# The Elusive Promise of Bioimpedance in Fluid Management of Patients Undergoing Dialysis

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There can be little doubt that bioimpedance measurements in patients undergoing dialysis have predictive value. In a systematic review of cohort studies in which multivariable survival models were reported, 32 out of 38 found that overhydration determined by bioimpedance was associated with worse survival independently of other known predictors such as age, comorbidity, and serum albumin (1). Meta-analysis, regardless of the bioimpedance method used, found mortality to be approximately doubled in the top 15% of overhydrated patients. The increased risk is apparently independent of BP and synergistic with inflammation. Surely all we need to do is to use bioimpedance to normalize hydration in the dialysis population and many lives would be improved or prolonged.

"Would that it were so simple," to quote the amusing scene in the movie *Hail, Caesar* by the Coen brothers. It is of the greatest importance that using bioimpedance to guide fluid management is properly tested by appropriately designed, randomized, controlled trials. Just because an association is strong it cannot be inferred that a causal relationship exists or that it can be manipulated, especially if such manipulation might cause harm. Normalizing hemoglobin did not turn out to be the optimal strategy in this population. The evidence that bioimpedance does provide reasonably accurate estimates of tissue hydration and lean body mass is fairly good (2), particularly if multifrequency spectroscopy is used, but there are other issues to be considered. In fact, the relationship between tissue hydration and lean body mass is also affected by nutritional health. Whether deliberately starved or malnourished because of poverty, as fat and muscle mass decreases there is not necessarily a proportional reduction in the extracellular fluid. This means that even healthy individuals that are malnourished (all too commonly the case in those on dialysis) will appear to be relatively overhydrated, but it is far from clear that the removal of this relative excess in extracellular fluid would automatically improve nutrition. It should also be remembered that bioimpedance cannot distinguish between extravascular and intravascular fluid excess, and how this is partitioned will be determined by other factors, most notably serum albumin levels. This is of particular importance to patients undergoing peritoneal dialysis in whom serum albumin is influenced to a large extent by peritoneal losses and local intraperitoneal inflammation. In addition to these difficulties in interpreting the meaning of bioimpedance evidence of overhydration, it should not be forgotten that normalizing hydration status may not be without risk. Bioimpedance-guided volume depletion, when applied aggressively, may increase the risk of premature loss of residual kidney function, and there is concern associated with aggressive ultrafiltration rates in patients undergoing hemodialysis.

Undertaking and reporting trials that test bioimpedance-guided management of fluid status has proved difficult. The UK Medical Research Council (MRC) advises that an intervention should be considered complex in a number of situations, many of which are encountered when evaluating bioimpedance-guided fluid management (see Table 1) (3). Among these challenges is the appropriate choice of clinical outcome, choice of bioimpedance device, the defining of an appropriate algorithm that incorporates the bioimpedance measure into what is effectively complex decision making, and the satisfactory recording of the actual decision making by clinicians during the course of the study. Despite these challenges, MRC guidance favors an experimental design when evaluating complex interventions if at all possible, and a number of trials have been reported and attempts to synthesize these results have been made (4,5). The trial reported by Tian *et al.* (6) in this volume of *CJASN* is an important addition when considering the overall pattern of findings that emerges.

To date, only two trials have chosen all-cause mortality as their primary outcome (4–6). In both cases it can be argued that this was both overambitious, with power calculations on the basis of a relative mortality reduction with the intervention of between 0.33 and 0.5, and underpowered, given they were modest-sized, single-center studies. It seems very unlikely that such a huge reduction in mortality could ever be achieved regardless of how effective clinicians are at implementing bioimpedance-guided treatment. In the study by Tian *et al.* there was a *post hoc* decision to extend the trial up to 3 years so as to explore whether there was a continued effect of the intervention. They observed 13 deaths in the bioimpedance group and 31 in the control group (the study randomized 240 participants), which is a large difference, but again, caution must be expressed in assuming this could all be attributed to the

