight between dialysis, and are resistant to reducing their pre-dialysis weight, calcium antagonists may help to lower BP, either alone or in combination with RAS blockade. However, the BP often remains resistant to treatment unless they can be persuaded to reduce their salt intake.

## Introduction

Blood pressure (BP) is the major risk factor for cardiovascular disease (stroke, myocardial infarction and cardiac failure) in the general population.<sup>1</sup> In individuals with end-stage renal failure (ESRF), cardiovascular mortality is 20-fold greater than in a population who are age and sex-matched but without renal failure.<sup>2</sup> In individuals who require dialysis (i.e. in whom there is virtually no kidney function) raised BP occurs in 80% of cases<sup>3,4</sup> and there is clear evidence that this raised BP continues to be a major risk factor for cardiovascular disease.<sup>5,7</sup> However, haemodialysis (HD) patients with low BP, especially diastolic BP, have an excess mortality.<sup>8-11</sup> The low BP in these patients is usually a consequence of malnutrition<sup>10</sup> or severe myocar-

dial dysfunction,<sup>12</sup> and therefore it is not surprising that this group is at increased risk.

## Mechanisms underlying the control of blood pressure in haemodialysis patients

In individuals on HD, the excretory functions of the kidney are largely replaced by dialysis. These individuals absorb water and salt in the same way as people with normal renal function, but they have no way of excreting these substances and therefore these must be removed each time they are dialysed. In general, HD patients in the UK are dialysed three times a week, gaining 1-3 litres of extracellular (EC) fluid in between each dialysis. These constant fluctuations in extracellular volume (ECV) are likely themselves to put a severe strain on the cardiovascular system, but are also largely part responsible for raising BP.

The main drive to fluid intake is thirst, and the over-riding stimulus to thirst is plasma osmolality.<sup>13</sup> The major determinant of plasma osmolality is serum sodium concentration<sup>13</sup> and, in HD patients, this depends upon dietary salt intake and the net sodium gained or lost during dialysis. Individuals with normal renal function experience a small increase in plasma sodium on a high-salt diet.<sup>14</sup> This draws fluid from the intracellular (IC) to the EC fluid space, but at the same time stimulates the hypothalamus and pituitary, resulting in thirst and thereby increased water consumption, which will tend to dilute the plasma sodium back to normal. Within 0.5-1 hour, there is also an increase in urinary sodium excretion.<sup>15</sup> Exactly the same happens in individuals on dialysis, except that they cannot excrete the sodium and therefore the increase in plasma sodium is likely to be longer lasting and may thereby stimulate thirst to a greater extent than in an individual with normal renal function. Therefore, limiting salt intake is vital in reducing thirst and inter-dialytic weight gain.

During dialysis, both sodium and water are removed and this will depend on the amount of fluid removed or weight reduction. This fluid will contain the same sodium concentration as dialysate sodium. However, differences between individual plasma sodium and dialysis sodium will affect the amount of sodium removed. One way of making more room for sodium is to dialyse

individuals against a lower dialysate sodium, for example 130–135 mmol/L compared to the standard 140–142 mmol/L, so that when these individuals come off dialysis their plasma sodium concentration is lower. In theory this would allow more salt to be consumed before the plasma sodium concentration that we associate with normality (~140 mmol/L) is reached. However, it is unclear whether the stimulus to thirst is determined by relative changes in, or absolute levels of, plasma sodium. There is some evidence that a dialysate sodium concentration of around 140 mmol/L may promote greater haemodynamic stability during the dialysis session. This is claimed to be particularly important when dialysis is carried out for shorter periods of time and large amounts of sodium fluid are removed rapidly. However, those dialysis units, for example at Tassin in France, who continue dialysis for a longer duration (eight hours), claim to be able to use lower dialysate sodium concentrations of around 138 mmol/L.<sup>5</sup>

In normal individuals, short-term changes in ECV only lead to small changes in BP, due to the buffering effect of the renin-angiotensin system (RAS). This is illustrated by the observation that, in changing from a low- to a high-salt intake, normal individuals gain approximately 1.5–2 kg in weight, but there is little change in BP as the RAS is suppressed.<sup>14</sup> Experiments with angiotensin II (Ang II) antagonists in individuals with essential hypertension and angiotensin-converting enzyme (ACE) inhibitors in normal and hypertensive subjects have shown that this suppression of the RAS is responsible for the fact that these individuals only have small increases in BP with large changes in ECV.<sup>16–18</sup>

