The use of bioimpedance spectroscopy to guide fluid management in patients receiving dialysis

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**Abstract**

***Purpose of Review***

To summarize the findings of recent trials and meta-analyses designed to determine whether bioimpedance spectroscopy adds value to the clinical assessment of fluid status is dialysis patients so as to achieve a normally hydrated weight and put these in a contemporary context.

***Recent Findings***

8 trials (published 2010-2018) and 2 meta-analyses (2017) are reviewed. Both haemodialysis (HD) and peritoneal dialysis (PD) modalities are represented. Despite considerable heterogeneity in intervention, all are open-label randomised comparisons of a bioimpedance intervention with normal clinical practice in which clinicians were blinded to bioimpedance data. In a total of 1,443 patients studied no significant differences in mortality, cardiovascular or adverse events between groups was observed. Bioimpedance use associated with a reduction in overhydration, especially when residual kidney function was not present and a greater reduction in blood pressure. A modest correlation in the change in fluid status and fall in systolic blood pressure was seen compared to baseline. A more rapid fall in urine volume was seen in the two studies with the greatest change in fluid status, with significantly higher risk of anuria in one. How bioimpedance was integrated with the complex process of decision making by clinicians was variable and not always explained.

***Summary***

The usefulness of bioimpedance spectroscopy in guiding fluid management in dialysis patients is not yet clear. Bioimpedance can drive clinical decisions that lead to significant changes in fluid status but the best way to apply this in clinical practice requires further studies.

**3 Keywords**

**Fluid status; Blood Pressure; Bioimpedance**

**Introduction**

Achieving optimal management of fluid status is a key objective in dialysis patients. Poor management is associated with bi-directional risk: failure to correct overhydration may contribute to the increased mortality risk, for example that associated with the 3-day break in haemodialysis (HD) patients,(1) cause life-threatening pulmonary or laryngeal oedema(2) and contribute to progressive hypertensive cardiac injury.(3) Overly zealous volume depletion can contribute to intradialytic organ injury, e.g. cardiac stunning (4) and reduced cerebral perfusion(5) and accelerate the rate of loss of residual kidney function,(6) consistently shown to be associated with improved survival and quality of life on dialysis.(7) Although peritoneal dialysis (PD) may reduce this risk to some extent, there is evidence that higher ultrafiltration associated with increased glucose prescription precedes faster loss of urine volume.(8) PD also has its own challenges regarding fluid management – ultrafiltration failure being an important cause of technique failure, with membrane function being critical in anuric patients.(9) The overhydration associated with hypoalbuminaemia is also much more evident in PD patients, where it causes extravascular volume expansion without affecting plasma volume.(10)

There is also strong evidence that clinicians and patients struggle to set and keep to their target weights for optimal fluid status, often termed the ‘dry weight’ – although this review will adopt the term ‘normally hydrated weight’. Actual post-dialysis weights in HD patients recorded as being >2kg either above *or* below the set target weight are associated with significantly and symmetrically increased all-cause and cardiovasular mortality.(11,12) It is clear that any tool that might assist clinicians in setting the normally hydrated weight more accurately would be of considerable value. This review will discuss the current evidence that bioimpedance devices can add value in guiding fluid management. It will focus on the use of bioimpedance spectroscopy (multifrequency) but include for completeness and comparison data using single frequency devices. In addition, the relationship between longitudinal change in fluid status and blood pressure reported in these trials will be examined for the first time.

**What does bioimpedance tell us about dialysis patients?**

Some of the best evidence that the problems associated with optimal fluid management are due to tissue over-hydration comes from the bioimpedance literature. In a recently published, wide ranging systematic literature review and meta-analysis we were able to show that over-hydration almost doubles the mortality risk in studies which had already adjusted for comorbidity and that this effect was independent of the type of bioimpedance measurement taken (e.g. single frequency *v.* spectroscopy, vector analysis *v.* extrapolated volumes).(13) In two large studies this mortality risk was seen to be synergistically associated with indicators of systemic inflammation (14) and to be present independent of the ‘U’ shaped associated of blood pressure with survival.(15) It is, however important to remember what bioimpedance is actually measuring when interpreting these findings. All bioimpedance methodologies are based on the relationship between measures of resistance (inversely proportional to total body water, i.e. intra and extracellular fluid combined) and reactance (proportional to cell mass as cell membranes can act as capacitors).(16) Muscle wasting is highly prevalent in dialysis patients and when seen in the non-dialysis population, malnourished for whatever reason (e.g. HIV or poverty),(17) is associated with disproportionately increased extracellular fluid. Longitudinal studies of PD and HD patients indicate that, at least in part, the progressive increase in *relative* overhydration over time is a consequence of changing body composition due to loss in muscle mass.(18,19) In other words, bioimpedance is excellent at identifying sick patients who have either absolute *or* relative extracellular fluid excess and quantifying their worse prognosis; however, it is clear that some of the causes of this overhydration may not be amenable to simple dialysis interventions.

