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*Original Article*

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# Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload

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**Abstract**

**Background.** Hypertension and fluid overload (FO) are well-recognized problems in the chronic kidney disease (CKD) population. While the prevalence of hypertension is well documented, little is known about the severity of FO in this population.

**Methods.** A new bioimpedance spectroscopy device (BCM—Body Composition Monitor) was selected that allows quantitative determination of the deviation in hydration status from normal ranges (ΔHS). Pre-dialysis systolic blood pressure (BPsys) and ΔHS was analysed in 500 haemodialysis patients from eight dialysis centres. A graphical tool (HRP—hydration reference plot) was devised allowing ΔHS to be combined with measurements of BPsys enabling comparison with a matched healthy population ($n = 1244$).

**Results.** Nineteen percent of patients ($n = 95$) were found to have normal BPsys and ΔHS in the normal range. Approximately one-third of patients ($n = 133$) exhibited reasonable control of BPsys and fluids (BPsys <150 mmHg and ΔHS <2.5 L). In only 15% of patients ($n = 74$) was hypertension observed (BPsys >150 mmHg) with a concomitant ΔHS >2.5 L (possible volume-dependent hypertension). In contrast, 13% of patients ($n = 69$) were hypertensive with ΔHS <1.1 L (possible essential hypertension). In 10% of patients ($n = 52$), BPsys <140 mmHg was recorded despite ΔHS exceeding 2.5 L.

**Conclusion.** Our study illustrated the wide variability in BPsys regardless of the degree of ΔHS. The HRP provides an invaluable tool for classifying patients in terms of BPsys and ΔHS and the proximity of these parameters to reference ranges. This represents an important step towards more objective choice of strategies for the optimal treatment of hypertension and FO. Further studies are required to assess the prognostic and therapeutic role of the HRP.

**Keywords:** bioimpedance spectroscopy; fluid status; fluid overload; haemodialysis; hypertension

## Introduction

The treatment of hypertension and fluid overload (FO) are issues of major importance in chronic kidney disease patients. While the genesis of left ventricular hypertrophy (LVH) is multifactorial, hypertension and FO are known to be highly relevant precursors to the development of LVH that remains prevalent in the haemodialysis (HD) population [1]. A number of studies have shown that a significant proportion of deaths in HD patients can be attributed to LVH [2,3]. As a number of studies have indicated, LVH may not be an irresolvable problem if improved clinical management strategies are applied [4–6]. In reality, improved treatment is difficult to deliver because the tools for assessment of major cardiovascular (CV) risk factors such as FO are not sufficiently adequate [7]. It was estimated in the HEMO study [8] that 72% of the chronic HD patients in the USA suffer from hypertension despite any intervention with antihypertensive medication (AHT). This offers at least one indication that there must be a further drive to investigate alternative treatment options.

The use of blood pressure (BP) as one of the clinical indicators of fluid status is universal in the assessment of chronic HD patients [9]. Although, it is often presumed that conditions of FO predispose to hypertension in the majority of patient cases, several studies have shown that this relationship is far from clear [10–14]. There are a number of possible reasons that could explain this contrariness of findings. Firstly, there are those patients in whom low BP is exhibited regardless of fluid status [15]. A number of studies have shown that the mortality risk is increased in patients presenting BPsys <100 mmHg [16,17]. It is likely that cardiac insufficiency could explain such observations [18], particularly in the context of congestive heart failure.

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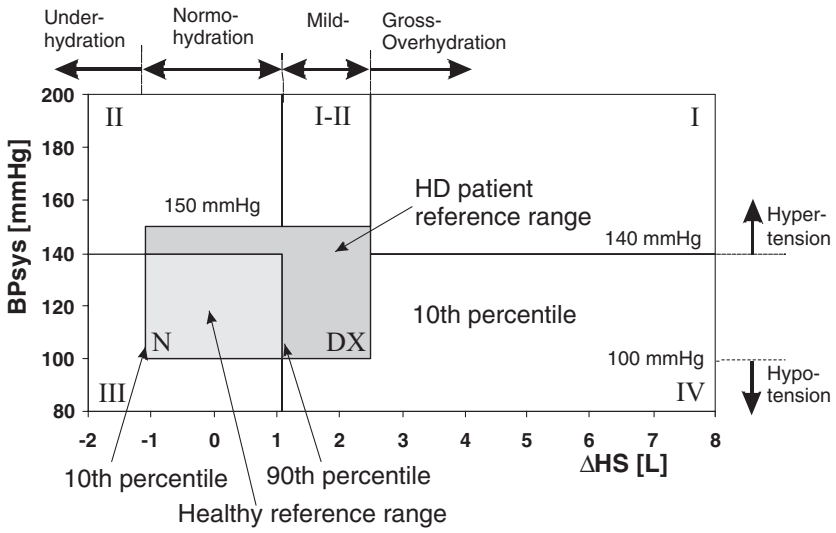