**Table 1. Bioimpedance-guided fluid management fulfils many of the criteria of a complex intervention**

| Characteristics of a Complex Intervention (UK Medical Research Council, 2008) (3) | Examples of How This Might Be Reflected in Bioimpedance-Guided Fluid Management |
|---|---|
| Interacting components within experimental and control interventions | Other measures (*e.g.*, BP, chest x-ray) might conflict the with the bioimpedance guidance |
| Behaviors of those delivering or receiving the intervention | Clinicians or patients may have strong preferences for fluid management |
| Complexity at the organizational level in delivering the intervention | Different staff, movement between dialysis facilities, center-level practices |
| Number and variability of outcomes | Which outcome is most important? Competing outcomes, *e.g.*, better BP control might sacrifice residual kidney function. Focusing on a single primary outcome may not be appropriate. |
| Flexibility in tailoring of the intervention is allowed | Changing target weight over a period of time according to individual tolerability |

intervention. Of the two published meta-analyses (4,5), no conclusive evidence regarding the benefits of bioimpedance-guided fluid management on mortality could be demonstrated.

Other primary outcomes that have been selected for trials include changes in left ventricular mass index (4,5), improved fluid status as determined from bioimpedance (7), and preservation of residual kidney function (8), with BP and other measures of cardiovascular health, such as pulse-wave velocity, being treated as secondary outcomes. The relevance of left ventricular mass index as a surrogate for improved cardiovascular outcomes in trials has recently been questioned (9), and the Fluid trial has not reported their results so far, although data presented at the 2018 International Society of Peritoneal Dialysis conference in Vancouver indicated that it was a negative study. There is, however, a signal that using bioimpedance to guide fluid management might improve BP control (4,5), although this is not supported by a recent study (6).

It can be argued that the most important outcome to consider at this point is whether bioimpedance-guided management results in an improved, *i.e.*, less overhydrated fluid status. Without any demonstratable effect on this outcome it is hard to see how the hoped-for clinical benefits might follow. This is more complicated to assess, for reasons already alluded to, but a pattern does emerge. The most striking finding of these trials is that when residual kidney function is present, fluid status as determined by the overhydration index or the extracellular/intracellular ratio or extracellular/total body water ratio, remains unchanged over time (typically 12 months). In contrast, when anuric patients are studied there is a greater likelihood that the extracellular/intracellular ratio will worsen in controls, making it easier to demonstrate a between-group difference at the end of the trial. This pattern was also apparent in the study by Tian *et al.* as shown in their Table 3. This trial has a high proportion of anuric patients (being more comparable to the anuric Shanghai group in the study by Tan *et al.* [7]) What is less certain, but entirely possible, is that worsening fluid status in the anuric control group is just as much a function of progressive muscle wasting, which, as we have already seen, will lead to a relative increase in the extracellular tissue fluid, as it is to inferior fluid management. It is striking in the study by Tian *et al.* (6) that one of the most significant longitudinal changes was an improvement in nutritional status of the intervention group, as judged from the subjective global assessment.

There are further difficulties in interpreting these results when we remember that bioimpedance is being used to guide a complex clinical decision—guidance that the clinician must be able to override on the grounds of clinical safety. Unless this is captured and reported in bioimpedance trials, along with the clinical intervention to change fluid status, interpretation will remain problematic. Usually this has been inadequately recorded, and when it is, it is clear that in some trials that no real attempt was made by clinicians to normalize the fluid status according to bioimpedance readings (8). In others, there was a definite center effect in the fluid management of patients undergoing peritoneal dialysis: in centers where the target weight was reduced in nonanuric patients so as to improve BP control, total body weight dropped (possibly because of loss of lean body mass), but if anything, the extracellular/total body water ratio worsened, and not surprisingly there was no effect on BP (7). A recent Dialysis Outcomes and Practice Patterns Study analysis of fluid management in patients undergoing hemodialysis also shows clear center effects in fluid management (10).

We should not give up in light of these difficulties in trial design, but rather learn from earlier studies in an attempt to establish the role, if any, of bioimpedance in clinical practice. Lessons learned include the choice of appropriate outcomes for which trials can be realistically powered, the need to stratify for residual kidney function and possibly for specific types of comorbidity (*e.g.*, heart failure), recording of center-level practices, and the implementation of templates that capture the process of clinical decision making, including how bioimpedance measurements were incorporated when making these decisions. In designing Bioimpedance Spectrospopy to Improve Renal Output (11), which is examining whether using bioimpedance spectroscopy to avoid extremes of fluid status, in particular underhydration, might benefit preservation of residual kidney function, we have attempted to take these issues into account. Undoubtedly more such trials will be needed if the potential for bioimpedance to guide fluid management is to be realized.

## Disclosures

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