Individuals with ESRF as a consequence of chronic glomerulonephritis or glomerular arteriosclerosis, as occurs in severe or malignant hypertension, have marked distortion of the glomerular architecture. This causes ischaemia of the juxtaglomerular apparatus (JGA) which results in inappropriate secretion of renin.<sup>19,20</sup> There is a higher prevalence of glomerulonephritis or arteriosclerosis, as opposed to tubulo-interstitial disease, in individuals with ESRF who have elevated plasma renin activity (PRA).<sup>21</sup> Glomerulosclerosis results in a progressive decline in glomerular filtration, leading to a reduction in the presentation of sodium chloride to the macula densa, as well as reduced stimulation of baroreceptors in this region of the nephron, that may result in increased renin secretion by the JGA. Conversely, the salt and water wasting that often accompanies renal tubular disease, resulting in large amounts of sodium being presented to the distal tubular macula densa cells, may suppress renin secretion.

Remarkably, despite almost complete loss of renal excretory function, the majority of individuals on HD have kidneys that still retain the ability to secrete renin and respond to changes in volume and PRA may indeed increase over time in these individuals.<sup>22</sup> However, there appears to be a resetting of the renin-salt-volume feedback mechanism

in many hypertensive HD patients and these individuals usually secrete inappropriately high levels of renin for their volume status compared with normal subjects or normotensive HD patients.<sup>20</sup> Given that most HD patients are chronically volume overloaded and a significant number also have inappropriate activity of the RAS, it is not surprising that the majority are hypertensive.

### **Evidence for expansion of the extracellular volume in haemodialysis patients**

Using radiolabelled isotope dilution techniques, Weidmann *et al.* demonstrated that, even in HD patients on a very low salt intake (1–1.5 grams per day), there were higher levels of exchangeable sodium (NaE) than in normal controls, and the plasma volume (PV) was significantly expanded in those with raised BP.<sup>19</sup> Other workers have demonstrated expanded blood volume (BV), PV or ECV using radio-labelled isotope dilution techniques<sup>23–25</sup> electrical bioimpedance techniques<sup>26–28</sup> and inferior vena cava diameter as measured by transthoracic echocardiography;<sup>24</sup> this volume expansion was greater in those with high BP on dialysis than in those with normal BP.

A number of studies have investigated the relationship between interdialytic weight gains and BP: some authors have found higher interdialytic weight gains to be associated with hypertension,<sup>29,30</sup> whilst others have not.<sup>31–33</sup> However, none of these studies have examined the activity of the RAS and without this knowledge these studies are uninterpretable.

The importance of volume overload in individuals with ESRF was evident in the early days of HD, where there were few effective BP-lowering drugs, and BP was controlled by reduction of ECV through ultrafiltration on dialysis and a gradual reduction in pre-dialysis weight.<sup>34</sup> However, it was found that in a few individuals, particularly those with malignant hypertension, progressive weight loss did not in fact lower BP but raised it. It was then realised that over-activity of the RAS had become the major driver to the raised BP in these patients.<sup>35</sup> In these individuals, bilateral nephrectomy was shown to be effective in lowering BP and reducing the high levels of renin.<sup>36,37</sup> However, these individuals represent an extreme in the spectrum and what has not been sufficiently realised is that many hypertensive HD patients have inappropriately increased PRA relative to their salt and volume status, as compared with normal subjects, and it is this combination that is responsible for the elevation of their BP.<sup>20</sup>

