Sodium, volume and pressure control in haemodialysis patients for improved cardiovascular outcomes

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ABSTRACT

Chronic volume overload is pervasive in patients on chronic haemodialysis and substantially increases the risk of cardiovascular death. The rediscovery of the three-compartment model in sodium metabolism revolutionizes our understanding of sodium (patho-)physiology and is an effect modifier that still needs to be understood in the context of hypertension and end-stage kidney disease. Assessment of fluid overload in haemodialysis patients is central yet difficult to achieve, because traditional clinical signs of volume overload lack sensitivity and specificity. The highest all-cause mortality risk may be found in haemodialysis patients presenting with high fluid overload but low blood pressure before haemodialysis treatment. The second highest risk may be found in patients with both high blood pressure and fluid overload, while high blood pressure but normal fluid overload may only relate to moderate risk. Optimization of fluid overload in haemodialysis patients should be guided by combining the traditional clinical evaluation with objective measurements such as bioimpedance spectroscopy in assessing the risk of fluid overload. To overcome the tide of extracellular fluid, the concept of time-averaged fluid overload during the interdialytic period has been established and requires possible readjustment of a negative target post-dialysis weight. ^{23}Na-magnetic resonance imaging studies will help to quantitate sodium accumulation and keep prescribed haemodialytic sodium mass balance on the radar. Cluster-randomization trials (e.g. on sodium removal) are underway to improve our therapeutic approach to cardioprotective haemodialysis management.

Keywords: bio-impedance spectroscopy, cardiovascular disease, haemodialysis, sodium metabolism, time-averaged fluid overload

INTRODUCTION

Haemodialysis (HD) is a life-saving treatment, although patient survival is poor. Rates of death are substantially higher than in the general population and at least 50% of patients die due to cardiovascular disease [1–3]. The unique nature of cardiovascular disease in chronic kidney disease Stage 5 dialysis (CKD5D) patients is illustrated by the prevalence of left ventricular remodelling leading to stiffening and failure [4]. A major aetiological driver of this pathway appears to be sodium (Na+) and fluid retention [5, 6]. Yet, achieving adequate volume and blood pressure (BP) control often remains an unmet need in this highly vulnerable population [7–9]. Several reasons are commonly proposed to explain this fact that include short treatment time schedule [9, 10], poor reliability in clinical fluid assessment [11, 12], difficulty in restoring extracellular fluid (ECF) volume by dialysis [13], poor salt diet observance [14] and loss of residual kidney function [15].

Optimal fluid volume and BP control in dialysis patients is an essential component of dialysis adequacy. Yet, the intermittency of treatment creates an 'unphysiological profile' and challenging clinical condition exposing patients to up (interdialytic period) and down (intradialytic period) fluid volume changes mirroring a large variability of BP changes [16]. The exposure to cardiocirculatory stress may be double edged, reflected by chronic fluid overload (FO) during the interdialytic period or by acute fluid depletion during the intradialytic period. The intensity of cardiac stress is directly related to fluid volume changes and time exposure within these different periods. Fluid removal rates >10–13 mL/h/kg are associated with increased mortality [17–19] and fluid removal 'toxicity' seems to even start much earlier, at >6–7 mL/h/kg [20, 21].

In this context, treatment time must be recognized as a significant disease modifier of cardiocirculatory stress leading to end-organ damage via repetitive subclinical ischaemic insults, e.g. cardiac stunning, cerebral white matter injury and gut ischaemia [22].

The rediscovery of a kidney-independent reservoir and third salt-storage glycose-aminoglycan-related skin compartment demands readjustment of the concept that Na+ haemostasis depends solely on the kidney's crucial function to regulate volume and BP by renal pressure–natriuresis.

Water-free stored Na+, so-called osmotically inactive tissue Na+, must be differentiated from osmotically and haemodynamically active Na+, both of which may contribute to systemic toxicity via local tissue and organ damage [23].

Given the lack of Na+ homoeostasis and dependence on HD for Na+ removal, it seems likely that CKD5D patients are more susceptible to this form of Na+ accumulation, leading to Na+ toxicity, and their resultant adverse effects.

Managing Na+ imbalance in CKD5D patients requires innovative approaches to assess Na+ excess in the body and HD management that adequately restores salt and water homoeostasis [23]. In this article, we propose a comprehensive vision of Na+, fluid and pressure management in CKD5D patients, which may have strong potential for reducing cardiac burden.

HUMAN SODIUM HOMOEOSTASIS AND IMPAIRED SODIUM METABOLISM

Total body Na+ is a critical determinant of extracellular volume, plasma volume and BP [24, 25].

Healthy persons in the steady state balance Na+ homoeostasis through dietary intake and urinary output of Na+ [26].

In 1958, Strauss et al. first put forward the concept of a Na+ set point to uphold this balance [27]. A person who was in balance on a low salt diet, when given even a trace amount of sodium chloride (NaCl), promptly excreted that amount [27, 28]. When, in contrast, the total amount of Na+ in his body was reduced further by a diuretic, and balance on a low Na+ intake was achieved, his response to an increment of Na+ was dramatically different [27, 28]. He did not excrete the additional NaCl until the amount lost following diuretic administration was replaced [27, 28].

In accordance with experimentally observed variations in plasma Na+, a variable set point regulatory system seems likely [29].

In 1972, Guyton's work illustrated the traditional nephrocentric two-compartment model of Na+ homoeostasis: the ECF volume within the intravascular space being in constant equilibrium with the interstitial space volume while the kidneys regulate the balance between Na+ intake, extracellular and BP [30, 31].

The central feature of the model is the linkage between BP and Na+ balance, where any imbalance between salt intake and excretion leads to a progressive alteration in the filling of the vascular system and thus changes in BP [32].