**How might bioimpedance be used to guide fluid management?**

Broadly, there could be two approaches: the first would use information from the bioimpedance device, for example the normally hydrated weight, to set a *treatment goal*, using extrapolated fluid volumes, which the clinician and patient would aim to achieve by various different means (e.g. changing the dialysis prescription, optimising dietary advice, prescribing diuretics). The second approach would be to use the bioimpedance information to identify changes in body composition and use this to inform decision making but not to aim for an absolute target. This approach recognises that the ability for even the best validated bioimpedance device to accurately estimate fluid volumes has some limitations, especially in individuals at extremes of body composition. To achieve the former of these approaches then it is appropriate to use the best validated method, which is bioimpedance spectroscopy (which measures resistance and reactance over a wide spectrum of electrical frequencies, so improving the estimate of excess/reduced tissue fluid).(16) It is also crucially important to recognise that bioimpedance is adding information to what is already a complex decision-making process, rather than providing a simple target applicable to all patients. In fact, this process itself is yet to be fully defined in the literature, let alone the validation of training packages that help clinicians incorporate the information from bioimpedance when setting the dry weight. This issue is not well described in many of the interventional studies designed to evaluate bioimpedance as a tool for guiding fluid management.

**Bioimpedance as a guide to fluid management – effects on outcomes**

In this section we will address both specific studies (randomised controlled trials)(19–26) and two recently published meta-analyses of the existing literature,(27,28) including that undertaken by the UK National Institute for Heath and Care Excellence (NICE) in which a review of the evidence was undertaken by the University of Aberdeen.(29) The number of trials is small enough to summarise individually in Table 1, which also indicates the study design (blinded, open), their inclusion in the two meta-analyses, the intervention approach (goal directed or not) and type of bioimpedance device used. There are some important differences in the scope and content of the two published meta-analyses: the NICE group decided to restrict their analyses to multifrequency (spectroscopy) devices and given that only one such device (the Body Composition Monitor, BCM) has been used in trials to date, their report only included studies using this approach, whereas the analysis of Covic *et al*. was more inclusive. Secondly, the NICE analysis identified two publications from Onofriescu (2012 (30) and 2014(23)) and were not clear as to whether these represented separate studies; given that Covic is both a co-author of the Onofriescu studies and lead author of the meta-analyses that treated this as a single study,(28) it can be concluded that they are indeed the same cohort.

**Effects on mortality, cardiovascular, adverse events**

No studies so far published have been sufficiently powered to address hard outcomes such as mortality or cardiovascular events although one study did report a significant benefit on survival. Grouping these studies together, neither meta-analysis found a significant effect on mortality, even though the hazard ratio (HR) tended to favour bioimpedance. NICE: pooled HR 0.69, 95%CI: [0.23,2.08],(27,29) Covic: HR 0.87 [0.54,-1.39].(28) Insufficient trials reported cardiovascular events for a meaningful meta-analysis. Although one trial was designed to determine the effect on hospitalisation events, mainly due to cardiovascular complications, there was no difference in admission rate when comparing the bioimpedance intervention group with control, HR 1.19 [0.79-1.8].(24) In other studies that reported adverse events the these were not different between groups.

**Effects on surrogate (intermediate) outcomes**

***Fluid status.*** It would be anticipated that in the intervention group, in which clinicians were using BI to direct the setting of normally hydrated weight that fluid status would provide the clearest evidence of benefit, reduced overhydration. For those studies included in the analyses, this was the case for both absolute (reduction in litres of overhydration), Covic: -0.43 [-0.71,-0.15]; NICE: -0.39 [-0.62,-0.15] and relative overhydration, defined as the ratio of fluid overload to extracellular fluid volume, NICE: -1.54 [-3.01,-0.07]. It should be noted that the relative overhydration data included both the Onofriescu publications, so the effect may be over-estimated. Some studies using a different device or study design were excluded from these analyses. In the UK-Shanghai PD study (19) fluid status was stable in all groups studied except for the control anuric Chinese patients in whom a significant worsening of relative fluid status, defined as the ECW/TBW ratio was seen, +0.04, [0.01,0.06]. Similar to this study, the more recently published COMPASS study,(25) also in PD patients did not observe any differences between active and control groups. The common theme here may be that when patients have well preserved residual kidney function, fluid status is more stable so showing a benefit for bioimpedance is not easy without risking volume depletion.