**Fig. 1.** Hydration reference plot (HRP).

In patient cases with low BPsys, there is a possible risk that obvious FO is not treated. A second flaw in the use of BP as an indicator of FO occurs from the use of AHT [19]. If AHT is even partially effective in BP control, the sensitivity of BP as a marker of FO is likely to be blunted. A third drawback concerns circumstances of hypertension where FO is not implicated but other factors play an important role [14]. This leads to the obvious difficulty in differentiating the influence of FO from other factors in the manifestation of hypertension.

Given the difficulties in the interpretation of BP in the context of HD patients, it is clear that an objective measure of deviations from normal hydration status (ΔHS) has been long overdue. Although many indicators of ΔHS are available [15,20–22], these methods are invariably too subjective, indirect and endpoints are difficult to define. Recently it has been shown that the performance of bioimpedance spectroscopy (BIS) is significantly better in the detection of ΔHS both in terms of sensitivity and specificity [23]. Furthermore, developments in body composition analysis [24,25] and volume validation [26] have led to a new device allowing objective, quantitative measurement of ΔHS for the first time.

While the importance of BP control is well established, we propose that the interpretative value of BPsys in HD patients could be enhanced by introduction of an objective measurement of ΔHS. The purpose of the current work therefore, was to identify the different patient groups that result from measurements of BPsys and ΔHS alone.

## Materials and methods

### *Evaluation of hydration status*

Hydration status can be measured in terms of extracellular water (ECW) or total body water (TBW) in proportion to body weight and is also dependent upon body composition. A recent development has been the method for calculation of normal hydration status, i.e. the expected normal values of ECW or TBW that result with healthy kidney function [25]. As normal ECW or TBW can be determined for a given weight and body composition, ΔHS can be calculated from the difference between the normal ECW expected and the measured ECW. A new device, the BCM Body-Composition-Monitor (Fresenius Medical Care), provides a convenient method to obtain ECW and TBW that has been validated previously [27]. These volumes are determined by the measurement of the whole body impedance at 50 frequencies via electrodes placed on the wrist and ankle. Using the model described above [25], the BCM calculates not only ΔHS, but normally hydrated lean tissue mass (LTM) and adipose tissue mass (ATM) in addition. Normal hydration status has been reported in litres and validation studies have been performed [27–30]. Although patients' plasma fluid contains minerals and other solutes, the difference in volume between pure water and fluid is negligible for all practical purposes [25]. Therefore, the terms 'fluid status' and 'hydration status' may be used interchangeably in this context.

### *Description of the hydration reference plot*

The hydration reference plot (HRP) combines ΔHS and BPsys together in a manner that allows rapid identification of subtly different regions (see Figure 1). Essentially, the regions within the plot allow differentiation between hypotensive and hypertensive patients as well as distinguishing FO from the state of normohydration. A key element of the plot is the healthy reference region (N) that allows the severity of ΔHS and hypertension to be easily assessed. The following sections review regions within the HRP of particular interest.

*Region N*. This defines a healthy population, established with data from a previous study based on a population of 1247 healthy Caucasian controls [31]. In a healthy population, it is expected that ΔHS is nominally zero although a distribution around zero results from daily bodily functions

that influence both weight and hydration status [32]. In order to define a normohydration range, the positions of the 10th and 90th percentiles of the healthy distribution were calculated [31], yielding to −1.1 L and +1.1 L, respectively. Subjects with values of ΔHS greater than the 90th percentile (+1.1 L) were considered to be overhydrated while underhydration was reflected in values of ΔHS lower than the 10th percentile (−1.1 L).

Analysis of BPsys in a reference population derived from a previous study [31] revealed 10th and 90th percentiles at ∼100 and 140 mmHg, respectively. Patients were considered hypertensive above 140 mmHg and hypotensive below 100 mmHg. By combining measurements of ΔHS and BPsys, a normal healthy population reference region (N) is established. Thus patients appearing in the N region represent a fluid status and pre-dialysis BPsys comparable to the healthy reference population.