This in turn alters Na+ excretion, a feature defined as the pressure–natriuresis relationship [32]. A key aspect of this concept is that it puts the kidney at the very centre of long-term BP control. This means that any chronic change in BP must have been accompanied by an alteration in the pressure–natriuresis relationship [32].

In recent years, the two-compartment model has been challenged by two major findings: firstly, clinical observation that on a fixed Na+ diet intake total body Na+ content could exceed weight gain, suggesting that Na+ accumulated without being osmotically active and that salt was stored in a third body compartment [33]. Secondly, availability of measuring tissue Na+ content in skin and muscles using ^{23}Na-magnetic resonance imaging (sodium-MRI) [34]. The traditional physiological concept placing the kidney as key player of the regulation of extracellular volume and BP homoeostasis has been challenged by the group of Titze et al. after studying a group of astronauts simulating a long-term flight to Mars [33]. In this closed environment, Titze et al. were able to quantify very precisely Na+ mass balance under stepwise fixed salt diet regimes. While salt intake was fixed, they noticed large variations in urinary Na+ excretion, and also changes in total body Na+ exhibited rhythmic fluctuations within a day, which were not associated with parallel changes in body weight or extracellular water. Interestingly, these Na+ variations correlated positively with urinary aldosterone excretion and inversely to urinary cortisol. The most striking finding finally was that total body Na+ content exceeded weight gain, suggesting that Na+ had accumulated in another compartment that is not osmotically active. Skin and skeletal muscle represent the body's major Na+ ECF compartment without concomitant water accumulation (free-water Na+), bound to negatively charged glycosaminoglycan (GAG) [35–37]. Osmotically inactive skin Na+ can be mobilized by salt deprivation (e.g. salt diet restriction) and depletion (e.g. dialysis), which induces a reduction of the negatively charged skin GAG content [33]. Conversely, dietary salt loading is associated with an increased synthesis of negatively charged GAG in the skin. These observations suggest that the storage of osmotically inactive Na+ in the skin is an active process. Skin Na+ is stored directly under the keratinocyte layer in a microenvironment that is hypertonic to plasma. The skin phagocytes sense the hypertonic accumulation of Na+ in the skin leading to activation of tonicity-responsive enhancer-binding proteins, the secretion of vascular endothelial growth factors (VEGF-C) and a local modulation of the capillary lymphatic system in the skin [38].

Hence, lymphatics may control how much Na+ is released to the blood from the tissue store and thereby the amount the kidney 'sees' [39].

Taken together, observations of salt storage in the skin to buffer free extracellular Na+ and macrophage modulation of the extracellular matrix and lymphatics suggest that electrolyte homoeostasis in the body is not achieved by renal excretion alone, but also relies on extrarenal regulatory mechanisms involving a kidney-like countercurrent system [40].

Sodium-MRI has been introduced as a feasible diagnostic tool to assess tissue Na+ content in patients with kidney disease.

The skin Na+ content in 99 patients with mild to moderate CKD was measured by sodium-MRI and could be correlated with the amount of left ventricular mass, proposing that skin Na+ content may play a yet to be defined pathophysiological role, unaffected by BP and total body overhydration [41].

Recently, sodium-MRI was utilized to compare tissue Na+ and its removal in HD and age-matched healthy control patients [42]. Older (>60 years) HD patients showed increased Na+ and water in skin and muscle and lower VEGF-C levels compared with age-matched controls [42]. After HD, patients with low VEGF-C levels had significantly higher skin Na+ content compared with patients with high VEGF-C levels [42]. The finding that tissue Na+ could be rapidly mobilized in response to intravascular volume reduction by HD therapy supports

the idea that an adequate dialysis dose can prevent excess Na+ storage in HD patients [42]. Although the mechanisms by which Na+ is rapidly removed from skin and muscle remain unclear, these data suggest that a pro-lymphangiogenic serum profile does facilitate this process [42].

Quantifying Na+ tissue removal, e.g. with sodium-MRI studies, could improve strategies for managing HD patients. However, it remains unclear whether or not tissue Na+ excess contributes to cardiovascular morbidity or mortality, and whether or not the accumulation of hidden and thus toxic Na+ in kidney failure may be reversible. Prospective trials on the relationship between tissue Na+ content and hard clinical endpoints are required to clarify whether increased Na+ storage is a cardiovascular risk factor and whether reducing skin Na+ content might improve cardiovascular outcomes in these patients.

THE BURDEN OF FLUID OVERLOAD AND CARDIAC DISEASE IN HAEMODIALYSIS

ECF overload is a major factor in morbidity of the HD population. In a prospective study among 176 790 prevalent HD patients, Arneson et al. [43] have reported that, during a 2.5-year follow-up, 14% of the patients required hospital admission for one or more episodes of FO, heart failure or pulmonary oedema necessitating urgent fluid removal. Also, Plantinga et al. [44] have reported from a US cohort including 215 251 prevalent HD patients a 23% rate of readmission during a 30-day period after discharge, 44% of them being related to pulmonary oedema. When pulmonary oedema was the cause of the first admission, then pulmonary oedema represented 70% of the cause of readmission. This suggests that fluid excess may have been inadequately handled when transitioning from the hospital to the dialysis unit. In a report by the Dialysis Outcomes and Practice Patterns Study (DOPPS), Goodkin et al. [45] identified the prevalence of congestive heart failure in, respectively, 46% and 25% of the patients in the USA and in Europe. In the same study, hypertension was present in 83 and 73% of the US and European patients. It may be hypothesized that fluid excess was the major underlying determining factor. Long-term exposure to chronic FO triggers cardiac and vascular remodelling and the development of diastolic dysfunction and chronic heart failure in dialysis patients [46]. ECF excess is present early during the CKD progression as shown by Essig et al. [47], and acts as a continuum all along the CKD progression. These data partly explain the increased prevalence of cardiac events all along the course of CKD [48] and the high prevalence of left ventricular hypertrophy (LVH) and other cardiac abnormalities in incident HD patients. In the Chronic Renal Insufficiency Cohort patients [49], 85% of the incident HD patients had LVH. LVH is an adaptative mechanism to pressure and volume overloads. Initially, LVH allows adequate stroke volume and adapted myocardium energy consumption. Later, the LVH becomes maladaptive, with diminished myocardial capillary density, cardiomyocyte death and fibrosis leading to heart failure [46].