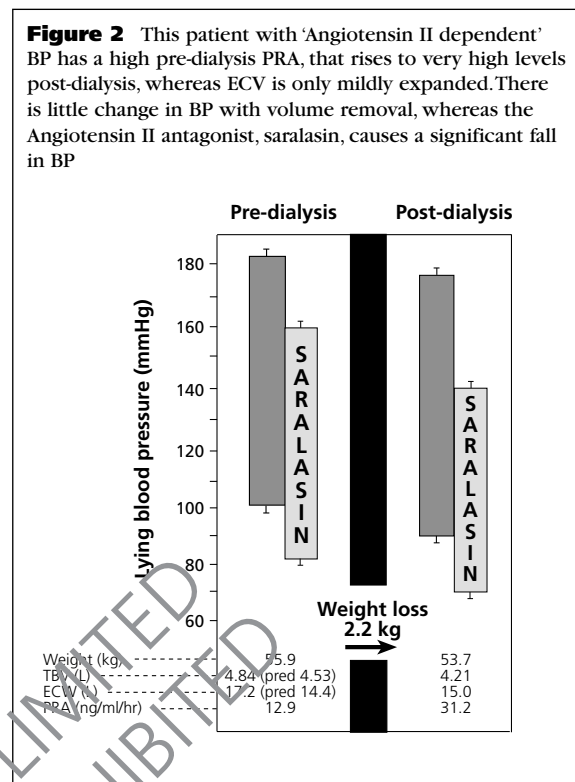
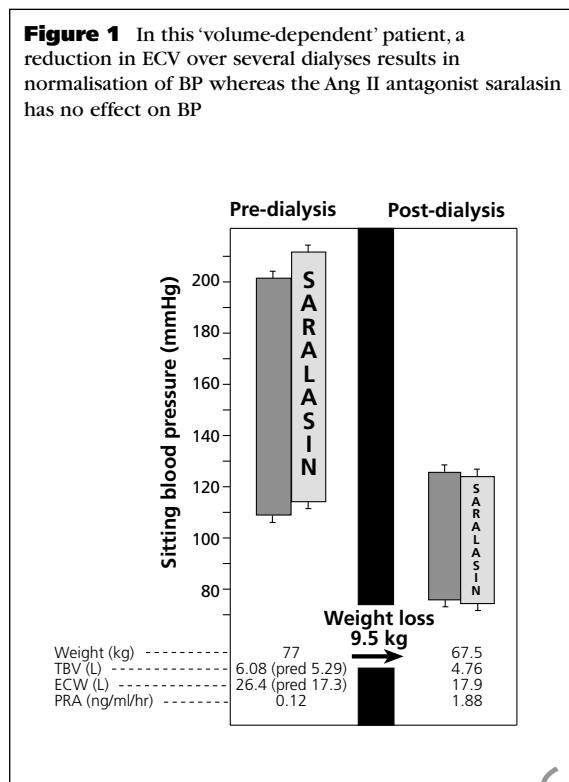
### **Evidence for over-activity of the renin-angiotensin system**

For any given level of NaE and PV, PRA is two-fold higher in hypertensive HD patients than in normotensives<sup>19</sup> and plasma Ang II levels are higher in hypertensive individuals with chronic renal failure (CRF) compared with normotensives.<sup>38</sup> Furthermore, where it has been measured, the product of the NaE and the PRA is higher in hypertensives

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than in normotensives on HD and directly correlates with mean BP.<sup>39</sup>

There are several studies in HD patients looking at the responses of the RAS to changes in volume. For instance, those individuals whose BP was found to respond to changes in volume had larger increases in BP following intravenous saline infusion, with only small reductions in PRA and Ang II, compared with subjects who were less volume-sensitive but had greater reductions in PRA and Ang II.<sup>40</sup> In a separate but similar study, it was found that individuals with a high PRA prior to saline loading had a large increase in BP whereas those with a normal or low PRA did not, and there was no suppression of PRA with saline loading in those in whom it started high.<sup>41</sup> Other workers have found that BP is more volume-sensitive in hypertensive HD patients than in normotensives, and that degrees of volume sensitivity were normally distributed within their study population.<sup>42</sup> It was proposed by the authors of this latter study that the RAS may be central to determining volume sensitivity in HD patients, although, surprisingly, RAS activity was not measured.<sup>42</sup>

There needs to be more focus on the relationship between changes in BP, volume and the response of the RAS. By measuring ECV and PRA before and after dialysis, and by administering Ang II antagonists, it is possible to show the predominant mechanisms of hypertension in an individual HD patient.<sup>43</sup> These illustrative studies were conducted with saralasin, a peptide that is a competitive inhibitor of Ang II receptors. However, saralasin exhibits agonist activity when plasma Ang II levels are low, and only lowers BP when plasma angiotensin levels are raised.

