New insights into mechanisms of blood pressure regulation in patients with uraemia

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Abstract. There is no doubt that in patients with end-stage renal failure sodium/water retention and (often unrecognized) hypervolaemia is the single most important determinant for elevated blood pressure. More detailed analysis reveals that in the renal patient susceptibility to hypervolaemia is increased due to inappropriately elevated activity of pressor systems (and/or decreased activity of depressor systems). These abnormalities comprise inappropriately activated renin-angiotensin system (RAS) (circulating and local) as well as sympathetic activity, but more hypothetical possibilities must also be considered, e.g. abnormalities of renal vasodilators (medullipin), L-arginine-derived agmatin, endothelin and NO.

Key words: ADMA; agmatin; hypertension; medullipin; renin-angiotensin system; sodium; uraemia

Introduction

Hypertension is of crucial importance, not only for progression of renal failure in the phase prior to end-stage renal failure [1], but also as a potent determinant of patient survival on renal replacement therapy. This was first well documented by Degoulet et al. [2]. As shown in Table 1, over a relatively limited period of time, cardiovascular mortality and particularly stroke mortality are linked to systolic, and even more closely to diastolic blood pressure. The relative risk of cardiovascular mortality in the lowest compared to the highest tertile of systolic pressure is elevated by a factor of 1.7, and even more in the respective tertiles of diastolic blood pressure, i.e. by a factor of 2.4. The increment in the relative risk of stroke was even greater: 3.5 and 6.9, respectively.

Not all studies have been able to clearly show a relation between blood pressure and patient survival on dialysis [3]. There are several reasons to account for such negative findings. In short-term studies, one important confounder is the non-linear type of relationship: individuals with poor chances of survival tend to have lower blood pressures, as in studies on the non-renal population, thus obscuring the relationship. Even more importantly, it appears that what has been considered 'acceptable blood pressure' in most centres is far above the blood pressure level which is optimal for patient survival. In the study of Charra et al. [4], survival at 15 years for patients with a mean arterial pressure (MAP) of <99 mmHg was 67% vs 43% in subjects with MAP ≥ 99 mmHg. These levels are well within the range of normotension by WHO criteria. It is obvious that nephrologists have to face the question of whether target blood pressure should be lower than conventionally accepted in patients on dialysis [5].

A rational approach to this problem necessitates

Table 1. Death as a function of blood pressure in dialysis patients (observed/expected)—results of the Diaphane Study (after Degoulet et al. [2])

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Overall mortality</th>
<th>Cardiovascular mortality</th>
<th>Stroke mortality</th>
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<tr>
<td>Systolic BP (mmHg)</td>
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<tr>
<td>138</td>
<td>0.94</td>
<td>0.86</td>
<td>0.55</td>
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<tr>
<td>138-155</td>
<td>0.74</td>
<td>0.68</td>
<td>0.51</td>
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<tr>
<td>155</td>
<td>1.33</td>
<td>1.46</td>
<td>1.9</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td>78</td>
<td>0.89</td>
<td>0.65</td>
<td>0.27</td>
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<tr>
<td>78-89</td>
<td>0.88</td>
<td>0.83</td>
<td>0.88</td>
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<tr>
<td>89</td>
<td>1.27</td>
<td>1.57</td>
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insight into the pathomechanisms underlying hypertension in renal failure. In the following we try to discuss some salient features. Because of restriction of space this overview must remain restricted.

The role of hypervolaemia

Although the role of hypervolaemia in the genesis of hypertension in renal disease was clearly recognized by Traube more than 100 years ago [6], hypervolaemia continues to be a therapeutically neglected aspect of the management of the patient with renal failure [7]. From an evolutionary perspective [7], the mammalian kidney has evolved to conserve rather than excrete sodium. Sodium excretory capacity is reduced even early on in renal disease [9]. A rational concept to explain the overriding role of the kidney in the long-term setting of blood pressure has been provided by Guyton [10]. He postulated a sequence of pathogenetic mechanisms through which hypervolaemia may increase blood pressure, i.e. by increasing venous return and cardiac output and thus creating a hypervascular state with increased tissue perfusion. In the long run, he postulated, tissue overperfusion would be limited by autoregulation (Figure 1). Ample documentation of expanded exchangeable sodium and increased plasma volume has been provided in early and advanced renal failure [11,12].