Recently Siriopol et al. [50] confirmed previous findings, reporting an increased risk for cardiovascular mortality in patients with moderate or severe FO and that rapid changes or the variability of fluid status could be of clinical importance.

Zoccali et al. evaluated the relationship between baseline and cumulative FO exposure and mortality over 1 year in 39 566 incident end-stage renal disease (ESRD) patients in a large dialysis network in 26 countries. The magnitude of death risk attributable to chronic FO was comparable with that of coronary artery disease or congestive heart failure per se or an increase in biological age of >12 years [6].

The risk of FO was almost equally strong in hypertensive (≥160 mmHg) and hypotensive (<130 mmHg) patients and such risk also remained substantial in normotensive (130–160 mmHg) patients as defined by pre-dialysis systolic blood pressure (pre-BP) [6].

EuCliD® (European Clinical Data System) is an international electronic health record repository that allows continuous point-of-care data collection of routine clinical practice and lab test information in HD patients from Fresenius Medical Care (FMC) clinics across 20 neighbouring countries across Europe, the Middle East and Asia. Among 31 349 incident (2010–14) chronic HD patients in the EuClid database, Cox models were used to prospectively study the association between FO, pre-BP and all-cause mortality risk, controlling for differences in demographics (age and gender), diabetes, congestive heart failure and body mass index.

We report an inverse relationship between FO, pre-BP and all-cause mortality risk (FMC, unpublished data on file, Figure 1).

As Figure 1 indicates, the highest all-cause mortality risk was found in patients presenting with high FO but low pre-BP. The second highest risk was found with both high pre-BP and FO, while high pre-BP but normal FO related to only moderate risk. This finding, supported by Zoccali et al. [6], described above, points out that neither pre-BP nor FO should be treated as
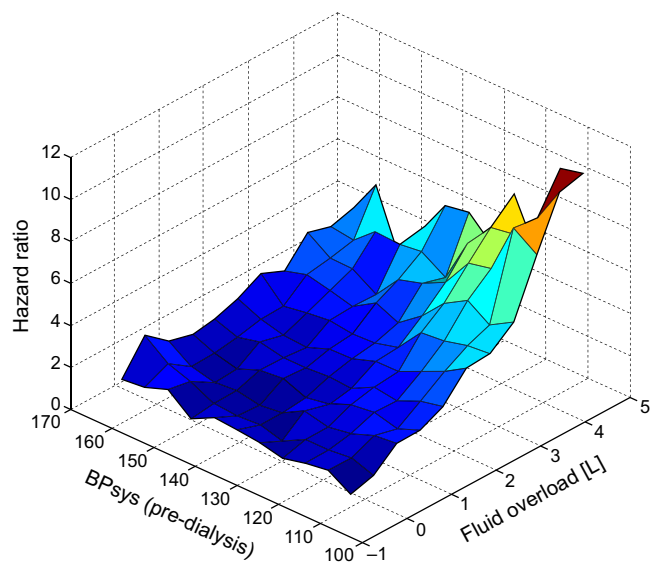
FIGURE 1: All-cause mortality hazard related to pre-dialysis systolic blood pressure (BPsys) and fluid overload in 31 349 incident haemodialysis patients observed over a period of four years from 2010 to 2014. The highest risk is seen for patients with high fluid overload and low blood pressure.

isolated factors, but the combination of both needs to be considered.

Recently, Bansal et al. reported a linear association between higher systolic BP and risk of mortality in HD patients when systolic BP was measured outside of the dialysis unit despite there being a U-shaped association between pre-BP and risk of mortality [51]. This finding indicates that out-of-dialysis-unit systolic BP may be more important, feasible and of value for cardiovascular risk assessment than previously thought [51].

VOLUME MONITORING, AND CLINICAL AND DIAGNOSTIC MANAGEMENT TOOLS

The attempt to achieve proper dry body weight appears to be of paramount importance in HD patients. Ideally, it has been defined as 'the postdialysis body weight that allows normal blood pressure before and at the end of the HD session without antihypertensive medication, without clinical sign of over- or underhydration and despite the interdialytic weight gain (IDWG)' [52, 53].

Yet, target weight determination is frequently based on trial-and-error methods and its correct evaluation is difficult to obtain [11]. Because traditional clinical signs of FO , such as peripheral oedema and lung crackles, lack sensitivity and specificity, and intradialytic hypotension may be blurred by increased ultrafiltration (UF) rate, our clinical judgment in probing for 'dry weight' needs to be complemented by objective measurements [14].

A number of technologies or biomarkers have been proposed, some of which, like the vena cava diameter to measure intravascular volume, have not proven useful in daily routine for a variety of reasons. Other instrumental options, such as intradialytic blood volume monitoring from haematocrit or protein concentration changes to determine plasma refilling from ECF accumulated in the interstitial spaces, are also knowingly limited by confounding factors such as hypoalbuminaemia. More recently, lung echography assessing pulmonary hydration by B-lines (comets) count has been proposed. A recent randomized trial with a lung ultrasound-guided strategy showed no effect of dry-weight reduction on short-term BP variability despite BP decrease [54]. A trial testing the effect of a treatment policy guided by lung ultrasound in high-risk patients on HD, the Lung Water by Ultrasound-Guided Treatment to Prevent Death and Cardiovascular Complications in High-Risk ESKD Patients with Cardiomyopathy, is ongoing (ClinicalTrials.gov Identifier: NCT02310061).