***Blood pressure***. All the studies reported blood pressure. In those trials in which the Body Composition Monitor (BCM) was used, systolic blood pressure was modestly reduced in the bioimpedance guided group. In the Covic meta-analyses, a significant overall reduction compared to the control intervention was seen in the BI directed management: -2.73 mmHg, [-5.00, -0.46]. In the NICE analysis a significant reduction in blood pressure associated with bioimpedance use became insignificant when the Onofriescu 2012 publication was excluded.

***Relationship of blood pressure change to fluid status change.*** This has not been examined before, but it is reasonable to ask whether a change in fluid status from baseline might be associated with a change in blood pressure compared to baseline. To do this we have extracted the relevant information from 6 of the primary study publications (one study stratified randomisation by country and presence of urine output/anuria so providing two additional data pairs) and expressed these as a scatter plot (see figure 1). It can be seen that there is a modest relationship between reduction in overhydration and a fall in systolic blood pressure, (r=0.45, P<0.01) with considerable variation between studies – some showing very little change over time, others similar change in both study limbs. This can be explained in some studies by the heterogeneity in fluid overload at the start of the trial.

***Arterial stiffness (pulse-wave velocity).*** Two trials examined this surrogate measure of cardiovascular risk; in one trial this improved significantly, -2.2 m/s [-3.1, -1.3] compared to the control group, but when followed longitudinally after the trial had completed the values returned to baseline very rapidly, raising the question as to whether actual structural change within the cardiovascular tree had actually occurred. The other study found no change.

**Echocardiographic measures.** Only one trial reported these in which left ventricular mass, (LVM), was the was the primary outcome. LVM did decrease significantly compared to baseline, regressing from 131 ±36 to 116 ±29 g/m2 (P<0.001),(26) without significant change in the control groups, although the proportion of patients with left ventricular hypertrophy fell similarly in both groups. Of relevance to this observation, the Frequent Dialysis Study reported a reduction in left LVM in the short daily dialysis trial that was associated with an improvement in overhydration as determined from single frequency bioimpedance.(31) However, is should be remembered the value of LVM as a surrogate endpoint is yet to be confirmed.(32)

***Residual Kidney Function (Urine volume).*** Not always reported in these trials, two studies found a reduction in urine output associated with bioimpedance use,(21,26) in one case leading to a significantly increased risk of anuria.(26) It may be relevant that these two trials were the most aggressive in their intention to achieve a goal of normal hydration. In the two PD trials in which the intervention did not differ from controls, in which either residual function was the primary endpoint,(25) or in which randomisation was stratified by presence or absence of anuria,(19) use of bioimpedance was not associated with a faster fall. In fact, in UK non-anuric patients it was relatively preserved compared to the control group.(19)

**Conclusion**

The number of studies examining the effect of using bioimpedance to guide fluid management, and thus the conclusions that be drawn, remain modest at this stage. There are, however some patterns developing that are worthy of comment as well as lessons that can be learned regarding study design.

First, it is evident that bioimpedance can be used to drive change in fluid status (in the same way as it can be used to document the change in fluid status due to a specific intervention such as icodextrin in PD patients or more frequent dialysis on HD patients). The more definitive that change is – the more likely there will be a change in an intermediate measure such in blood pressure, pulse wave velocity or LVM. ON the other hand, more aggressive interventions might risk residual kidney function; how these benefits and risks are best balanced is not clear, although preservation of kidney function in dialysis patients is increasingly recognised as valuable.

Second, there is as yet no evidence of mortality, cardiovascular or adverse event risk in either direction associated with use of bioimpedance guided treatment, in contrast to the clear association between overhydration identified by this technology and mortality risk.

Third, and importantly, there is considerable heterogeneity in the way these trials have been reported and conducted. For example, several approaches to presenting data are used (e.g. absolute or relative fluid overload, proportion of patients with fluid overload, various bioimpedance parameters) and several algorithms for applying bioimpedance findings (ranging from longitudinal vector plotting to their use in setting either pre or post dialysis target weights or combining these to calculate ‘time-averaged fluid overload’). But perhaps most important of all, how the bioimpedance is actually used to guide the complex intervention of setting a desirable normally hydrated weight is hard to capture. This complex decision has to take many things into account, including patient level factors such as comorbidity, blood pressure, nutrition, plasma albumin and residual kidney function, all of which suggest the need for a stratified approach in optimising fluid status as well as centre level practice patterns, such as dialysate sodium concentration or whether the residual kidney function is even routinely measured. Some of the trials discussed try to capture the factors that were behind these decisions, but many do not. In designing the BISTRO trial, which is investigating whether using bioimpedance to prevent volume depletion and thus preserve residual kidney function is of value, we have attempted to minimise or explore some of these issues.(33)