Sodium retention
   ↓
Plasma + ECV volume
   ↓
Cardiac output ↑→ blood pressure ↑
   ↓
Autoregulation
   ↓
Peripheral resistance ↑

Fig. 1. Relation between sodium retention and blood pressure elevation, modified after Guyton [10].

What is the evidence that hypertension is related to sodium? A convincing demonstration was provided by Koomans et al. [13] who showed that blood volume (Figure 2a) and mean arterial blood pressure (Figure 2b) increased with increasing extracellular fluid expansion in patients with renal failure. Whilst excessive sodium is therefore a necessary condition for hypertension, the question arises whether it is also a sufficient condition. In another study by Koomans et al. [14], patients with advanced renal failure (CCr approximately 10 ml/min) and healthy controls were equilibrated on 20 and 120 mmol/day sodium. While blood pressure increased markedly in the former individuals (Figure 3a), it failed to do so in the latter even at substantially greater sodium intakes (Figure 3b). Such extremely high sodium intakes were chosen in order to compare patients and controls at similar daily sodium loads per unit GFR. It is obvious, then, that sodium

![Graph](a)

![Graph](b)

Fig. 2. Relation between mean arterial blood pressure (a) and blood volume (b) and extracellular fluid volume (per kg lean body mass) in patients with nephrotic syndrome (---) and renal failure (—). Note the marked increase of blood pressure with increasing extracellular volume in patients with renal failure as opposed to nephrotic syndrome [13].
is necessary, but it causes greater hypertension in renal patients than in control subjects, leading to the conclusion that hypertensive renal patients are particularly susceptible to sodium loads and to hypervolaemia. This may explain the observation that hypertension in patients with preterminal renal failure is observed even on normal sodium intake [16].

Why is it that patients are so sensitive to sodium loads? Logical explanations would be: (i) altered vascular structure with elevated vascular resistance; (ii) inappropriate activity of (or inappropriate suppression during volume expansion of) pressor systems; or (iii) a combination of these two possibilities. Indeed, an abnormal relation between exchangeable sodium and the circulating renin system was noted by Beretta-Piccoli et al. [11], who found an elevated sodium-renin product in patients with renal failure. That normotensive and hypertensive patients do not differ by their degrees of hypervolaemia, but by different levels in total peripheral vascular resistance, was documented by Kim et al. [17]. Both normotensive and hypertensive haemodialysed patients had a high cardiac index (4.55 ± 1.05 vs 4.39 ± 0.14 l/min/m²), while total peripheral resistance index (TPRI) was substantially greater in hypertensive (2.703 ± 120 s/cm⁻⁵/m²) compared to normotensive patients (1670 ± 61). The reasons for such inappropriate elevation of peripheral vascular resistance are unclear. An acute increase in blood volume in animals causes an initial decrease in vascular resistance [18], while chronically an increase in resistance is noted [19]. It appears that in the short term blood pressure is regulated at the expense of increased cardiac output, while in the long term cardiac output normalizes, but at the expense of increased vascular resistance via some kind of 'autoregulation' as postulated by Guyton [10]. The relative roles of (i) blood flow autoregulation independent of reflex control (Baylis effect), (ii) endothelium-independent, pressure-dependent myogenic regulation via opening of non-specific cation channels and (iii) flow-dependent regulation causing vasodilatation by endothelium-dependent mechanisms through generation of NO, as well as their quantitative interactions, are currently unclear [18]. The role of flow-dependent dilatation in renal failure has not yet been investigated, but would be a prime candidate for inappropriately low degree of vasodilatation [18].

It has been postulated that plasma renin activity in renal patients is not appropriately suppressed by sodium loads [20,21], although this has not been consistently noted in all studies [14]. Furthermore, inappropriately elevated sympathetic activity is well documented [22]. In view of these observations, it appears appropriate to briefly review what is known about these and other mechanisms that may potentially cause an inappropriate elevation of peripheral vascular resistance.