Bioimpedance spectroscopy (BIS) provides measurement of total body and ECF compartments from the analysis of an alternative electric current pathway through tissues at different levels of frequency [55]. The Body Composition Monitor® (BCM Monitor, Fresenius Medical Care, Bad Homburg, Germany) is a multi-frequency bioimpedance device. It provides for each patient a normohydrated target weight from a database of healthy subjects according to age, gender, weight and height. Important datasets relating BCM monitoring to ECF and outcomes allow us to disentangle the respective relationship between mortality and both ECF overload and BP.

It is well-established that correcting FO improves BP control. A pilot intervention trial probing dry weight with BCM compared with conservative clinical assessment found that every 1 L change in pre-dialysis FO was accompanied by a 9.9 mmHg change in systolic pre-BP [56]. Machek et al. [57] demonstrated that correction of severe FO led to improvement in BP and reduced the use of antihypertensive medication by 35%. In addition, correction of previously unrecognized dehydration led to 73% less intradialytic adverse events. In a randomized controlled trial led by Onofriescu et al. [58], BIS-guided dry weight adjustment led to an improvement in both surrogate and hard endpoints in 131 patients. These findings show that objective BIS-guided correction of fluid status can be very beneficial in clinical routine [59, 60].

'Body volume rises between dialysis sessions and falls during treatments, like waves on the ocean. These dialysis tide waves are only part of the total volume status—underlying the waves is the postdialysis volume status, which ranges from volume depletion to overload and can be compared to the level of tide' [53]. Nephrologist stakeholders stress the point that chronic FO (defined as >15% above 'normal' ECF, equivalent to >2.5 L on average), unlike IDWG, exhibits a >2-fold increased mortality risk [53].

A cohort study from 3632 patients in 60 HD centres from four countries demonstrated a significant inverse association between FO and IDWG [53]. HD patients who reached a state of volume depletion after HD seemed to subsequently gain greater amounts of weight [53]. High IDWG is actually associated with better outcomes in unadjusted mortality analyses [61] and thus may only partially reflect the risk of ECV expansion [61].

Nephrologists should, therefore, target the control of chronic FO beyond the mere evaluation of IDGW [53].

In standard HD therapy, the target weight is prescribed to allow the patient to leave the HD unit proposedly 'euvolemic' (see Figure 2). During the 44 or 68 h of the interdialytic interval, the cardiovascular system will be exposed to a 'time-averaged fluid overload' (TAFO), comparable to the time-averaged concentration of a toxin. At normohydrated status, the TAFO is equivalent to half of the IDWG.

Hur et al. [62] have addressed the concept of TAFO in their interventional controlled study with the BCM®. They have prescribed the UF volume to target normohydration not at the end of the session but in the middle of the interdialytic period (Figure 2). Within 6 months of the study period, the BP, the pulse wave velocity and the ventricular mass index decreased significantly compared with the control group. Moreover, in a large cohort study with the BCM®, Dekker et al. [63] found a better survival in patients with estimated post-dialysis overhydration below −1.1 L. Thus, a negative fluid balance at the end of the dialysis session may have a protective effect on the patient's cardiovascular system.

Related to this concept (TAFO), the risk of IDWG has to be placed in context with the objective volume status; relatively large interdialytic weight gains in patients who are dehydrated at the end of dialysis are less of a risk signal than relatively small interdialytic weight gains in patients who are chronically fluid
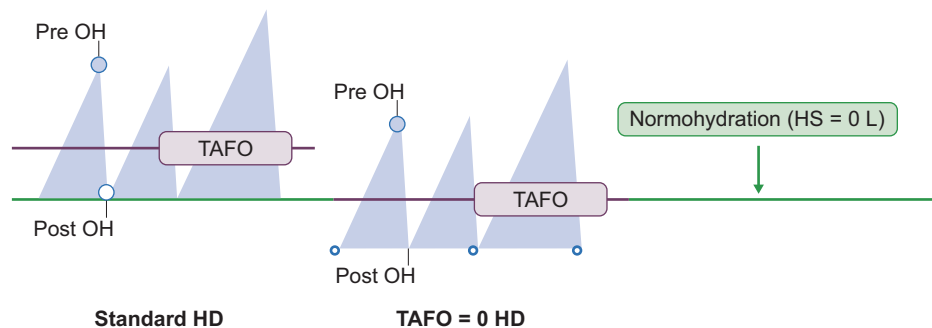
FIGURE 2: During the standard dialysis session, the prescription of post-dialysis body weight targets normal extracellular fluid balance at the end of the dialysis session. Yet, this exposes the patient to fluid accumulation all along the interdialytic interval, realizing a 'time-averaged fluid overload' (TAFO = half of the interdialytic weight gain). To avoid the exposure to TAFO during the interdialytic period (TAFO = 0), the post-dialysis fluid status should be negative. OH, overhydration.

overloaded. A moderately negative target weight would be desirable in both of these groups of patients.

We are aware that this concept may appear highly provocative bearing in mind how deleterious the effects of overestimated fluid removal rate can be. Yet we believe that the concept expands our understanding of how to reduce the large cardiovascular morbidity and mortality in HD patients.

DIALYSATE SODIUM PRESCRIPTION, SODIUM BALANCE AND SODIUM REMOVAL

A recent cross-sectional snapshot of all EuCliD patients (data from ≥52 000 HD patients, as of July 2019, FMC unpublished data on file) demonstrated that dialysate Na+ (DNa+) prescriptions range from 134 to 143 mmol/L. A DNa+ concentration of 138 mmol/L is utilized in roughly 50% of all patients and 140 mmol/L is the second most common, with 15%.

Whereas Eastern European countries tend to utilize lower DNa+ concentrations, and Russia seems to prescribe the lowest concentrations between 135 and 137 mmol/L in two-thirds of patients, Italy prefers higher DNa+ concentrations, ≥140 mmol/L.