*Region Dx*. The BCM has the advantage that measurements of ΔHS can be performed at any time, as this does not affect the calculation of normal hydration. The only restriction that applies is the measurement immediately post-treatment where disequilibrium effects can influence measurements of ECW and intracellular water (ICW). Although this is avoided by a 30-min post-treatment measurement, this is less convenient [28]. Thus, it is appropriate to measure ΔHS pre-dialysis when other observations are available pre-dialysis. As a patient presents pre-dialysis the peak ΔHS, a second reference range can be defined, the border of which takes into account a typical weight gain of 2.5 L. A patient with ΔHS of 2.5 L pre-dialysis is brought to the middle of the healthy reference range, i.e. ΔHS = 0 L by 2.5 L of ultrafiltration. The selection of 2.5 L is completely arbitrary and serves as a guide only. Any boundary could be selected for the upper end of the pre-Dx range for a given dialysis centre, and the normalization of ΔHS to other variables such as ECW or LTM is also possible.

Regarding the upper BPsys limit for the Dx range, a pre-dialysis BPsys of 140 mmHg has been proposed in the KDOQI guidelines [33]. However, a range between 140 and 160 mmHg pre-dialysis has been considered optimal with respect to mortality [34]. In our study we selected 150 mmHg as a practical upper limit for pre-dialysis BPsys values as proposed elsewhere [35].

*Region I.* This region represents patients with a ΔHS >2.5 L and an increased BPsys >140 mmHg. There is a high likelihood that hypertension in these patients is indicative of the gross FO observed.

*Region I–II.* This represents a population with mild elevation of ΔHS between 1.1 and 2.5 L concomitant with an increased BPsys >150 mmHg.

*Region II*. This represents patients in a state of normohydration but BPsys >150 mmHg. Patients in this region are clearly hypertensive but there is far less likelihood that volume is a contributing factor.

*Region III*. It characterises underhydrated patients with normal or low BPsys <140 mmHg.

*Region IV*. This represents patients with gross FO, ΔHS > 2.5 L and a normal or low BPsys <140 mmHg. In this patient population, the gross FO is not reflected in BPsys.

### *Patients*

Five hundred HD patients were selected randomly from eight centres. Patients with a pacemaker or implanted defibrillator, amputation of a major extremity, pregnancy or lactation period and those who were HIV positive were excluded. Otherwise, no other selection criteria were applied ensuring that a range of co-morbid conditions could be captured. All patients gave an informed consent. Table 1 reports the basic characteristics of the patient

**Table 1.** Characteristics of the patient population and a patient population analysed by Li [46]

| | All patients (mean ± SD) | Male (mean ± SD) | Female (mean ± SD) | Population from Li [46] (mean ± SD) |
|---|---|---|---|---|
| *n* | 500 | 265 | 235 | 69 590 |
| Age (years) | 63 ± 14 | 60.6 ± 13.6 | 65.6 ± 14 | 60.9 ± 15.1 |
| BMI (kg/m$^2$) | 26.5 ± 5.4 | 26 ± 4.8 | 27 ± 6 | |
| BSA (m$^2$) | 1.79 ± 0.19 | 1.89 ± 0.19 | 1.68 ± 0.17 | 1.83 ± 0.25 |
| Months on dialysis | 50 ± 60 | 47 ± 58 | 53 ± 63 | 41 ± 43 |
| BPsys (mmHg) | 141 ± 23 | 141 ± 23 | 140 ± 23 | 153 ± 21 |
| BPdia (mmHg) | 75 ± 13 | 76 ± 13 | 73 ± 13 | 79 ± 12 |
| Post-BPsys (mmHg) | 131 ± 24 | 133 ± 23 | 130 ± 25 | 138 ± 20 |
| Post-BPdia (mmHg) | 71 ± 13 | 73 ± 13 | 70 ± 13 | 72 ± 11 |
| Preweight (kg) | 73.6 ± 15.2 | 78.2 ± 14.1 | 68.3 ± 14.6 | |
| Postweight (kg) | 71.6 ± 14.9 | 76.1 ± 13.9 | 66.5 ± 14.3 | |
| Weight loss (kg) | 2.0 ± 1.1 | 2.1 ± 1.2 | 1.9 ± 1 | 2.9 ± 1.2 |
| IDWG (%) | 2.8 ± 1.5 | 2.9 ± 1.5 | 2.8 ± 1.5 | |
| ECW (L) | 16.9 ± 3.4 | 18.6 ± 2.9 | 15.0 ± 2.8 | |
| ICW (L) | 18.0 ± 4.4 | 20.4 ± 4.1 | 15.2 ± 2.8 | |
| TBW (L) | 34.9 ± 7.3 | 39.0 ± 6.4 | 30.3 ± 5.2 | |
| ΔHS (L) | 1.5 ± 1.8 | 1.7 ± 1.8 | 1.3 ± 1.8 | |