Role of the renin-angiotensin system

Early studies showed inappropriate plasma renin activity (PRA) relative to exchangeable sodium space, indicated by an increased renin × sodium product [11], and evidence for blunted suppression of PRA by sodium [20,21]. The following observations suggest an important role of excessive renin secretion in relation to the state of sodium/volume balance, implying that in the presence of elevated exchangeable sodium even normal PRA may be inappropriate. When this procedure was still carried out, bilateral nephrectomy normalized blood pressure in haemodialysed patients with hyper-reninaemia and volume-resistant hypertension [23]. Blood pressure can now be reduced in many of these patients by the administration of angiotensin-converting enzyme (ACE) inhibitors.

Inappropriate activation of the renin system can be noted early on in renal disease; an example is autosomal dominant polycystic kidney disease (ADPKD) [24]. In patients with ADPKD, immunohistological investigation shows positive staining for renin outside of the juxtaglomerular apparatus [25]. Tubulocystic endothelium was shown to synthesize renin [26]. Postcaptopril PRA was higher in patients with ADPKD (Figure 4) than in pressure-matched

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<th>Table 2. Characteristics of ADPKD patients (from [29])</th>
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<tr>
<td>Age (years)</td>
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<td>SBP (mmHg)</td>
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<tr>
<td>DBP (mmHg)</td>
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<tr>
<td>GFR (ml/min/1.73 m²)</td>
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<tr>
<td>RPF (ml/min/1.73 m²)</td>
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<tr>
<td>Sodium ex (mmol/kg)</td>
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<tr>
<td>Plasma vol. (ml/kg)</td>
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<td>Renin act. (µU/ml)</td>
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Fig. 4. Comparison of PRA in patients with ADPKD and hypertension and patients with essential hypertension matched for blood pressure [27].

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Blood pressure regulation in uraemia [27]. It is therefore not surprising that reversible acute renal failure may occur after ACE inhibitors in patients with ADPKD [28].

Table 2 illustrates the higher blood pressure, lower renal plasma flow, increased exchangeable sodium and inappropriately increased renin activity even in young individuals with ADPKD at normal GFR [29].

Why is the circulating renin system activated? It is obvious that ectopic synthesis of renin [25,26] may be one cause; renal ischaemia and activation of the intra-renal baroreceptor mechanism may be another, since Weidmann et al. [30] noted higher PRA in patients with vascular renal disease. In 1980, Guyton [31] pointed to the potential importance of patchy areas of ischaemia in the kidney. Such areas in effect would produce a 'two kidney' type of Goldblatt hypertension. He reasoned that arterial pressure in the ischaemic areas could never rise enough to provide normal glomerular pressure and filtration, so that these areas would continue to secrete renin indefinitely and expose the residual kidney to high pressures and high circulating renin.

It also deserves mentioning that it is not only circulating renin which is elevated; Kuczera et al., using the perfused hindlimb preparation of subtotally nephrectomized rats, provided evidence for increased activity of the local RAS in the vascular wall as well [32].

Role of adrenergic activity

In the past, elevated noradrenaline in patients with renal failure was described by several authors [33,34], but the interpretation of these findings was uncertain, amongst other reasons because catecholamine reuptake is reduced in renal failure. More recently, more solid evidence for sympathetic overactivity has been produced [22]. Anti-adrenergic agents are very effective in the treatment of hypertension of renal patients. This was shown by Schohn et al. [35]. They examined the effects of adrenergic blockade by debrisoquine on blood pressure in haemodialysis patients (Figure 5). In contrast to healthy controls, debrisoquine reduced supine, and more markedly upright, blood pressure in normotensive as well as hypertensive dialysis patients. The important influence of autonomic factors in the genesis of hypertension of renal failure was also illustrated by the observation of McGrath et al. [36], who noted a substantial decrease in blood pressure upon total autonomic blockade. The vascular reactivity to noradrenaline in renal failure is somewhat difficult to assess. Some experimental [37] and clinical [38] observations provided evidence for diminished alpha-adrenergic responsiveness, while other studies argue for increased responsiveness [35]. The most solid documentation for sympathetic overactivity has been provided by direct microneurographic recording of sympathetic nerve activity in dialysed patients [39]. Increased reactivity was shown using microelectrode recordings of post-ganglionic sympathetic action potentials in the peroneal nerves of chronic haemodialysis patients. In uraemic patients who had their kidneys left in situ, activity was higher than in control

![Fig. 5. Effect of adrenergic blockade by debrisoquine on supine and upright blood pressure in dialysis patients [35].](image_url1)

![Fig. 6. Blood pressure in 5/6 nephrectomized rats (with chronic renal failure) is significantly attenuated by dorsal rhizotomy [41].](image_url2)
subjects, while overactivity was no longer demonstrable in individuals who had been subjected to bilateral nephrectomy. This points to the kidney as the source of excitatory afferent signals.