Future studies are necessary to understand cultural behaviour, ethnic factors, common beliefs or eminence to explain the unit-, region- and provider-specific DNa+ prescription pattern practices in Europe and bordering the Mediterranean Sea.

In HD patients, Na+ balance depends on dietary intake and Na+ removal during HD [64]. An excessive Na+ load is associated with high mortality [25]. A *post hoc* analysis from The Hemodialysis Study considering 1800 chronic HD patients showed a significantly increased risk of death with a dietary Na+ load >2.5 g/die [25]. Patient education for low salt diet may reduce IDWG by 30% [65]. However, recent data suggest that educating patients with kidney disease to reduce dietary Na+ does not lead to the desired outcome [14].

The dialyser must serve as the salt-excretory function and should precisely remove the amount of Na+ that has accumulated during the interdialytic period. Na+ removal during HD occurs via convective (~78%) and diffusive losses (~22%) between dialysate and plasma Na+ concentration [64]. The diffuse Na+ gradient during HD 'fine tunes' Na+ balance.

A clear modifiable source of Na+ exposure in HD patients and a promising intervention to improve cardiovascular mortality is to reduce DNa+ during HD treatment [13].

The recent Cochrane review evaluated 12 randomized trials of low (<138 mmol/L) versus neutral (138–140 mmol/L) or high (>140 mmol/L) DNa+ for HD patients, including 310 patients, did not examine hard clinical endpoints such as cardiovascular or all-cause mortality [66]. The authors rated the quality of evidence as low and concluded that the effect of the intervention on overall patient health and well-being is currently unknown [66].

The questions at heart remain whether lowering DNa+ prevents cardiac remodelling and sudden cardiac death by improving Na+ regulation and FO or whether the benefit of lowering DNa+ in reducing left ventricular mass is offset by increased myocardial stunning and micro-injury [10, 13]. The ongoing global Randomised Evaluation of SOdium dialysate Levels on Vascular Events (RESOLVE) Trial investigates whether lower DNa+ may improve cardiovascular outcomes and will determine comparative effectiveness of two default DNa+ concentrations (ClinicalTrials.gov Identifier: NCT02823821).

On the contrary, a proof of principle study of the '0 Na diffusion' concept—an option developed for newer HD machines — was recently undertaken and proved that automated DNa+ individualization by 'Na+ control' approaches isonatraemic dialysis in the clinical setting without the need to determine the plasma Na+ concentration [67]. Automated Na+ control holds the promise to avoid diffusive Na+ load or removal during HD and future studies are needed to determine whether isonatraemic dialysis could have any effect on hard clinical endpoints [67].

HOW TO BEST APPROACH EUVOLAEMIA— STATE OF THE ART 2020

The heterogeneity in the ESRD population challenges the nephrologist in HD practice to combine disease management with the patient's attainable treatment goal and prognosis [68].

The context is complex and a multidimensional approach to Na+, fluid and pressure management in HD patients may be required to improve cardiovascular outcomes in HD patients (Figure 3). The pillars of clinical, instrumental and patient
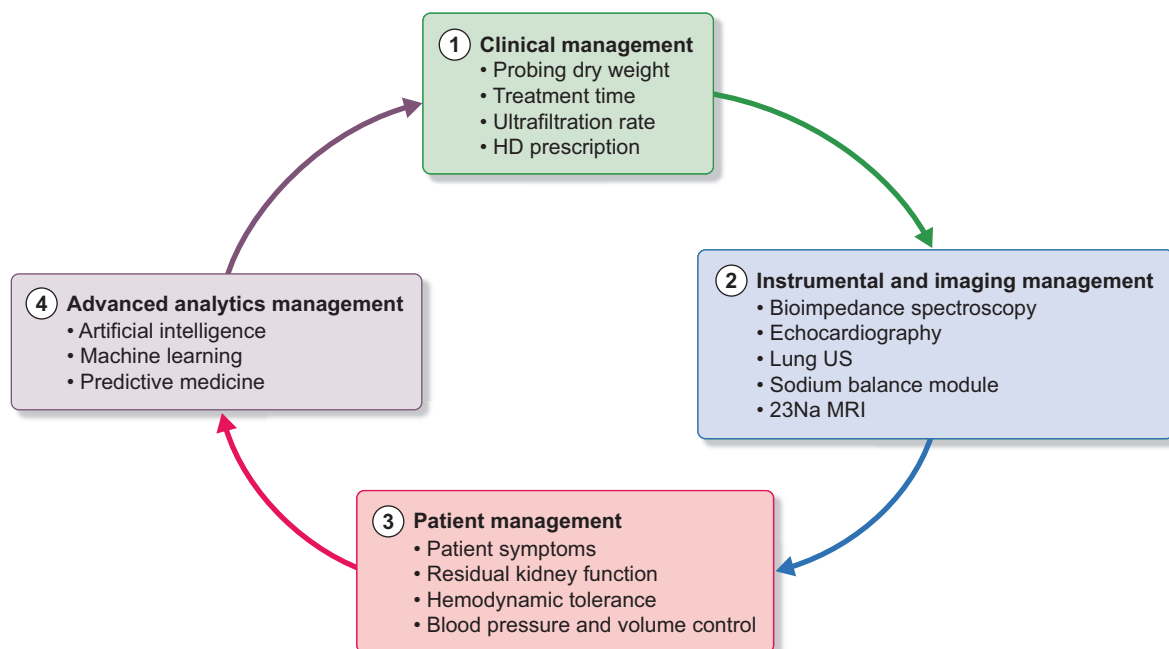
FIGURE 3: Multidimensional approach to sodium, fluid and pressure management in haemodialysis patients. US, ultrasound; 23Na MRI, magnetic resonance imaging of tissue sodium stores.

management need to complement each other to correctly assess the patient's dry weight, and achieve BP control and haemodynamic tolerance of HD therapy, while reassuring patient acceptance of HD duration and sequence.

