

Importance of Whole-Body Bioimpedance Spectroscopy for the Management of Fluid Balance

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Key Words

Fluid overload · Bioimpedance spectroscopy · Normohydration target · Haemodialysis

Abstract

Introduction: Achieving normohydration remains a non-trivial issue in haemodialysis therapy. Preventing the deleterious effects of fluid overload and dehydration is difficult to achieve. Objective and clinically applicable methods for the determination of a target representing normohydration are needed. **Methods:** Whole-body bioimpedance spectroscopy (50 frequencies, 5–1,000 kHz) in combination with a physiologic tissue model can provide an objective target for normohydration based on the concept of excess extracellular volume. We review the efficacy of this approach in a number of recent clinical applications. The accuracy to determine fluid volumes (e.g. extracellular water), body composition (e.g. fat mass) and fluid overload was evaluated in more than 1,000 healthy individuals and patients against available gold standard reference methods (e.g. bromide, deuterium, dual-energy X-ray absorptiometry, air displacement plethysmography, clinical assessment). **Results:** The comparison with gold standard methods showed excellent accordance [e.g. R^2 (total body water) = 0.88; median \pm SD (total body water) = -0.17 ± 2.7 litres]. Agreement with high-quality clinical assessment of fluid status was demonstrated in several hundred patients (median \pm SD = -0.23 ± 1.5 litres).

The association between ultrafiltration volume and change in fluid overload was reflected well by the method (median \pm SD = 0.015 ± 0.8 litres). The predictive value of fluid overload on mortality underlines forcefully the clinical relevance of the normohydration target, being secondary only to the presence of diabetes. The objective normohydration target could be achieved in prevalent haemodialysis patients leading to an improvement in hypertension and reduction of adverse events. **Conclusion:** Whole-body bioimpedance spectroscopy in combination with a physiologic tissue model provides for the first time an objective and relevant target for clinical dry weight assessment.

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Introduction

Chronic volume overload causes left ventricular hypertrophy [1], while dehydration can cause intradialytic adverse events; both are linked to an increased morbidity [2] in haemodialysis patients. The task of fluid management in end-stage renal disease patients is to guide the patient on the narrow but safe path between the deleterious effects of volume overload and dehydration. Without the availability of an objective target [2], this task is difficult and can be very time-consuming when reliant on trial-and-error methods [3–5]. As volume overload and dehydration both influence the extracellular water vol-

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ume (ECW), it is reasonable that this essential target could be based on the concept of an individual, normal extracellular volume (normohydration). The absolute quantity of extracellular water is not only influenced by the hydration status, but also by the underlying body composition [6]. Measures of body composition such as intracellular water, fat mass or body weight [7] thus must also be taken into account for the determination of a normohydration target. The lack of clearly defined endpoints limits to a large extent the possibility to obtain objective measures with methods for fluid status assessment such as clinical assessment, inferior vena cava diameter, echocardiography measurements or chest X-rays. Several authors have discussed the possible application of bioimpedance spectroscopy for fluid management [8, 9]. However, several bioimpedance-based methods are available. Single-frequency bioimpedance has been the mainstay for several decades and the empirical equations used depend on assumed population constants. Bioimpedance spectroscopy by contrast offers the possibility to determine intra- and extracellular volume independently [10]. This is especially important to calculate the body composition irrespectively of the fluid overload. Segmental methods [11] and some whole-body methods [12] have focussed solely on intradialytic monitoring of the patient, which aim to indicate when the patient achieves dry weight by continual titration. By contrast, interdialytic whole-body monitoring allows the determination of a normohydration target in a single measurement step, which is the ideal basis for a mid-term fluid management strategy (several dialysis treatments). Determining a target and thus the objective comparison between patients or patient groups is therefore only possible with interdialytic whole-body bioimpedance spectroscopy.

Methods

Measuring Device and Body Composition Model

A method for calculating normal hydration status (normohydration) [13] has been presented recently. This method is based on the hypothesis of constant tissue hydration properties [14] and the assumption that fluid overload in dialysis patients is primarily expressed in an expanded extracellular volume. A normal ECW then represents the normohydration goal. However, normal ECW in healthy adults ranges from 13 to more than 21 litres. Besides the obvious influence of body weight, this wide range is also strongly dependent on body composition (weight, muscle and fat content). Thus, any method to determine normal ECW in patients with an impaired hydration status must take into account body composition.

