Volume Is Not the Only Key to Hypertension Control in Dialysis Patients

Aghogho Odudu^{a, b} Christopher McIntyre^{a, b}

^aDepartment of Renal Medicine, Derby Hospitals NHS Foundation Trust, Derby, and ^bGraduate Entry Medical School, University of Nottingham, Nottingham, UK

Key Words

Haemodialysis • Hypertension • Volume expansion • Peritoneal dialysis • Sodium

Abstract

There is a widely held belief that hypervolaemia due to excess intake or inadequate removal of salt and water is the principal cause of hypertension in dialysis patients. The risk of failing to consider additional pathophysiological elements is that inadequate or inappropriate therapeutic strategies may be adopted. This review aims to highlight multiple alternative mechanisms for hypertension in this setting along with the risks of probing for normotension by empirical dry weight reduction if dry weight is imprecisely defined.

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Introduction – Hydration Status and Empirical Association with Blood Pressure

There is a high prevalence of hypertension in end-stage renal disease (ESRD) with estimates from 25 to 80%. The cause of this has been principally attributed to loss of renal regulation of salt and water excretion leading to extracellular volume overload with consequent adverse cardiac remodelling [1, 2]. As such, the principle approach is to use a combination of ultrafiltration by dialysis to dry weight and antihypertensive therapy to control blood pressure (BP). There is a strong and linear risk association

of BP to cardiovascular morbidity in the general population with the risk reduced by drug therapy. In ESRD, the relationship of risk with hypertension is fundamentally more complicated. Large observational studies of haemodialysis (HD) patients consistently show a J- or U-shaped association, with a paradoxical survival advantage in hypertensive patients and the highest mortality in hypotensive patients after multivariable adjustment [3]. Based on these data some have cautioned against using drug therapy to lower BP in hypertensive dialysis patients. Detailed discussion of this controversy is beyond the scope of this review. However, meta-analyses suggested benefit of drug therapy, but the heterogeneity of the trials did not allow the benefit to be isolated to a particular class nor could the interaction with volume status be examined [4].

The existence of overhydration in hypertensive dialysis patients is far from universal. Wabel et al., measured pre-dialysis systolic BP and fluid status by bioimpedance in 500 HD patients compared to a matched healthy population [5]. Only 15% of patients fitted the stereotype of overhydration with hypertension. 13% of patients had hypertension despite underhydration and 10% had overhydration despite normal or low BP. Similar findings were seen in another study using the same methodology in 639 patients using peritoneal dialysis (PD) [6]. These studies highlight that although physicians often estimate hydration status by BP, the two factors are often dissociated in the setting of the physiological derangements characteristic of ESRD. A wide variety of pathophysiological mechanisms may contribute to this dissociation.

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Christopher McIntyre
Department of Renal Medicine, Derby Hospital NHS Foundation Trust
Uttoxeter Road
Derby DE22 3NE (UK)
Tel. +44 133 278 9344, E-Mail aghogho.odudu@nhs.net

Overactivity of the Renin-Angiotensin System

Despite losing renal excretory function, dialysis patients have inappropriately high renin levels relative to their salt and volume status [7]. A subgroup of patients with volume-independent hypertension do not respond to salt or volume removal but are sensitive to ACE inhibitors [7]. This subgroup can have hypertension despite low volume.

Increased Arterial Stiffness

Arterial stiffness resulting from calcifying or non-calcifying alterations in the arterial wall is a characteristic consequence of advanced kidney disease. Blacher et al. [8] performed a study of 241 patients, divided into 3 groups depending on the degree of central arterial stiffness determined by pulse wave velocity. After 6 years of follow-up, those with the greatest stiffness had the highest mortality and this was more prognostic than age or BP. Our group assessed the relationship of vascular calcification to arterial stiffness and its progression with time in 134 patients (60 on HD, 28 on PD, 46 with stage 4 CKD) assessed at baseline and 2 years by femoral artery computed tomography and pulse wave velocity. We showed increased arterial stiffness correlated with vascular calcification and increased with progressive stage of CKD. Vascular calcification was strongly predictive of death, being present in 20 of the 21 patients who died. This was highly correlated with decreasing diastolic BP and increasing pulse pressure [9]. In this setting, the principal driver of hypertension is not overhydration but a reduction in arterial compliance. This allows hypertension to occur despite normal hydration or underhydration. Arterial stiffness will also further aggravate hypertension in those with overhydration.

Advanced Glycation End Product Tissue Deposition

A relatively novel risk factor in increasing arterial stiffness is the formation and tissue deposition of advanced glycation end products (AGEs). These heterogeneous compounds were classically described as end products of a complex non-enzymatic reaction between glucose and proteins with a long half-life such as collagen. It is now known that AGEs accumulate by a variety of non-glucose-mediated methods including ingested processed food, hyperlipidaemia, oxidative stress, carbonyl stress

and reduced renal clearance. AGE formation has therefore been proposed to be a direct result of cumulative metabolic stress [10]. AGE accumulation causes cross-linking of collagen fibres directly increasing arterial stiffness. AGE levels are markedly increased in dialysis patients and predictive of mortality [10]. This may be as a result of reduced arterial compliance and increased endothelial dysfunction.