BMI = body mass index; BSA = body surface area; BP = pre-dialysis blood pressure; post-BP = post-dialysis blood pressure; IDWG = intradialytic weight gain relative to body weight; ECW = extracellular water; ICW = intracellular water; TBW = total body water; ΔHS = difference in the hydration state to a healthy subject.

**Table 2.** Classification of 500 patients in the hydration reference plot. The patients are classified by the regions (N, DX, I–IV) on the basis of the pre-HD measurement

| Region | N | Dx | I | I–II | II | III | IV |
|---|---|---|---|---|---|---|---|
| *n* | 95 | 133 | 74 | 50 | 69 | 27 | 52 |
| Percentage of patients (%) | 19 | 27 | 15 | 10 | 13 | 5 | 10 |
| Age (years) | $63 \pm 16^{o}$ | $65 \pm 12^{o}$ | $62 \pm 13^{o}$ | $63 \pm 14^{o}$ | $65 \pm 11^{o}$ | $64 \pm 18^{o}$ | $59 \pm 16^{o}$ |
| Male percentage (%) | 46 | 50 | 70 | 54 | 48 | 37 | 63 |
| BPsys (mmHg) | $126 \pm 12^{d}$ | $134 \pm 14$ | $159 \pm 17$ | $164 \pm 12^{b}$ | $166 \pm 11^{e}$ | $102 \pm 19$ | $122 \pm 14^{N}$ |
| BPdia (mmHg) | $73 \pm 12^{Dx}$ | $71 \pm 11^{N,d}$ | $80 \pm 14^{b,e}$ | $83 \pm 11^{a,b}$ | $82 \pm 13^{a,e}$ | $63 \pm 12$ | $68 \pm 11^{Dx}$ |
| Post-BPsys (mmHg) | $120 \pm 17^{d}$ | $129 \pm 18$ | $148 \pm 21^{b,e}$ | $145 \pm 20^{a,b}$ | $145 \pm 22^{a,e}$ | $100 \pm 21$ | $120 \pm 20^{N}$ |
| Post-BPdia (mmHg) | $69 \pm 13^{Dx,d}$ | $70 \pm 12^{N,d}$ | $77 \pm 14^{b,e}$ | $76 \pm 11^{a,b}$ | $77 \pm 13^{a,e}$ | $60 \pm 15$ | $67 \pm 13^{N,Dx}$ |
| ΔHS (L) | $0.17 \pm 0.66^{b}$ | $1.34 \pm 0.77$ | $3.89 \pm 1.55^{d}$ | $1.69 \pm 0.4$ | $0.11 \pm 0.79^{N,c}$ | $-0.46 \pm 1.65^{b}$ | $3.69 \pm 1.06^{a}$ |
| UFV (mL) | $1.87 \pm 1^{Dx,b,e}$ | $1.8 \pm 1^{N,b,e}$ | $2.44 \pm 1.2^{d,e}$ | $2.15 \pm 1.1^{N,Dx,a,b}$ | $1.7 \pm 1.2^{N,Dx}$ | $1.1 \pm 1.3$ | $2.4 \pm 1.0^{a}$ |

*n* = absolute distribution of patients pre-HD; percentage of patients = relative distribution of patients in region; male percentage = percent of males in region; BPsys = systolic pressure before the HD session; BPdia = diastolic pressure before the HD session; post-BPsys = systolic pressure after the HD session; post-BPdia = diastolic pressure after the HD session; ΔHS = difference in the hydration status to a healthy subject, UFV = ultrafiltration volume.
Significantly different to patient groups in all other regions if not depicted otherwise.
[a]not significantly different (n.s.d.) to patients in region I.
[b]n.s.d. to patients in region II.
[c]n.s.d. to patients in region III.
[d]n.s.d. to patients in region IV.
[e]n.s.d. to patients in region I–II.
[N]n.s.d. to patients in region N.
[Dx]n.s.d. to patients in region Dx.
[o]n.s.d. between all regions.

population. BIS and BP measurements were performed directly before HD treatments, after a short interdialytic interval, with patients in the supine position. BP was measured post-dialysis in addition. To improve the reproducibility of the BP measurement, the average values of the last six HD treatments were used. For each patient, all measurements represent the first encounter of the patient with the BIS device to exclude possible bias.