Fluid overload can be calculated from the difference between the normal expected ECW and the actual measured ECW. The normohydration target is thus defined as the difference between the weight at the time of the measurement and the fluid overload.

A new device, the body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany), provides a convenient method to obtain ECW and total body water precisely (table 1). These volumes are determined by measurement of whole-body bioimpedance spectroscopy at 50 frequencies via electrodes placed on the wrist and ankle. The inbuilt body composition model calculates not only the fluid overload but also normally hydrated lean tissue mass and normally hydrated adipose mass. Although patients' plasma fluid contains minerals and other solutes, the difference in volume between pure water and fluid is negligible for all practical purposes [13]. Therefore, the terms fluid status and hydration status may be used interchangeably in this context.

Findings from Clinical Studies

Validity of the Target/Validity of the Whole-Body Bioimpedance Spectroscopy Results

The BCM model has been validated in multicentre studies against the respective gold standards in healthy subjects and in haemodialysis patients as shown in table 1. Dilution methods are considered as gold standard for measuring extracellular (sodium bromide) and total body (deuterium, tritium) volumes (total body water), whereas the total body potassium method is used to determine intracellular volume. The calculated body composition has been validated in more than 500 healthy subjects and patients against the reference methods dual-energy X-ray absorptiometry, air displacement plethysmography [15] and 4-compartment modelling [16]. The validity of the calculated fluid overload has been demonstrated via clinical assessment in several hundred haemodialysis patients [17, 18] and additionally via the withdrawn ultrafiltration volume [19]. A very good agreement in all gold standard comparisons was achieved (table 1).

Clinical Relevance of the Normohydration Target

The impact of fluid overload on mortality demonstrates the clinical relevance of the normohydration target. In a recent study by Wizemann [unpubl. data], the 3.5-year mortality of 269 haemodialysis patients was analysed. The cut-off for the fluid overload was set to 2.5 litres above the normohydration target. The Cox adjusted hazard ratios (HR) revealed that age (HR = 1.051/year; $p < 0.001$), systolic blood pressure (HR = 0.9861/mm Hg; $p = 0.014$), diabetes (HR = 2.766; $p < 0.001$), peripheral vascular disease (HR = 1.68; $p = 0.045$) and relative fluid

Table 1. Overview of the available validation data (n >1,000) for the combination of whole-body spectroscopy technology and the physiologic tissue model described

	Gold standard method	Number	R ²	Mean ± SD	Reference
ECW	bromide	120 healthy subjects 32 HD patients	0.76	-0.1 ± 1.8 litres	32
ICW	total body potassium		0.78	0.2 ± 2.3 litres	
TBW	deuterium		0.88	-0.2 ± 2.3 litres	
	tritium	42 healthy subjects	0.94	-1.06 ± 1.9 litres	
Fat	dual-energy X-ray absorptiometry	41 HD patients 19 liver patients 130 cancer patients 321 healthy subjects	0.82	-1.1 ± 4.2 kg	15
	air displacement plethysmography	25 HD patients 19 liver patients 141 healthy subjects	0.84	1.0 ± 4.1 kg	
FFM	4-compartment modelling [33]	25 HD patients 141 healthy subjects	0.9	SEE = 3.4% -0.2 ± 3.5 kg	16
	dual-energy X-ray absorptiometry	22 HD patients 222 healthy subjects	0.89	-0.9 ± 3.7 kg	
Fluid overload	clinical assessment	370 HD patients	n.a.	-0.23 ± 1.51 litres	17
	ultrafiltration volume	55 HD patients	R = 0.76	0.015 ± 0.8 litres	19

HD = Haemodialysis; ICW = intracellular water volume; TBW = total body water; FFM = fat-free mass; SEE = standard error of the estimate.

overload (fluid overload normalized to ECW; HR = 2.102; p = 0.003) were the only significant predictors of mortality in the analysed patient population. Wizemann [unpubl. data] concluded that fluid overload is an important and independent predictor of mortality in chronic haemodialysis patients secondary only to the presence of diabetes. In a recent paper, Chen et al. [20] showed that the ratio of ECW to intracellular water assessed with bioimpedance spectroscopy was a strong predictor of survival in peritoneal dialysis patients. It would be very interesting to reassess these results using the method to calculate the normal hydration status and to compare these results to the work of Wizemann.