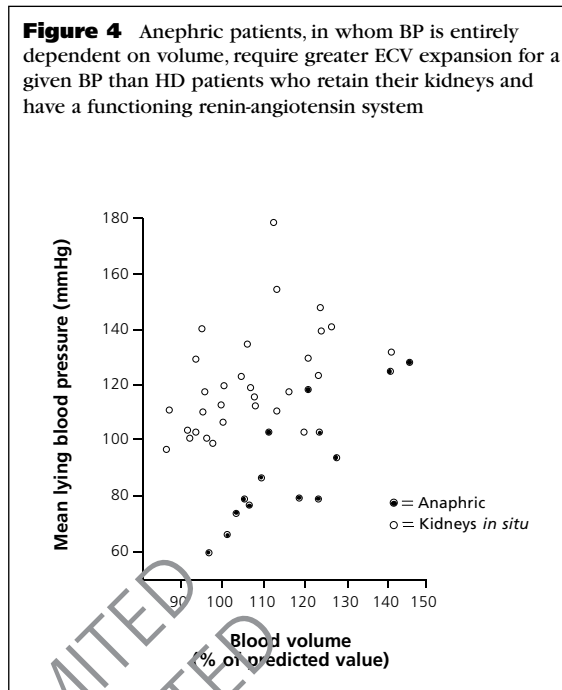
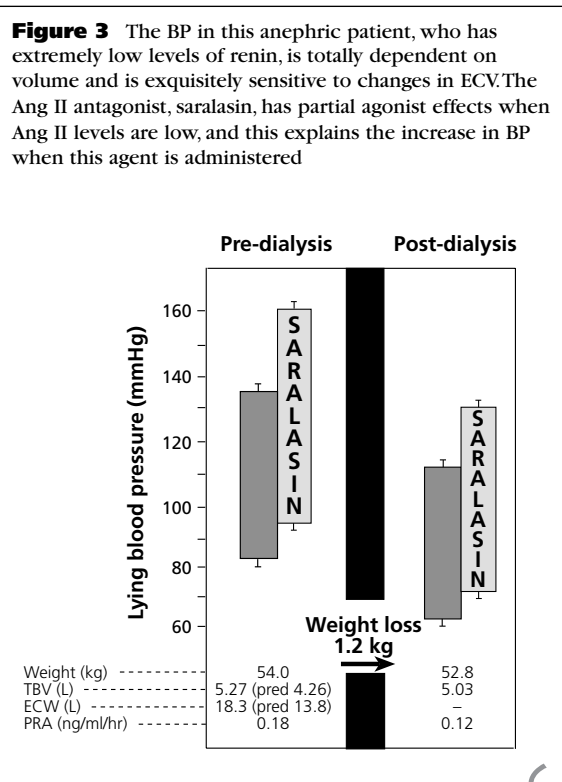
Figure 1 illustrates the finding in an individual

whose BP was volume-dependent and who, with normalisation of the expanded ECV over several dialyses, corrected his BP. PRA was very low when he was volume overloaded and came into the normal range as his volumes returned to those predicted for his age, sex and body mass index. The intravenous Ang II antagonist, saralasin, did not affect his BP.

In an individual in whom raised BP was dependent on elevated Ang II (Figure 2), PRA was greatly elevated prior to dialysis and there was only a mild expansion of ECV. With dialysis, volume was removed but PRA rose to even higher levels and there was little change in BP. Saralasin lowered BP before dialysis and to a greater extent following the dialysis, indicating the important interaction in this individual between the level of Ang II and volume in increasing BP.

Textor *et al.*<sup>44</sup> have also measured pre- and post-dialysis PRA and BP responses to saralasin. They identified two groups of subjects: on the one hand were those that had low pre- and post-dialysis PRA and no BP response to saralasin infusion. This group was classified as having volume-dependent hypertension, although no direct measurements of ECV were made. On the other hand, were those subjects with a high PRA pre-dialysis or whose PRA increased by > 30% post-dialysis. A large increase in PRA with dialysis was observed in this group, and subjects experienced a significant depressor effect on BP with infusion of saralasin, with a close correlation between PRA and BP fall. These subjects were classified as having renin-dependent hypertension.

Perhaps the most vivid illustration of the importance of volume and the response of the



RAS is found in anephric individuals, in whom both kidneys have been removed. These individuals have no functioning RAS and, as a consequence, very low levels of aldosterone. Their BP is entirely dependent on volume changes and is very sensitive to reduction in ECV (Figure 3) with no change in PRA or hypotensive response to saralasin. Furthermore, anephrics require a considerable increase in blood volume (BV) in order to maintain BP at the same level as dialysis patients with intact kidneys (Figure 4).<sup>45</sup>

In the early days of HD, if there were major difficulties with control of BP in individual patients who had high levels of renin, bilateral nephrectomy was performed. This is a major operation and, prior to the advent of recombinant human erythropoietin, condemned these individuals to being severely anaemic (haemoglobin ~4–5 g/dL). With a greater understanding of the mechanisms maintaining BP in these renin-dependent individuals, bilateral nephrectomy was abandoned, as drugs, particularly  $\beta$ -blockers, ACE-Is and now angiotensin receptor blockers (ARBs), effectively inhibit the RAS.