## Statistical methods

Basic statistics were reported in terms of mean and standard deviation. Statistical significance was tested using ANOVA.

## Results

Table 2 shows the distribution of 500 HD patients in the HRP resulting from pre-dialysis measurements. The largest fraction of the patient population measured (27%) was found to reside in the Dx region of the HRP. Only 19% of patients had values of ΔHS and BPsys that coincided with region N. Fifteen percent of patients exhibited ΔHS >2.5 L and BPsys >150 mmHg (region I). Thirteen percent of the patient population could be grouped into region II, representing values of ΔHS <1.1 L despite hypertension. In a relatively small number of patients (10%) BPsys <140 mmHg was recorded while ΔHS exceeded 2.5 L, represented by region IV. A minority of patients could be grouped into region III, characteristic of ΔHS < −1.1 L and BPsys <140 mmHg.

The age of the patients was not significantly different between all regions of the HRP, while 70% of all patients in region I were male. BPsys was not significantly different between patients in regions N and IV and between I–II and II. The mean ΔHS was highest in regions I (3.89 L) and IV (3.69 L), while being lowest in region III (0.46 L). The highest ultrafiltration volume (UFV) was found in patients located in regions I and IV (2.44 L and 2.4 L, respectively). In contrast, the UFV in region III was only 1.1 L.

The mean UFV in patients located in region II was found to be 30% lower than that of patients in region I, while the difference between BPsys and post-BPsys was nearly twice as great (21 versus 11 mmHg).

## Discussion

It is well known that normal BP is defined by a range and there are many factors leading to intra- and inter-subject variation within the range. Similarly, the reference data from the 1247 healthy subjects used in our analysis showed clearly that normohydration is defined by a range (−1.1 to 1.1 L). This is consistent with the work of Wystrychowski *et al*. who noted that different social habits lead to a range of hydration in healthy subjects [32]. This range can also be observed in healthy individuals when monitoring the fluid status over several days [36]. Thus the HRP combines the variables BPsys and ΔHS in a way that affords rapid interpretation of a patient's individual fluid status as well as providing objective comparison between patients. The proximity of the measurements with respect to the reference ranges allows the clinician to gauge the level of intervention necessary to correct fluid status and control BP. In the treatment of hypertension, it is essential to decide whether fluid reduction, AHT or a combination of both is the optimal strategy to achieve normotension [35,37]. Although not a substitute for clinical diagnosis, the HRP offers an

easy way to ascertain if hypertension is likely to be volume dependent or caused by other factors.

*Differences between patients with hypertension—regions I and II*

The various manifestations of hypertension have been reported by Coleman [38] and Bower [39]. These studies have identified patient groups in whom BP responds positively to volume removal (hypertension is fluid related—region I in HRP). In contrast, this response could be distinguished from the second patient group who were found to be so volume sensitive that even modest reductions in ECW of the order of only 500 mL were responsible for the difference between hypertension and vascular shock. This situation is comparable to regions II and I–II in the HRP where the cause of hypertension is likely to be multifactorial. Any factors that give rise to reduced vascular compliance will significantly reduce the tolerance to shifts in fluid status. Consequently, any attempt to control BPsys by fluid removal in these special cases is unlikely to be successful. Further evidence of the presence of regions II and I–II is given in a study that observed that not all hypertensive patients were strictly volume overloaded [14].

Patients in region II indicated a state of normohydration ($\Delta$HS = 0.11 L) but with an elevated mean BPsys (166 mmHg). Hegstrom [4] reported patient cases from 1961, who showed behavioural characteristic of region II patients; it was not possible to control hypertension with fluid removal because of heart ischaemia and hypotension. In our study, we also observed that patients in region II showed significant decreases in BPsys with relatively small reductions in $\Delta$HS. It remains to be demonstrated whether improved control of BPsys in region II is possible by following different treatment strategies, although this was outside the scope of our study. On one hand it is possible that a review of AHT might be effective. On the other hand, the experience of others [40] suggests that most patients can be managed with slow and sufficient ultrafiltration alone. It would be of interest to observe whether such a treatment approach results in a tolerable state of dehydration.