Some dialysis facilities have implemented incremental dialysis as a preventive measure at the start of renal replacement therapy. Other dialysis facilities permit a degree of initial overhydration to preserve residual renal function, which may improve outcomes [69]. A recent DOPPS analysis [70] confirmed the previous finding [71] for incident HD patients that urine output of at least 1 cup daily was associated with better survival and it may be of value to routinely ask patients a simple question about urine output. Diuretics may lessen chronic FO in patients with preserved residual kidney function, but this approach has not been evaluated [72].

Some experts have suggested imposing UF rate thresholds (such as 13 mL/h/kg) to reduce UF-related risk [73]. UF profiling (decelerating UF rate to match declining plasma refill rate) and sequential dialysis (isolated UF followed by combined HD and UF) are other potential HD prescription changes to reduce the harm of rapid UF rate [72].

Finally, as once demonstrated by the Tassin group, increased frequency or duration of HD sessions may bring high volume status, left ventricular mass and BP under control by more effectively reducing ECF load than conventional HD [9].

Unfortunately, classic randomized controlled trials in HD thus far have failed to yield any meaningful information in the area of dose and frequency of HD, mainly due to methodological issues, such as statistical errors, unfeasible trial efficiency, recruitment challenges and applicability of results to the research question [74]. Cluster randomization may be a novel and advantageous trial method and a potential mean to overcome these barriers [75].

Yet, before we know for certain, we need rigorous cardiovascular outcome studies and thorough study interventions such as the above-mentioned (e.g. effect of UF rate thresholds) on volume status, fluid-related hospitalizations and cardiovascular outcomes while ensuring the patient's acceptance to therapy.

ADVANCED ANALYTICS MANAGEMENT

Artificial intelligence (AI) is already successfully applied to support physicians in the decision-making process of patients' care presenting either with chronic (e.g. anaemia management) or acute kidney failure (e.g. fluid resuscitation in the intensive care unit) [76–79]. AI relies today on two main paths, known as symbolic reasoning (expert systems, symbolic AI) and machine learning (deep learning, neural networks, connectionist AI), each with their own advantages and limitations. Expert systems require perfect knowledge of physiological processes and interactions to provide reliable prediction based on rational algorithms. Machine learning (connectionist AI) requires a large amount of data (big data) to learn and define its own rules (open and not guided), in order to provide reliable prediction but lack of model interpretability. A third pathway is emerging, which combines the two approaches of symbolic reasoning (symbolic AI) and machine learning (connectionist AI) (such as deep symbolic learning and/or enabling neural networks). Yet, it is too early today to define what will be the best approach for future predictive and supportive medicine [80].

Expert systems based on AI outperform experienced nephrologists in assessing dry weight in HD patients [81]. Preliminary and proof-of-concept studies based on machine learning AI have been performed in the field of fluid and haemodynamic management of HD patients to train and validate models on a large patient dataset [82]. As shown, AI is able to predict reliably individual session-specific patient haemodynamic

reaction to dialysis-related prescriptions on multiple relevant haemodynamic parameters (e.g. intradialytic heart rate and BP changes and trends), dialysis efficiency parameters (e.g. UF rate, electrolyte composition), but also large sets of data including anthropometric, lab tests, medication and fluid volume status. Availability of accurate, longitudinal, real-life data is a key factor for the development of reproducible predictive models, meaning that such an approach relies on a fully digitalized and connected IT system that feeds cloud computing systems with big data flow. Predictive and supportive medicine including fluid, pressure and haemodynamic management of HD patients are in the pipeline, but more granular information and studies are required for generalizability.

CONCLUSION

Na+, fluid and pressure control are of critical importance in HD patients to reduce cardiac disease burden and improve outcome. As highlighted in this review, it is of utmost importance to restore Na+ and fluid homoeostasis by correcting chronic FO but at the same time prevent acute fluid depletion during HD sessions. This situation is challenging and complex and requires a multidimensional approach. New technology may facilitate monitoring (clinical, instrumental, imaging and analytics) and action (Na+ balancing algorithm, dialysis options), but should remain under scrutiny of pertinent clinical judgement, facilitated by measures such as increasing treatment time and diet modifications.

CONFLICT OF INTEREST STATEMENT

J.P. declares no conflict of interest. C.C., S.S., U.M. and B.C. are employed by Fresenius Medical Care.