### Aldosterone

The direct effects of aldosterone on BP have often been ignored, in part because its major action in those with normal renal function is to retain sodium, and therefore cause an elevation in BP. However, in dialysis patients, aldosterone can no longer act on the kidney to retain sodium, and therefore any BP effect it might have must be mediated either directly on receptors in the vasculature or through other mechanisms, for example in the central nervous system. Since indi-

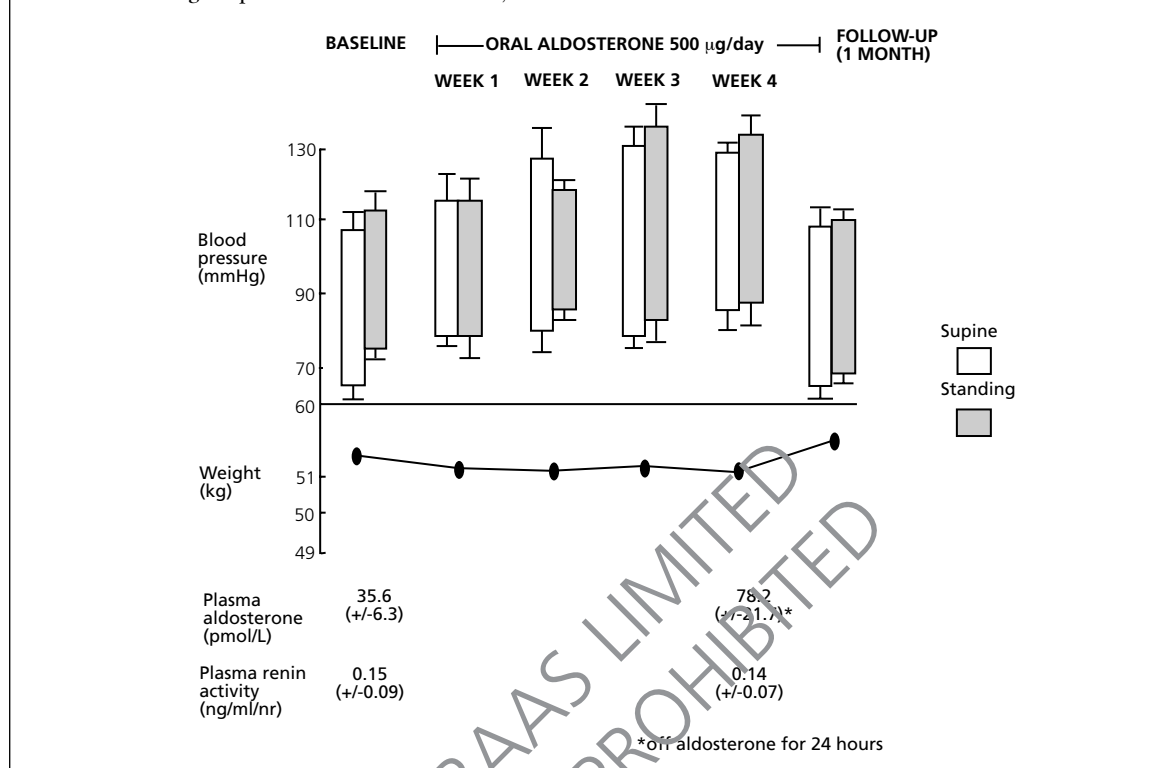
viduals on dialysis who have had bilateral nephrectomy have very low levels of renin and aldosterone, it was of some interest to give aldosterone to a group of anephric HD patients and see whether this had any effect on their BP whilst keeping their pre-dialysis weight constant (Figure 5).

In an unpublished study, we gave five anephric subjects 500  $\mu$ g aldosterone/day orally for one month. During this time, pre-dialysis BP increased with no change in pre-dialysis weight. One month after stopping aldosterone, BP had fallen to the pre-aldosterone levels, again with no change in weight. These results suggest that aldosterone does have direct effects on BP, independent of its effect on sodium and water balance. Indeed, in individuals who have had a bilateral nephrectomy who have very low BP and are symptomatic, it may be worthwhile giving them fludrocortisone.