There is indeed strong experimental evidence for this notion. In subtotally nephrectomized rats Bigazzi et al. [40] studied noradrenaline turnover in the posterior hypothalamic nuclei and in the locus coeruleus. Significant elevation was found compared to controls. The microinjection of 6(OH) dopamine into the posterior hypothalamic nuclei of uraemic rats normalized blood pressure. Furthermore, dorsal rhizotomy in 5/6 nephrectomized rats attenuated hypertension [41], as shown in Figure 6. The nature of the afferent signal, i.e. whether it results from stimulation of intrarenal baroreceptors or chemoreceptors, is currently unclear. These findings are of considerable interest because they help to explain in retrospect why sympathoplegic agents, e.g. clonidine, are so markedly effective in lowering blood pressure of renal patients.

Potential role of renal vasodilators

Following the early observation of Grollman et al. [42], hypertension after bilateral nephrectomy has been ascribed to loss of renal vasodilators. A series of elegant studies by Muirhead led to the concept that renal vasodilators, chemically characterized as lipids and designated as 'medullipin', played an important role in blood pressure regulation, as recently reviewed by Cowley [43]. More recent studies provide convincing evidence that the vasodilator substance is released from the kidney, not only after unclipping of a stenosed kidney [44], but also during modulation of renal perfusion pressure within the 'physiological' range [45]. On the other hand, an impressive relation was found between renal papillary flow, renal interstitial pressure and systemic blood pressure. Elective chronic infusion of captopril into the medullary interstitial space caused a sustained increase of medullary blood flow and a reduction of arterial pressure [46]. Conversely, chronic medullary infusion of L-NAME, an inhibitor of NO synthase, selectively reduced medullary blood flow and caused sustained systemic hypertension (Figure 7).

Based on these and other observations, Cowley [43] proposed the hypothesis that a feedback control mechanism exists which links systemic blood pressure and medullary flow. An increase of blood pressure (or hormonally mediated increase of medullary blood flow) increases interstitial fluid pressure and stimulates secretion of a principle (medullipin), which after further transformation acts as a vasodilator. This agent is thought to cause natriuresis and vasodilatation with lowering of arterial pressure, thus completing a feedback circle.

It is difficult to be dogmatic about this concept, while chemical isolation of the active principle has not been achieved. The clinical relevance is also not yet apparent. Nevertheless, in contrast to previous opinion that non-glomerular renal disease caused less hypertension, Küster and Ritz [48] noted that analgesic abusers with papillary necrosis had an excessive prevalence of hypertension even in the presence of normal GFR. This clinical observation may point to an important role of the renal papillae in blood pressure regulation of renal patients.

Novel effector mechanisms potentially related to blood pressure control in renal failure

Synthesis of, or response to, a number of vasopressor or vasodilator agonists may be altered in renal failure. relatively little is known concerning the vasodilator kallikrein system in renal failure, while even an increase in the synthesis of the vasodilator prostaglandin PGI₂ has been documented [49]. There is considerable controversy concerning circulating endothelin concentra-
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NO synthesis has been reported [60]. Such divergences late in renal failure [59]. In one system, even enhanced the fact that other guanidino compounds also accumu-

best. The situation is rendered complex, however, by account for only some of the inhibitory activity at

reduced after haemodialysis, but ADMA concentration renal failure were inhibitory on cellular test systems

This was not fully confirmed by other authors [57], concentrations, in the uM range, in dialysed patients

arginine (ADMA), an endogenous inhibitor of NO many but not all plasma

synthesis, accumulates in chronic renal failure [56]. Vallance et al. [58] demonstrated by Arese [57]. Many but not all plasma

arginine-derived substance with insulin-like activity [52] and more recently clonidine-like action on imida-
zoline receptors. Renal synthesis of this blood pressure-

lowering agent has been demonstrated by Morrisey et al. [53]. An obvious question is whether production of agmatin becomes insufficient in uraemia. One might speculate whether L-arginine deficiency will cause not only low production of NO, but also of agmatin. Of interest in view of potential inhibition of NO synthesis in uraemia (see below) is the idea that inhibition of NO synthase may shift substrate, i.e. L-arginine, to agmatin production. Currently there is no evidence for such a scheme.