**Key Points**

1. There is insufficient evidence to recommend that bioimpedance spectroscopy is used routinely to manage fluid status
2. There is considerable heterogeneity in studies that have investigated the added value of bioimpedance in setting the normally hydrated weight, especially in terms of how the information is applied by clinicians
3. Setting an aggressive bioimpedance target – e.g. fluid depletion post dialysis may accelerate loss or urine volume
4. Bioimpedance does add additional prognostic information and can both lead to a change in fluid status and blood pressure as well as monitoring the effect of an intervention designed to change fluid status

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**Conflicts of Interest**

The authors have no conflicts of interest.

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**Figure Titles and Legends**

**Figure 1.** Relationship between longitudinal changes from baseline in fluid status and systolic blood pressure. Each trial is represented by a pairs of points ( • ) BI intervention, (○) controls, with separate points for the trial that stratified randomisation by country and urine output. The change in overhydration in expressed as a percentage difference in the bioimpedance parameter used to estimate this in that trial, e.g. overhydration volume in litres or extracellular:total body water ratio.

**Table 1: Summary of trials designed to test the added value of bioimpedance in guiding fluid management in dialysis patients.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study Details** | **Trial Design/ intervention** | **N,**  **HD/PD** | **Bioimpedance (BI) metric** | **Primary outcome** | **Intermediate outcomes** | **Main Findings** |
| Darlan, ML; 2010(20)\* | RCT, open label, BI used to adjust dry weight v. usual practice (2 weeks) | 70, HD | BIA | BP (24-hour ambulatory) | Weight, intra-dialytic symptoms | BP reduced non-significantly in BI group |
| Luo, YJ; 2011(21)¶ | RCT, open label, (3m) Target driven weight using BI v. usual practice | 160, PD | BCM | Fluid status | BP | Overhydration less and BP reduced with larger decrease in urine volume in in BI group |
| Hur, E; 2013(26)\*¶ | RCT, open label, (12 m) Target driven weight using BI v. usual practice | 156, HD | BCM | Left ventricular mass | BP, Atrial volume, arterial stiffness | Left ventricular mass reduced in BI group; non-significant reduction in BP and arterial stiffness. Increased risk of anuria in BI group |
| Ponce,P; 2014(22)\*¶ | RCT, cluster randomised trial, 23 centres open or blinded to BI data, (12 m) | 189, HD | BCM (OH index) | Fluid status | BP, Deaths/  Hospitalization | BI group borderline significant less over-hydrated throughout study and at end (both groups improving from baseline). |
| Onofriescu, M; 2014(23)\*¶ | RCT, open label, (12 m) Target driven weight using BI v. usual practice | 131, HD | BCM | Mortality | BP, Arterial Stiffness | All-cause mortality lower in the BI group (event numbers small) |
| UK-Shanghai Bioimpedance Study Tan, BK; 2015(19)\* | **Pr**ospective **o**pen label randomised **b**linded to **e**ndpoint (PROBE). Clinicians instructed to maintain stable fluid status (12 m) | 302, PD  148 in UK  (18 anuric)  159 in Shanghai (75 anuric) | Longitudinal Vector plot | Fluid status volumes determined from bioimpedance: ECW/TBW ratio, ECW and TBW | BP, RKF | In non-anuric patients, fluid status was unchanged in control groups. In Chinese anuric patients the BI group remained stable, controls had worsening fluid status. BP and RKF not different |
| ABISAD-III  Huan-Sheng,C; 2016(24)\*¶ | RCT, open label (12 m) | 298, HD | BCM | All cause hospitalization | BP, Adverse events due to intervention | Dialysis hypotension, fluid overload and CV events less common in the BI group |
| COMPASS Trial  Oh, K-H; 2018(25) | RCT open label, longitudinal BI measures in active group only in which target was ±1L OH (12 m) | 137, PD | BCM (OH index) | RKF | Time to anuria, cardiovascular events, BP, CEHO parameters, arterial stiffness, fluid status | No differences between the groups at the end of the study in any measure. No prescription differences |

\* Studies included in the Covic et al., systematic review (28); ¶ Studies included in the NICE systematic review (27,29)

RKF = Residual Kidney Function; ECHO = Echocardiogram; OH = overhydration;

Figure