The Lag Phenomenon and Buffering of Water-Free Sodium

The Tassin group coined the term 'lag phenomenon' to explain a well-described time delay between normalization of extracellular volume in HD patients by ultrafiltration and a sustained further reduction in BP. This lag lasted several months, highlighting a dissociation between hypertension and hydration state [11]. The explanation for this may be linked to Jens Titze's work showing that large amounts of sodium can be buffered in the interstitial space without commensurate water retention [12]. Accumulation within resistance vessels may also contribute to increased tonic vasoconstriction, further favouring the development of hypertension. This extension to the traditional model of fluid homeostasis is supported by data showing that sodium is proinflammatory and is capable of direct adverse cardiovascular consequences independent of its effect on BP [12, 13].

The Role of Hyperglycaemia in Determining Extracellular Volume

Hyperglycaemia may be another factor in the dissociation of BP and hydration status. Patients with diabetes ingest water as a result of glucose-driven hypertonicity. Ramdeen et al. [14] performed a one-year balance study in 9 diabetic and 7 non-diabetic HD patients. This demonstrated sodium intake with commensurate water retention accounted for the entire inter-dialytic fluid gains in non-diabetic patients but only half the fluid gains in diabetic patients. The other half was pure water intake presumably driven by hyperglycaemia. In this setting, free water ingestion is not being driven by the conventional salt and water paradigm, and overhydration may even occur without hypertension.

Acute hyperglycaemia and hyperinsulinaemia can directly cause hypertension via vasopressor effects [15]. We have previously demonstrated that PD exchanges with

hypertonic glucose-based dialysate causes sustained hyperglycaemia and hyperinsulinaemia with resultant hypertension in both the fed and starved state [16]. In this setting, hypertension can occur despite the dehydrating effect of peritoneal ultrafiltration and is abrogated by the use of glucose-sparing dialysate.

Perils of Probing for Normotension by Empirical Dry Weight Reduction

There are inherent difficulties in using volume control to achieve normal BP and dry weight. Firstly, the component or timing of BP to target is not clear. Secondly, dry weight is empirically and imprecisely defined. Overhydration should be assiduously avoided, but we must also aim to achieve dry weight without causing underhydration and dialysis-related haemodynamic instability. Agarwal [17] studied 326 HD patients for a mean of 32 months and showed that home-monitored systolic BP was strongly associated with mortality, whilst diastolic BP and BP taken on the dialysis unit had no prognostic value. There was a bimodal distribution with the lowest mortality at systolic BP 110–130 mm Hg and highest mortality in both hypotensive and hypertensive patients. Furthermore, a significant portion of dialysis patients have attenuated diurnal variation in BP and it is speculated that this may mediate enhanced cardiovascular risk [18]. These data are concordant with Agarwal's finding that home-measured and ambulatory BP is the most useful guide to treatment.

Systemic Circulatory Stress and Cardiac Injury

Dialysis patients are uniquely susceptible to demand myocardial ischaemia. Their greater arterial stiffness means systolic pulse waves are more likely to be reflected from the periphery during diastole, shortening coronary filling time. In this way, arterial stiffness lowers the ischaemic threshold allowing myocardial ischaemia to occur even in the absence of large vessel coronary artery disease. This reduced coronary flow reserve is well described in dialysis patients [19]. To that end, it is unsurprising that lower diastolic BP is associated with greater vascular calcification, arterial stiffness and mortality in this setting [8, 9]. Dialysis patients also have endothelial dysfunction and impaired autoregulation of BP leaving the heart less able to buffer volume changes during HD. We performed a study demonstrating HD patients with the least barore-

flex sensitivity were more likely to have intradialytic hypotension [20]. Our proof-of-concept study in HD patients who had recent normal coronary angiography demonstrated that HD was characterised by a 30% global reduction in myocardial blood flow using the gold standard of $H_2^{15}O$ positron emission tomography [21]. The ischaemic segments matched segmental regional wall motion abnormalities (RWMA) identified by simultaneous 2-D echocardiography at peak stress (225 min into an HD session) compared to before HD [21]. This supported the use of stress RWMA by echocardiography as a surrogate measure of myocardial ischaemia as it was a feasible imaging modality for larger numbers of patients. Our subsequent natural history study in 70 prevalent HD patients showed that compared to pre-HD echocardiography, new RWMA developed at peak stress in 45/70 participants, and this associated with 20% mortality and 13% reduction in mean left ventricular ejection fraction after 1 year [22]. All segmental RWMA in the 36/45 survivors persisted at follow-up. In the cohort who had no abnormal segments at the start of the study, new segmental RWMA had developed. Multivariable regression analysis identified significant determinants of these stress RWMA as age, ultrafiltration volume, severity of intradialytic hypotension and serum troponin T concentration, displacing traditional risk variables including diabetes status and history of ischaemic heart disease [22]. In short, the RWMA characterise those who suffer ischaemia due to the haemodynamic stress of HD, and this might be limited by alternative strategies such as longer or more frequent HD.