### Attempts to limit weight gain between dialysis

If weight gain could be limited between dialysis, fluctuations in BP would be less. This requires that individuals drink less fluid between dialysis. Traditionally, the importance of dietary salt restriction has been emphasised to individuals on dialysis and yet presently this is nearly always neglected by dieticians, dialysis nurses and nephrologists, who often choose to exhort patients to restrict only their fluid intake.<sup>45</sup> Perhaps not surprisingly, these efforts meet with little success as the drive to thirst due to excessive salt intake is overwhelming.<sup>13</sup> This lack of interest in the importance of dietary salt is reflected by the very small numbers of studies in this area. Ozkahya and colleagues have shown, in uncontrolled studies, that dietary sodium restriction to 100 mmol/day or less (approximately 5–6 g salt), combined with close attention to control of ECV, lowers BP<sup>46</sup> and causes

**Figure 5** A group of five patients on regular haemodialysis, who had previously had bilateral nephrectomies and so had low levels of renin and aldosterone, were given 500 µg/day of oral aldosterone. Their weights remained unchanged, indicating that the increase in BP seen with administration of aldosterone was due to a direct effect of this agent on BP, rather than through expansion of ECV. Furthermore, BP returned to baseline levels when the aldosterone was discontinued



regression of left ventricular hypertrophy (LVH) in HD patients. Others have demonstrated that a very low sodium diet (less than 1 g per day) reduces inter-dialytic weight gain,<sup>48</sup> and reducing salt intake prior to a single dialysis session results in a 5 mmHg fall in mean arterial pressure.<sup>49</sup>

Another potential way of either losing or gaining sodium is the difference between dialysate sodium concentration and the patient's plasma sodium concentration. Reducing dialysate sodium concentration results in a net loss of sodium which is dependent on the fall in plasma sodium that occurs in the individual and the volume of distribution. It is important to realise that at the end of dialysis the plasma sodium of the individual will be the same as the dialysate sodium concentration. However, there are very few controlled studies looking at whether this technique affects BP control. Two small studies have suggested that combining a low-sodium dialysate (133-135 mmol/L) and modest dietary salt restriction (less than 6 g/day), without changes in dialysis time or dry weight, has beneficial effects on BP.<sup>45,50</sup> One study showed a significant fall in systemic vascular resistance with the low-sodium dialysate.<sup>50</sup> However, there were only eight and ten subjects, respectively, in these two studies and the majority of subjects were normotensive or had BP controlled by medication. There are no controlled studies looking at the efficacy of dietary salt restriction on its own, and no studies of whether thirst is solely dependent on changes in plasma sodium or also varies with the absolute level of plasma sodium.

One dialysis unit in Tassin, France, has claimed that BP can be controlled in nearly all individuals on HD without resorting to the use of antihypertensive medications.<sup>51</sup> One major difference between dialysis at Tassin and most other dialysis units is that they continue to dialyse their patients for eight hours, three times per week. On acceptance to HD, 89% of the Tassin patients require antihypertensive medication, whereas after two months it is claimed that less than 5% require such medication.<sup>51</sup> They claim that this fall in BP is achieved through the normalisation of ECV by long, slow ultrafiltration in the first month of dialysis, with euvolaemia being defined by standard clinical criteria. In addition, the Tassin group describe what they call the 'lag phenomenon', that is, the BP of patients dialysing at Tassin continues to fall for a number of months after normalisation of ECV, despite withdrawal of antihypertensive medications.<sup>51</sup> They believe this is due to improved clearance of vasoactive mediators such as asymmetric dimethylarginine (ADMA) with a longer duration of dialysis and support this with the observation that the main haemodynamic parameter by which the Tassin population differs from other HD populations is a reduction in systemic vascular resistance (SVR).<sup>52</sup> Also, others have shown that longer hours dialysis results in lower BP, and that a possible mechanism is a fall in vascular resistance, rather than reductions in ECV.<sup>53</sup> Furthermore, there is evidence that the fluid status of patients in Tassin does not significantly differ from both normotensive and hypertensive

patients receiving HD in other units.<sup>25</sup> However, although ADMA accumulates in individuals with chronic renal failure,<sup>54</sup> there is no direct evidence that longer hours dialysis increases removal of this substance. Moreover, one important fact which is not emphasised by the Tassin group is that they vigorously restrict their salt intake and use a lower dialysate sodium than many other units. We would argue that it is the lower salt intake of Tassin patients that is responsible for the lower BP seen in the majority of the Tassin HD population. Furthermore, it is well recognised that hypertrophy and hyperplasia of the JGA occurs in animals that are salt- and volume-depleted<sup>55</sup> and humans who abuse diuretics.<sup>56</sup> Similar effects on the JGA may occur in individuals receiving HD who experience marked fluctuations in their ECV every two to three days, and thereby have constantly changing stimuli to the RAS. This may explain why the RAS appears to become more active with increasing dialysis vintage.<sup>22</sup> It is possible that less pronounced fluctuations in ECV, as occurs with longer hours dialysis, will allow the associated juxtaglomerular hypertrophy to regress.