*Volume-dependent hypertension*

The link between FO and hypertension has been long recognized since the early days of dialysis [4,19,39,41,42]. In our study, there was a similar distribution of patients between regions I and II (15% versus 13%). This may well explain the contradictory reports in the more recent literature regarding the hypothesis that hypertension in the renal population is volume dependent [8,10–13]. It must be reiterated that in none of these previous studies there was any possibility of measuring $\Delta$HS objectively. We suggest that hypertension studies with a majority of patients located in region I are likely to find a strong association between fluid status and BP. In contrast it is quite unlikely to find such correlations if the patient population spans region I and region II in the HRP as the hypertension observed in patients in region II is not volume-dependent.

*Differences in highly fluid-overloaded patients—difference between regions I and IV*

Gross overhydration ($\Delta$HS >2.5 L) before HD (patients in regions I and IV) was found in 25% of our total patient cohort. Of this subgroup, 41% presented BPsys <140 mmHg, represented by region IV. Most patients located in regions I and IV did not reach a state of normohydration at the end of the treatment in our study ($\Delta$HS post-dialysis >1.2 L).

Even though the BPsys between the groups I and IV was significantly different (I—159 mmHg versus IV—122 mmHg), the mean $\Delta$HS in groups I and IV were comparable, 3.89 L versus 3.69 L (n.s.). Region IV patients run the risk that states of gross FO, even if clinically overt, are not treated as BPsys appears to reflect normality in these patients. Furthermore, it has been observed that even when clinical signs of FO are evident, patients are likely to show symptoms of apparent volume depletion [15]. High doses of AHT [39], underlying heart disease or low serum albumin levels [43] are all possible reasons that might explain the symptoms observed despite the presence of gross overload. Canella *et al*. [44] highlighted that by classifying patients as normotensive who are in reality hypertensive (and fluid overloaded), the association between hypertension and FO may be overlooked. This could potentially occur as the consequence of overzealous use of AHT. It has been highlighted that the use of AHT is not adequate for hyperhydrated patients [19] and that patient may experience episodes of hypotension during dialysis treatment despite volume overload [39].

The ‘U-shape’ relationship [45] between mortality and BP has attracted ongoing discussion [35]. It was concluded that cardiovascular risk was increased when BPsys was >180 mmHg or <110 mmHg. It is possible that most patients with low BPsys who run the highest mortality risk are actually volume-overloaded patients, in region IV. Li *et al*. [46] associated steadily falling BPsys over months in patients with a high mortality risk. This may be indicative of patients moving from regions I to IV with progressive worsening of cardiac sufficiency. D’Amico and Locatelli [47] hypothesized that the association between low BPsys and increasing mortality is attributed to cardiac failure as a consequence of long-term hypertension. Levin [39] suggested that BP should be controlled as early as possible before cardiomyopathy leads to permanent hypotension and early death.

Comparison of our population with the data from Li [46] shows that interdialytic weight gain is far bigger in the US data together with a higher BPsys (see Table 1). These data suggest that the Li patients suffer from higher $\Delta$HS than the patients in our study. This might be due to shorter treatment times in the USA compared to Europe [48] and may explain the observed higher mortality of dialysis patients in the USA [49].

Points of interest for future research would be to investigate how BP changes with time when fluid status and other factors are altered. Charra [50], for example, has described a ‘lag time’ between correction of FO (monitored by body weight) and normalization of BP. Further studies are required to assess the prognostic and therapeutic role of the HRP. For example, it would be interesting to study a larger

population of patients and investigate whether certain comorbid conditions predispose to the location of patients in the HRP or to analyse the impact of ΔHS on mortality. Frequent BIS measurements using a device such as the BCM to detect ΔHS directly could offer much greater insight into the effects of any clinical intervention that aims to optimise fluid status and BP.

*Conflict of interest statement*. P.C., T.J., P.M., U.M., P.P., P.T., C.T., J.V. and P.W. are partially or fully employed by Fresenius Medical Care. V.W. receives consultant fees. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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