Recently, adrenomedullin has been identified, which has some homology with the calcitonin-gene related peptide (CGRP), a potent hypertensive peptide. Adrenomedullin in itself is a potent vasodilator, the concentrations of which are increased in renal failure [54]. It is unknown whether this is a compensatory reaction. It is of some interest that adrenomedullin is a natriuretic peptide, which is localized in the kidney by immunohistochemical techniques and by demonstration of its mRNA [55]. The role of adrenomedullin in blood pressure regulation of renal failure remains to be resolved.

Much interest has focused on the observation of Vallance et al. [56] that asymmetrical dimethyl-L-arginine (ADMA), an endogenous inhibitor of NO synthesis, accumulates in chronic renal failure [56]. This was not fully confirmed by other authors [57], but our recent studies using different methodology show, not striking, but definitely elevated ADMA concentrations, in the μM range, in dialysed patients (Rambausek et al., in preparation). Rather complex regulation of NO synthesis in uraemia was demonstrated by Arese et al. [58]. Many but not all plasma samples from patients with moderate and terminal renal failure were inhibitory on cellular test systems with various NOS isoenzymes. Inhibitory activity was reduced after haemodialysis, but ADMA concentration accounted for only some of the inhibitory activity at best. The situation is rendered complex, however, by the fact that other guanidino compounds also accumulate in renal failure [59]. In one system, even enhanced NO synthesis has been reported [60]. Such divergences are almost certainly caused by different methodologies and use of different test systems. We have recently also speculated that high cardiovascular mortality in mal-nourished dialysis patients may be related to limited availability, not necessarily in the circulation, of L-arginine, the effect of which may be amplified in the presence of competitive inhibitors [61].

It has become increasingly clear that the altered kinetics of the Na⁺/H⁺ exchange is an important step in the genesis of essential hypertension. G-protein-

controlled abnormalities of exchange kinetics are probably genetically programmed, since they can be perpetuated in immortalized blood cells of patients with genetic hypertension [62]. In this context it is of note that metabolic acidosis also modified the activity of the Na⁺/H⁺ exchanger. Whether this is of relevance for blood pressure control remains to be seen.

Conclusions

The well-documented link between blood pressure and patient survival suggests that the need to strictly nor-

malize blood pressure in the dialysed patient is considerably more important than was perceived in the past [3–5]. Despite much recent progress, the mechanisms leading to elevated blood pressure in terminal renal failure have not been completely clarified. Nevertheless, insight into the overriding role of hypervolaemia [7] as well as more clear understanding of the contributory roles of activated pressor systems [16,39] provide a rationale for pharmacological intervention at the level of the RAS and sympathetic system.

However, it is necessary to point to some glaring gaps in our current state of knowledge. What is the role of structural alterations in the vessel wall of resistance arteries [64] and what are the haemodynamic consequences of altered compliance of elastic arteries [65] in renal patients, and more importantly what are the consequences for patient management? It is obvious that volume-independent factors are operative in the renal patient, since an increase in blood pressure in the interdialytic interval is noted even when volume is rigorously controlled [66]. Although direct measures-

ments are not available, we doubt whether the superb clinical results of Charra et al. [4] can only be explained by slow volume reduction and maintenance of a state of low exchangeable sodium. As scientists we should also pursue less obvious alternative possibilities, e.g. are pressor substances (e.g. ADMA) more effectively cleared during prolonged dialysis? Does a state of chronic relative hypervolaemia promote some type of autonephrectomy with diminished intrarenal genera-

tion of sympathico-excitatory signals? It is certain that resolution of these and other questions will keep nephrologists busy for the years to come.

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