Potential Risks of Overshooting Dry Weight in Other Vascular Beds

Probing for dry weight may also be at the risk of underperfusing other vascular beds including those of the kidney, gut and brain. Although it might seem counter-intuitive to be concerned about renal perfusion in a dialysis patient, it is well recognised that maintenance of residual renal function confers a survival advantage and improves volume control. Günel et al. [23] targeted normal BP as a surrogate for normal volume status in 78 PD patients by increasing ultrafiltration volumes with 3.86% glucose dialysate and salt restriction. They showed an impressive reduction in BP to a normotensive range at the expense of a 28% decrease in urine volume in the 19 patients with significant residual renal function. The gut is also an important vascular bed, extracting 25% of resting

cardiac output to maintain nutrition. 70% of gut bacteria possess profoundly proinflammatory and cardiotoxic endotoxin. In health, protection from endotoxin is afforded by energy-dependent tight junctions in the gut wall. Endotoxin translocation across leaking tight junctions in disease states with aberrant perfusion such as advanced heart failure and septic shock is well described in the study by Charalambous et al. [24]. We hypothesised that dialysis might also lead to aberrant gut perfusion and endotoxaemia and performed a study in 249 subjects without heart failure across the spectrum of CKD. Serum endotoxin levels were 1,000 times greater in HD patients compared to non-CKD patients, with a four-fold increase between pre-dialysis CKD stage 5 and commencing HD or PD [25]. These elevated levels correlated with intradialytic hypotension, systemic inflammation, and troponin T levels. Whether dialysis-associated endotoxaemia is a culprit or bystander in the pathophysiology of inflammation, malnutrition and adverse cardiovascular outcomes in this setting is subject to current studies. We have further proposed and are investigating the hypothesis that the cerebral microcirculation is also sensitive to dialysis-induced circulatory stress potentially explaining specific patterns of brain injury highly prevalent in the dialysis setting [26].

Optimising Hydration State without Jeopardy to Critical Vascular Beds

The frequent risk of dialysis-related hypoperfusion is due to imprecision in the assessment of dry weight. If dry weight could be accurately, reliably and practicably determined, then we would not have to resort to probing for this by trial and error with the risks we have outlined. A detailed review of practical technologies that assist in optimising hydration is beyond the scope of this review, but perhaps the most promising is bioimpedance analysis. This measures resistance which is proportional to tissue water and reactance which is proportional to cell mass, providing an index of body composition which can be longitudinally monitored. The difficulty arises in converting this measure of relative hydration into absolute volumes of fluid as this requires algorithms using assumptions from studies of healthy volunteers that perform poorly when applied to populations with disordered hydration. We conducted a study showing the added value of combining the relative hydration data from bioimpedance with the absolute hydration data using a novel deuterium breath-test by portable mass spectrometer.

This highlighted that higher co-morbidity scores led to increasing underestimation of extracellular volume by bioimpedance [27]. Recently, two novel approaches to quantify excess hydration by bioimpedance have been proposed. Assessment of continuous intradialytic calf bioimpedance ratios does not rely on geometric assumptions or comparison to population averages typical of whole-body methods [24]. Chamney et al. [28] proposed a three-compartment physiological tissue model allowing quantification of excess fluid compared to normal controls. Whilst requiring a population reference standard, the unique separation of extracellular volume into that due to excess and normal hydration is an important conceptual advance and has been shown to be of prognostic value in predicting mortality in a HD population [29]. Macheek et al. [30] used this new approach to perform bioimpedance-guided prescription of dry weight in 52 HD patients. They showed that not only did this assist in dealing with hypertension in the overhydrated, but it enabled a 73% reduction in intradialytic adverse events by increasing the target weight in the underhydrated group. These preliminary data are promising, but whether this will be of a discernible long-term value requires studies randomising clinicians to be blinded or have access to bioimpedance data, and such studies have commenced (ISRCTN 95439739).

Conclusion

In summary, overhydration does not always equate to hypertension. Factors such as arterial stiffness, high renin states, the osmotic effects of glucose and the non-osmotic effects of sodium lead to a complex interplay. We have delineated some of the risks inherent in using a BP-dominated definition of dry weight. Bioimpedance techniques show promise in assisting with a precise determination of hydration status allowing clinicians to control volume and BP without jeopardising short- or long-term perfusion to critical vascular beds.

Disclosure Statement

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