In our view, the predominant mechanism that controls BP in HD patients is the reciprocal relationship between salt and fluid intake, excess ECV and the inappropriate activity of the RAS. As dialysis patients cannot excrete fluid or sodium and have damaged kidneys, that inappropriately secrete renin for a given volume, it is not surprising that, until cardiac failure supervenes, the majority of HD patients have hypertension.

#### **Other factors that may be important in blood pressure control in dialysis patients**

These have been extensively reviewed elsewhere,<sup>57,60</sup> and are summarised in Table 1.

There is clear evidence that many dialysis patients may have overactivity of the sympathetic nervous system (SNS). Microneurographic studies have shown that uraemic subjects have higher post-ganglionic sympathetic nerve discharge to skeletal muscle blood vessels than normal subjects, and this is accompanied by increased vascular resistance in the calf.<sup>61</sup> Interestingly, the rates of sympathetic discharge in dialysis patients who had undergone bilateral nephrectomy did not differ from normal subjects, suggesting that the SNS activation is mediated by an afferent signal arising within the failing kidney.<sup>61</sup> Furthermore, there is evidence from animal models of CRF that hypertension is accompanied by increased noradrenaline turnover in the posterior hypothalamus and is virtually eliminated by selective renal deafferentation.<sup>62</sup> Increased sympathetic nerve discharge is also reduced by the ACE-I enalapril in individuals with CRF and raised renin levels, implying that Ang II has direct central feedback on the SNS in uraemic individuals.<sup>63</sup>

#### **Treatment of raised blood pressure in haemodialysis patients**

In general, control of BP in dialysis patients is

**Table 1** Reasons for hypertension in haemodialysis patients

Sympathetic overactivity
Impaired endothelium-dependent vasodilatation
Uraemic toxins (ADMA, homocysteine)
Correction of renal anaemia by rHuEpo
Secondary hyperparathyroidism
Haemodialysis regimen
Patient non-compliance

extremely poor and there are few well-controlled studies of the best regimes to adopt.<sup>64</sup> However, an understanding of the pathophysiology of BP control in these patients should suggest a common sense regime of trying to limit weight gain between dialysis by restriction of salt intake to less than 5 g/day and a gradual reduction in pre-dialysis weight (i.e. normalisation of ECV) in those individuals who have low levels of PRA. The use of a lower dialysate sodium concentration, for example 135 mmol/L, may be a useful technique for further limiting inter-dialytic fluid intake and improving BP control, although larger studies with longer periods of follow-up are required to examine the efficacy and potential disadvantages of reducing dialysate sodium concentration.

Ang II is a potent pressor agent that increases SVR via direct effects on vascular smooth muscle and through increased SNS activity. Such effects are abolished by drugs that block the RAS. Therefore, those individuals who have high PRA either pre- or post-dialysis will almost certainly need drug therapy with an ACE-I or an ARB. In those with increased activity of the RAS both pre- and post-dialysis, an increase in weight, combined with blockade of the RAS, usually results in improved BP control and a marked increase in well-being. In patients who are unable to limit their salt intake and their weight gain between dialyses, and are therefore volume-expanded with low levels of renin, BP can be lowered with the use of calcium antagonists, either alone or in combination with ACE-Is or ARBs.<sup>65</sup>

#### **Other effects of sodium retention and volume expansion**

Increased volume and excessive sodium retention will adversely affect the cardiovascular system in an additive and independent way to that caused by the raised BP. Firstly, aortic stiffness is an independent risk factor for cardiovascular mortality in patients with ESRF.<sup>66</sup> Increased salt intake in both normal human subjects and experimental animals decreases arterial compliance and causes greater stiffness of the aortic wall.<sup>67</sup> Furthermore, studies have shown that a low-salt diet reduces arterial stiffness, independent of the effects on BP.<sup>68,69</sup> Secondly, salt and water overload cause LVH and increased internal dimensions of the cardiac cavities.<sup>70</sup> LVH is

present in more than 60% of HD patients and, as with aortic stiffness, is an independent risk factor for cardiovascular mortality in this population,<sup>71,72</sup> whereas partial but significant regression of LVH reduces cardiovascular mortality.<sup>73</sup> Continuous fluctuations in volume, along with a combination of high BP, ischaemic heart disease and LVH, makes it inevitable that many individuals on dialysis will develop cardiac failure. It is possible that the salt and volume overload may also directly increase the risk of stroke, independent and additive to that of BP, in the same way that a high salt intake increases the risk of stroke independent of and in addition to its effect on BP in the normal population.<sup>74</sup>

### Other benefits and disadvantages of drugs that block the renin-angiotensin system

It has been claimed that ACE-Is may reduce mortality and cardiovascular morbidity in patients at high risk of cardiovascular events.<sup>75</sup> The Heart Outcomes Prevention Evaluation (HOPE) study and other cardiovascular outcome studies<sup>75,76</sup> excluded patients with significant renal dysfunction. There are no prospective studies specifically addressing the benefits of ACE-Is or ARBs on cardiovascular outcomes in patients with ESRF.