REFERENCES

1. Liyanage T, Ninomiya T, Jha V et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet 2015; 385: 1975–1982
2. DeJager DJ, Grootendorst DC, Jager KJ et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA 2009; 302: 1782–1789
3. USRDS: United States Renal Data System. 2018 Annual Data Report Volume 2: End-Stage Renal Disease. Chapter 5: Mortality. https://www.usrds.org/ (20 December 2019, date last accessed)
4. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. Lancet 2016; 388: 276–284
5. Charra B, Chazot C, Jean G et al. Role of sodium in dialysis. Minerva Urol Nefrol 2004; 56: 205–213
6. Zoccali C, Moissl U, Chazot C et al. Chronic fluid overload and mortality in ESRD. J Am Soc Nephrol 2017; 28: 2491–2497
7. Kundhal K, Lok CE. Clinical epidemiology of cardiovascular disease in chronic kidney disease. Nephron Clin Pract 2005; 101: c47–c52
8. Cozzolino M, Mangano M, Stucchi A et al. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant 2018; 33 (Suppl 3): iii28–iii34
9. Ok E, Asci G, Chazot C et al. Controversies and problems of volume control and hypertension in haemodialysis. Lancet 2016; 388: 285–293
10. Flythe JE, Mc Causland FR. Dialysate sodium: rationale for evolution over time. Semin Dial 2017; 30: 99–111
11. Wizemann V, Schilling M. Dilemma of assessing volume state–the use and the limitations of a clinical score. Nephrol Dial Transplant 1995; 10: 2114–2117
12. Agarwal R, Andersen MJ, Pratt JH. On the importance of pedal edema in hemodialysis patients. Clin J Am Soc Nephrol 2008; 3: 153–158
13. Marshall MR, Dunlop JL. Are dialysate sodium levels too high? Semin Dial 2012; 25: 277–283
14. Zoccali C, Mallamaci F. Mapping progress in reducing cardiovascular risk with kidney disease: managing volume overload. Clin J Am Soc Nephrol 2018; 13: 1432–1434
15. Shemin D, Bostom AG, Laliberty P et al. Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis 2001; 38: 85–90
16. Canaud B, Chazot C, Koomans J et al. Fluid and hemodynamic management in hemodialysis patients: challenges and opportunities. J Bras Nefrol 2019; 41: 550–559
17. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int 2011; 79: 250–257
18. Movilli E, Gaggia P, Zubani R et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant 2007; 22: 3547–3552
19. Saran R, Bragg-Gresham JL, Levin NW et al. Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS. Kidney Int 2006; 69: 1222–1228
20. Assimon MM, Wenger JB, Wang L et al. Ultrafiltration rate and mortality in maintenance hemodialysis patients. Am J Kidney Dis 2016; 68: 911–922
21. Chazot C, Vo-Van C, Lorriaux C et al. Even a moderate fluid removal rate during individualised haemodialysis session times is associated with decreased patient survival. Blood Purif 2017; 44: 89–97
22. Jefferies HJ, Virk B, Schiller B et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). Clin J Am Soc Nephrol 2011; 6: 1326–1332
23. Canaud B, Kooman J, Selby NM et al. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. Kidney Int 2019; 95: 296–309
24. Reinhardt HW, Seeliger E. Toward an integrative concept of control of total body sodium. News Physiol Sci 2000; 15: 319–325
25. Mc Causland FR, Waikar SS, Brunelli SM. Increased dietary sodium is independently associated with greater mortality among prevalent hemodialysis patients. Kidney Int 2012; 82: 204–211
26. Simpson FO. Sodium intake, body sodium, and sodium excretion. Lancet 1988; 2: 25–29
27. Strauss MB, Lamdin E, Smith WP et al. Surfeit and deficit of sodium; a kinetic concept of sodium excretion. AMA Arch Intern Med 1958; 102: 527–536
28. Hollenberg NK. Set point for sodium homeostasis: surfeit, deficit, and their implications. Kidney Int 1980; 17: 423–429
29. Risvoll GB, Thorsen K, Ruoff P et al. Variable setpoint as a relaxing component in physiological control. Physiol Rep 2017; 5: e13408
30. Guyton AC, Coleman TG, Cowley AV Jr et al. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 1972; 52: 584–594
31. Guyton AC. Blood pressure control–special role of the kidneys and body fluids. Science 1991; 252: 1813–1816
32. Malpas S. Editorial comment: Montani versus Osborn exchange of views. Exp Physiol 2009; 94: 381–382
33. Rakova N, Juttner K, Dahlmann A et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell Metab 2013; 17: 125–131
34. Kopp C, Linz P, Wachsmuth L et al. (23)Na magnetic resonance imaging of tissue sodium. Hypertension 2012; 59: 167–172
35. Titze J, Shakibaei M, Schafflhuber M et al. Glycosaminoglycan polymerization may enable osmotically inactive Na+ storage in the skin. Am J Physiol Heart Circ Physiol 2004; 287: H203–H208
36. Schafflhuber M, Volpi N, Dahlmann A et al. Mobilization of osmotically inactive Na+ by growth and by dietary salt restriction in rats. Am J Physiol Renal Physiol 2007; 292: F1490–F1500

37. Fischereder M, Michalke B, Schmockel E *et al*. Sodium storage in human tissues is mediated by glycosaminoglycan expression. *Am J Physiol Renal Physiol* 2017; 313: F319–F325

38. Machnik A, Neuhofer W, Jantsch J *et al*. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med* 2009; 15: 545–552

39. Wiig H, Luft FC, Titze JM. The interstitium conducts extrarenal storage of sodium and represents a third compartment essential for extracellular volume and blood pressure homeostasis. *Acta Physiol* 2018; 222: e13006

40. Titze J, Luft FC. Speculations on salt and the genesis of arterial hypertension. *Kidney Int* 2017; 91: 1324–1335

41. Schneider MP, Raff U, Kopp C *et al*. Skin sodium concentration correlates with left ventricular hypertrophy in CKD. *J Am Soc Nephrol* 2017; 28: 1867–1876

42. Dahlmann A, Dorfelt K, Eicher F *et al*. Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. *Kidney Int* 2015; 87: 434–441

43. Arneson TJ, Liu J, Qiu Y *et al*. Hospital treatment for fluid overload in the medicare hemodialysis population. *Clin J Am Soc Nephrol* 2010; 5: 1054–1063

44. Plantinga LC, King LM, Masud T *et al*. Burden and correlates of readmissions related to pulmonary edema in US hemodialysis patients: a cohort study. *Nephrol Dial Transplant* 2018; 33: 1215–1223

45. Goodkin DA, Young EW, Kurokawa K *et al*. Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. *Am J Kidney Dis* 2004; 44 (Suppl 2): 16–21

46. Weiner DE, Brunelli SM, Hunt A *et al*. Improving clinical outcomes among hemodialysis patients: a proposal for a "volume first" approach from the chief medical officers of US dialysis providers. *Am J Kidney Dis* 2014; 64: 685–695

47. Essig M, Escoubet B, de Zuttere D *et al*. Cardiovascular remodelling and extracellular fluid excess in early stages of chronic kidney disease. *Nephrol Dial Transplant* 2008; 23: 239–248

48. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305

49. Bansal N, Keane M, Delafontaine P *et al*. A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study. *Clin J Am Soc Nephrol* 2013; 8: 355–362