Percentage of Fluid Overload Patients

An analysis of 1,500 prevalent European haemodialysis patients (mean age: 64 ± 14 years; mean BMI: 26.8 ± 5.4; mean systolic blood pressure: 141 ± 24 mm Hg) from 22 European haemodialysis centres revealed that 25% of patients are more than 2.5 litres above the normohydration target before the treatment [unpubl. data]. Of these grossly fluid-overloaded patients 38% presented normal

blood pressure (<140 mm Hg) despite fluid overload being present.

Achieving the Target of Normohydration

Machek et al. [21] adjusted the fluid status of the complete patient population of one dialysis centre towards the normohydration target over one year. The fluid status was assessed frequently (at least monthly) in all patients (n = 62) with the BCM. Attempts were made to achieve a target of a predialytic volume overload of no more than 2.5 litres above the normohydration target. Where possible the target for the end of the dialysis session was set between -1.1 and 1.1 litres. To analyse the impact of the fluid status change, the patient population was divided into three groups: the hyperhydrated group (fluid overload >3 litres; n = 12), the adverse event group (patients with more than 16% adverse events in the previous 4 weeks; n = 12) and the remaining patients (n = 32). In the hyperhydrated group, fluid overload was reduced by 2.2 litres (p < 0.001) without increasing the occurrence of adverse events. This resulted in a reduction in systolic blood pressure of 20 mm Hg (p = 0.029). Ad-

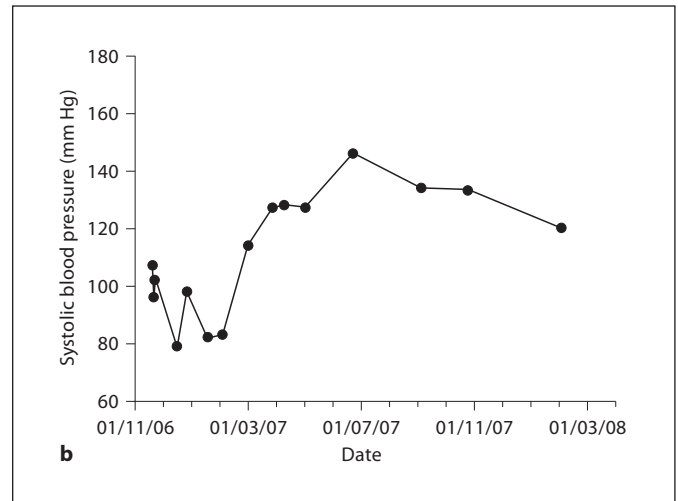
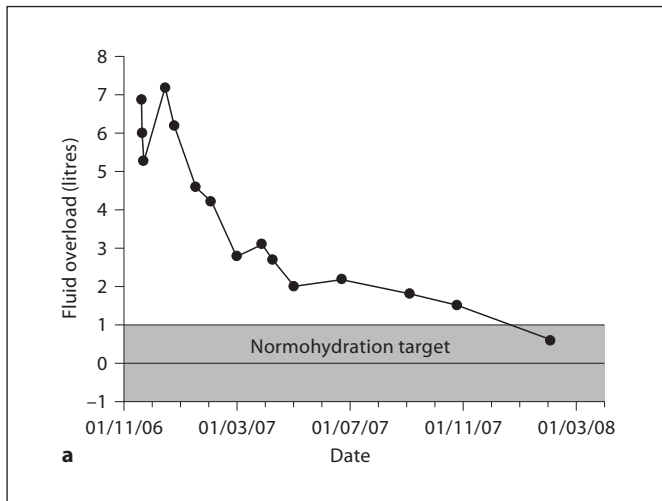


Fig. 1. Achieving the normohydration target in a patient with cardiac problems. The slow reduction in fluid overload targeted by the whole-body spectroscopy method improves the patient status dramatically. Shown are the fluid overload (a) and the systolic blood pressure (b) both measured before treatment.

Table 2. Following the target of normohydration in all haemodialysis patients in one centre (data from Machek et al. [21])

	Hyperhydrated patients		Adverse event patients	
	start	after fluid adjustment	start	after fluid adjustment
Fluid overload before dialysis, litres	4.2 ± 0.6	2 ± 0.8 (p < 0.001)	0.4 ± 0.8	1.7 ± 0.8 (p = 0.004)
Fluid overload after dialysis, litres	2 ± 1.1	-0.7 ± 1.2 (p < 0.001)	-2.3 ± 1.2	-1 ± 0.7 (p = 0.010)
Blood pressure before dialysis, mm Hg	153 ± 17	133 ± 31 (p = 0.042)	155 ± 27	159 ± 19
	89 ± 10	70 ± 25	82 ± 15	77 ± 9
Antihypertensive medication	1.6 ± 1.5	1 ± 1.2 (p = 0.031)	0.5 ± 0.8	0.25 ± 0.45
Adverse events (in previous 4 weeks), %	0.7 ± 2.4	0.7 ± 2.4	25.7 ± 10	6.9 ± 7.8 (p < 0.001)