Interestingly, in a retrospective study in a HD population, Efrati *et al.* found that those subjects who had received an ACE-I had a mortality reduction of 52% compared with patients who had been on other hypertensive medication, though this study was a retrospective one.<sup>77</sup> ACE-Is have been shown to significantly reduce left ventricular mass index over a twelve-month period in hypertensive patients with severe renal impairment but not on dialysis.<sup>78</sup> Similarly, lisinopril<sup>79</sup> and losartan<sup>80</sup> reduce LVH independently of their BP-lowering effects in normotensive<sup>79</sup> and hypertensive<sup>80</sup> HD patients, respectively. Losartan reduced left ventricular mass significantly more than enalapril and amlodipine in the latter study, but the follow-up was short and there was no control group.<sup>80</sup> The FOSIDIAL study investigators have randomised approximately 400 HD patients with LVH to fosinopril or placebo, with a composite endpoint of fatal and non-fatal major cardiovascular events.<sup>81</sup> They have recently concluded follow-up and the results will be awaited with interest.

In some circumstances, Ang II is a dipsogenic substance and ACE-Is have been shown to significantly reduce thirst and inter-dialytic weight gain in HD patients.<sup>82</sup> Therefore, in addition to direct effects on BP through blockade of the RAS, ACE-Is may possibly affect BP by reducing thirst. Furthermore, ACE-Is modulate the overactivity of the SNS observed in patients with advanced renal failure.<sup>63</sup>

High-dose ACE-Is suppress erythropoiesis and induce resistance to the erythropoietin (rHuEpo) therapy that is used to treat anaemia in patients with CRF, requiring larger doses of rHuEpo in patients receiving this class of drug.<sup>83</sup> On the other hand, ARBs do not seem to contribute towards anaemia in patients with ESRF.<sup>84</sup> The combination

of AN69 dialysis membranes and ACE-Is may cause severe, and occasionally fatal, anaphylactoid reactions in HD patients due to elevated bradykinin levels.<sup>85</sup> In addition, ACE-Is and ARBs may be associated with increases in plasma potassium concentrations in maintenance HD patients, presumably due to reduced gastrointestinal excretion or impaired cellular uptake of potassium,<sup>86</sup> and therefore pre-dialysis plasma potassium should be monitored in all HD patients receiving an ACE-I or ARB.

### Summary

Patients on HD have little or no renal function and are unable to excrete salt and water. Their fluid intake will be determined predominantly by their salt intake. For individuals who do not restrict their salt intake, this results in large inter-dialytic fluid gains that are often in excess of 3L, and this retained fluid has to be removed during each dialysis. Attempts to remove such large volumes during a single dialysis session often result in haemodynamic instability that limits further fluid removal, and may even necessitate giving intravenous saline, resulting in chronic ECV expansion.

Surprisingly, in view of the absence of other excretory and endocrine functions of the kidney, many individuals on dialysis still have a functioning RAS. However, in a number of patients there is an apparent resetting of the sodium-volume-renin feedback mechanism, resulting in inappropriate levels of renin for a given ECV or sodium status. Therefore, it is not surprising that the majority of haemodialysis patients have high BP.

A better understanding of these mechanisms leads to a more rational approach to control of their BP. All dialysis patients who are hypertensive should have careful measurements of BP before and after dialysis, allowing time for the equilibration of extracellular fluid that occurs after dialysis. Where BP is raised, this should be treated in the first instance by gradual reduction in pre-dialysis weight (i.e. normalisation of ECV) by a combination of salt restriction to limit fluid intake and an increased reduction in fluid removal during dialysis, with a gradual reduction in post- and, therefore, pre-dialysis weight. In those patients who remain compliant, but whose BP is resistant to this regime, measurements of PRA pre- and post-dialysis should also be taken. If PRA is raised, either pre- or post-dialysis, the judicious use of drugs that block the renin system, such as an ACE-I or an ARB, will result in better control of BP. In those whose BP is not controlled, and in those unable to restrict or salt or limit weight gain, calcium antagonists, alone or in combination with ACE-Is or ARBs, may help to lower BP, though BP usually remains poorly controlled until individuals reduce their salt intake.

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