50. Siriopol D, Siriopol M, Stuard S *et al*. An analysis of the impact of fluid overload and fluid depletion for all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2019; 34: 1385–1393

51. Bansal N, McCulloch CE, Lin F *et al*. Blood pressure and risk of cardiovascular events in patients on chronic hemodialysis. *Hypertension* 2017; 70: 435–443

52. Charra B, Laurent G, Chazot C *et al*. Clinical assessment of dry weight. *Nephrol Dial Transplant* 1996; 11 (Suppl 2): 16–19

53. Hecking M, Karaboyas A, Antlanger M *et al*. Significance of interdialytic weight gain versus chronic volume overload: consensus opinion. *Am J Nephrol* 2013; 38: 78–90

54. Loutradis C, Sarafidis PA, Theodorakopoulou M *et al*. Lung ultrasound-guided dry-weight reduction in hemodialysis patients does not affect short-term blood pressure variability. *Am J Hypertens* 2019; 32: 786–795

55. Kotanko P, Levin NW, Zhu F. Current state of bioimpedance technologies in dialysis. *Nephrol Dial Transplant* 2008; 23: 808–812

56. Moissl U, Arias-Guillen M, Wabel P *et al*. Bioimpedance-guided fluid management in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; 8: 1575–1582

57. Machek P, Jirka T, Moissl U *et al*. Guided optimization of fluid status in haemodialysis patients. *Nephrol Dial Transplant* 2010; 25: 538–544

58. Onofriescu M, Hogas S, Voroneanu L *et al*. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am J Kidney Dis* 2014; 64: 111–118

59. Covic A, Ciumanghel AI, Siriopol D *et al*. Value of bioimpedance analysis estimated "dry weight" in maintenance dialysis patients: a systematic review and meta-analysis. *Int Urol Nephrol* 2017; 49: 2231–2245

60. Tabinor M, Davies SJ. The use of bioimpedance spectroscopy to guide fluid management in patients receiving dialysis. *Curr Opin Nephrol Hypertens* 2018; 27: 406–412

61. Hecking M, Moissl U, Genser B *et al*. Greater fluid overload and lower inter-dialytic weight gain are independently associated with mortality in a large international hemodialysis population. *Nephrol Dial Transplant* 2018; 33: 1832–1842

62. Hur E, Usta M, Toz H *et al*. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis* 2013; 61: 957–965

63. Dekker MJ, Marcelli D, Canaud BJ *et al*. Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort. *Kidney Int* 2017; 91: 1214–1223

64. Lee SW. Sodium balance in maintenance hemodialysis. *Electrolyte Blood Press* 2012; 10: 1–6

65. Kayikcioglu M, Tumuklu M, Ozkahya M *et al*. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant* 2009; 24: 956–962

66. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. *Cochrane Database Syst Rev* 2019; 1: Cd011204

67. Sagova M, Wojke R, Maierhofer A *et al*. Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis. *Artif Organs* 2019; 43: 1002–1013

68. Vandecasteele SJ, Kurella Tamura M. A patient-centered vision of care for ESRD: dialysis as a bridging treatment or as a final destination? *J Am Soc Nephrol* 2014; 25: 1647–1651

69. Obi Y, Streja E, Rhee CM *et al*. Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. *Am J Kidney Dis* 2016; 68: 256–265

70. Hecking M, McCullough KP, Port FK *et al*. Self-reported urine volume in hemodialysis patients: predictors and mortality outcomes in the International Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2019; 74: 425–428

71. Shafi T, Jaar BG, Plantinga LC *et al*. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the choices for healthy outcomes in caring for end-stage renal disease (CHOICE) study. *Am J Kidney Dis* 2010; 56: 348–358

72. Assimon MM, Flythe JE. Rapid ultrafiltration rates and outcomes among hemodialysis patients: re-examining the evidence base. *Curr Opin Nephrol Hypertens* 2015; 24: 525–530

73. Agar JW. Personal viewpoint: limiting maximum ultrafiltration rate as a potential new measure of dialysis adequacy. *Hemodial Int* 2016; 20: 15–21

74. Twardowski ZJ, Misra M. A need for a paradigm shift in focus: from Kt/Vurea to appropriate removal of sodium (the ignored uremic toxin). *Hemodial Int* 2018; 22: S29–S64

75. Ford I, Norrie J. Pragmatic trials. *N Engl J Med* 2016; 375: 454–463

76. Barbieri C, Mari F, Stopper A *et al*. A new machine learning approach for predicting the response to anemia treatment in a large cohort of end stage renal disease patients undergoing dialysis. *Comput Biol Med* 2015; 61: 56–61

77. Barbieri C, Molina M, Ponce P *et al*. An international observational study suggests that artificial intelligence for clinical decision support optimizes anemia management in hemodialysis patients. *Kidney Int* 2016; 90: 422–429

78. Celi LA, Hinske LC, Alterovitz G *et al*. An artificial intelligence tool to predict fluid requirement in the intensive care unit: a proof-of-concept study. *Crit Care* 2008; 12: R151

79. Davoudi A, Malhotra KR, Shickel B *et al*. Intelligent ICU for autonomous patient monitoring using pervasive sensing and deep learning. *Sci Rep* 2019; 9: 8020

80. Stuart Russell PN. *Artificial Intelligence: A Modern Approach*, Global edn. Harlow, UK: Pearson Education Limited, 2016.

81. Niel O, Bastard P, Boussard C *et al*. Artificial intelligence outperforms experienced nephrologists to assess dry weight in pediatric patients on chronic hemodialysis. *Pediatr Nephrol* 2018; 33: 1799–1803

82. Barbieri C, Cattinelli I, Neri L *et al*. Development of an artificial intelligence model to guide the management of blood pressure, fluid volume, and dialysis dose in end-stage kidney disease patients: proof of concept and first clinical assessment. *Kidney Dis* 2019; 5: 28–33