The hyperhydrated patients presented with more than 3 litres fluid overload at the time of the first BCM measurement. Patients with more than 16% adverse events in the 4 weeks prior to the BCM measurement were categorized as adverse event patients.

ditionally, a 37.5% reduction in antihypertensive medication (p = 0.031) was achieved. In the adverse event group, the fluid status was increased by 1.3 litres (p = 0.004) resulting in a 73% reduction in intradialytic adverse events (p < 0.001) without increasing the blood pressure as reported in table 2.

Discussion

Whole-body bioimpedance spectroscopy has been shown to be as precise as the gold standard reference methods. The combination of this technology with the

BCM model described in Chamney et al. [13] allows for the first time a target normohydration to be calculated. This target has the potential to bring about dramatic improvements to haemodialysis patients.

At least 25% of the haemodialysis patients are likely to be more than 2.5 litres away from the normohydration target [22].

When aiming for the normohydration target it is possible to reduce the fluid overload safely whilst avoiding dehydration. It is necessary to approach the target slowly, but without losing sight of the target. It may take more than 1 month or in extreme cases even 4–5 months to reach normohydration [23, 24]. The studies reviewed to

date indicate that a gradual change in fluid status is successful in improving hypertension control without causing additional adverse events, reducing antihypertensive medication and improving the well-being of the patient as reported in table 2.

To illustrate these experiences a patient case is shown in figure 1. This patient suffered from severe cardiac dysfunction, was prone to intradialytic adverse events and presented a high fluid overload of 7 litres above the normohydration target combined with a predialytic systolic blood pressure below 100 mm Hg. The patient was no longer able to walk and had lost his appetite. The clinical staff approached the normohydration target very slowly giving his circulatory system time to adjust to the reduction in fluid status. In the first 6 months, the fluid status was reduced by around 1 l/month. This rate of reduction was further reduced to 500 ml/month once a predialytic fluid overload of 2 litres was achieved.

During the entire dry weight reduction period the patient did not present any intradialytic adverse events. His quality of life improved significantly, he regained his appetite and could recommence everyday activities. Together with the reduction in fluid status, the systolic blood pressure rose towards normal ranges, very similar to a congestive heart failure patient described by Ronco et al. [25].

The 'U-shape' relationship [26] of mortality and blood pressure has attracted ongoing discussion [27]. It has been concluded that cardiovascular risk is increased when systolic blood pressure is lower than 110 mm Hg. It is possible that most patients with low systolic blood pressures who run the highest mortality risk are actually severely volume-overloaded patients such as the example presented in figure 1. D'Amico and Locatelli [28] hypothesized that the association between low systolic pressure and increasing mortality is attributed to cardiac failure as a consequence of long-term hypertension. Further-

more, Li et al. [29] associated steadily falling systolic blood pressure over months with a high mortality risk. Levin [30] has suggested that blood pressure should be controlled as early as possible before cardiomyopathy leads to permanent hypotension and certain early death. Wabel et al. [22] showed that at least 10% of haemodialysis patients can be expected to have high fluid overload and low blood pressure – a situation that often remains undetected. As the BCM is invaluable for the objective assessment of fluid overload it is likely to bring further insight into the discussion of the 'U-shaped' mortality and blood pressure relationship.

The normohydration target is a reference against which individual targets can be set. In some centres [31], attempts are made to achieve normohydration before dialysis, which implies some dehydration after dialysis. However, there may be multimorbid haemodialysis patients with, for example, cardiac output failure where the individual target may need to be set above the normohydration target. In situations where cardiac dysfunction might be indicated, further confirmation should be sought with additional investigations such as echocardiography measurements.

Conclusion

Whole-body bioimpedance spectroscopy in combination with a physiologic tissue model provides for the first time an objective target which can be used for clinical management of fluid balance. These preliminary studies indicate that achieving optimal fluid status is likely to have a profound impact on reducing mortality. Less intradialytic adverse events and better hypertension control can be achieved even against the background of a history of long-term fluid overload.

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