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ARTICLE

Body composition, energy expenditure and physical activity

Fluid balance and phase angle as assessed by bioelectrical impedance analysis in critically ill patients: a multicenter prospective cohort study

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Abstract

Background Bioelectrical impedance analysis (BIA) is a validated method to assess body composition in persons with fluid homeostasis and reliable body weight. This is not the case during critical illness. The raw BIA markers resistance, reactance, phase angle, and vector length are body weight independent. Phase angle reflects cellular health and has prognostic significance. We aimed to assess the course of phase angle and vector length during intensive care unit (ICU) admission, and determine the relation between their changes (Δ) and changes in body hydration.

Methods A prospective, dual-center observational study of adult ICU patients was conducted. Univariate and multivariable regression analyses were performed, including reactance as a marker of cellular mass and integrity and total body water according to the Biasioli equation ($TBW_{Biasioli}$) and fluid balance as body weight independent markers of hydration.

Results One hundred and fifty-six ICU patients (mean ± SD age 62.5 ± 14.5 years, 67% male) were included. Between days 1 and 3, there was a significant decrease in reactance/*m* (−2.6 ± 6.0 Ω), phase angle (−0.4 ± 1.1°), and vector length (−12.2 ± 44.3 Ω/m). Markers of hydration significantly increased. Δphase angle and Δvector length were both positively related to Δreactance/*m* ($r^2 = 0.55$, $p < 0.01$; $r^2 = 0.38$, $p < 0.01$). Adding $\Delta TBW_{Biasioli}$ as explaining factor strongly improved the association between Δphase angle and Δreactance/m ($r^2 = 0.73$, $p < 0.01$), and Δvector length and Δreactance/*m* ($r^2 = 0.77$, $p < 0.01$).

Conclusions Our results show that during critical illness, changes in phase angle and vector length partially reflect changes in hydration.

Introduction

Patients admitted to the intensive care unit (ICU) often suffer from the loss of muscle mass (MM) due to immobility, inflammation, and malnutrition [1, 2]. Loss of MM is associated with delayed weaning from mechanical ventilation, infection, increased morbidity and mortality, and prolonged functional disability [3–5]. Although intensively studied, muscle wasting remains difficult to quantify in critically ill patients [6–8].

Bioelectrical impedance analysis (BIA) is a simple, noninvasive, inexpensive method to assess body composition at the bedside [9–12]. BIA measures the opposition to an alternating current that passes through body compartments (resistance, *R)* and the delay in conduction by membranes (reactance, Xc) [13]. Xc thereby reflects cellular mass and integrity. BIA can be used to estimate the mass of body compartments such as MM, body cell mass (BCM), and fat-free mass (FFM) from the parameters resistance and reactance. One of the conceptual assumptions of these calculations is a normal fluid status [14, 15]. Critical illness-related alterations in hydration and fluid distribution thereby affect the reliability of MM and BCM calculations. In a study in dialysis patients, BIA-derived BCM was suggested

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to be less driven by changes in fluid balance than FFM and would therefore be a more suitable marker body composition in patients with severe hydration disturbances [16]. However, both MM and BCM equations require body weight, which is often unreliable during critical illness.

BIA also allows calculation of the phase angle, as the arctangent of Xc/*R*, which appears to be a composite index of cellular health. In critically ill patients, phase angle on ICU admission was independently associated with patient outcome [17–20]. The measurement of phase angle does not require body weight. However, phase angle does seem to vary with hydration [21–23]. Low-phase angle may therefore be caused by low-cellular mass and quality, but also by fluid overload [19]. Older studies demonstrated that height-normalized impedance (vector length) is inversely related to total body water (TBW) [21, 24]. Vector length is also weight independent. Up to now, a systematic evaluation of the association between alterations in body hydration and changes in phase angle, vector length, MM, and BCM in critically ill patients has not been published.

The aim of this study was to determine to what extent the change in phase angle and vector length during ICU admission is associated with changes in cellular mass and integrity (reactance) and to what extent this change is additionally associated with changes in body hydration. Secondary aims were to determine the relation between changes in MM and BCM, and changes in body hydration.

We hypothesized that increased body hydration would be associated with a decline in phase angle and vector length due to decreased membrane quality and cellular health. Furthermore, we hypothesized that increased body hydration would lead to overestimation of MM and BCM.

Methods

Study design and subjects

This prospective observational cohort study was conducted in the mixed medical surgical ICU of the Amsterdam University Medical Center, location VUmc between October 2014 and May 2015 and the University Medical Center Groningen between September 2016 and February 2018. We included patients within 24 h of ICU admission if the expected length of stay (LOS) was ≥72 h. Exclusion criteria were end of life care, BMI ≥ 35, pregnancy, immunodeficiency, missing limb or hemiplegia, skin defects on hands or feet, inability to lay still or supine, admission during the weekends when no investigator was present, and the presence of external fixators. BIA parameters and fluid balance were assessed on days 1, 3, and 7 of ICU admission.

The study protocol was approved by the local research ethics committee (VU University Medical Center, amendment to METc reference number 2013.318, UMC Groningen, METc 2016.691). Since all patient data were coded and BIA is noninvasive with a low patient burden the need for informed consent was waived.

Data collection and management

Clinical data were obtained from the patient data management system (EPIC® (Verona, WI, USA) or Metavision® (Itémedical, Tiel, The Netherlands)) and included basic demographics, admission type and diagnosis, severity of illness scores, ICU and hospital LOS.

Height was mostly obtained from the patient, his representative, or measured with a tape while the patient was in supine position. Pre-ICU admission weight was obtained from either EPIC® or Metavision® when patients had been weighed in the hospital before their ICU admission or by asking the patient or a representative. If feasible, patients were weighed on study days using a bed scale.

Baseline BIA was performed within 24 h of ICU admission and repeated on days 3 and 7 with a BIA 101 Anniversary edition apparatus (GLNP Life Sciences, AKERN, Florence, Italy), a single-frequency device (50 kHz) using Bodygram PLUS software. The conventional body compartment assessment is enhanced by an innovative analysis of BiaVector powered by artificial intelligence. Patients were measured in (semi-)supine position. After alcohol cleaning, single-use gel electrodes (AKERN BIATRODES, AKERN, Florence, Italy) were placed dorsally on the hand and foot, preferably on the right side and/or non-cannulated side of the body. However, in some patients a left-sided configuration was required because of bandages or cannulas on the right side. Two electrodes were placed on the third metacarpophalangeal and metatarsophalangeal joint of the hand and foot. The other two electrodes were placed in alignment with and proximal to the first electrode at a minimum distance of 5 cm. Arms and legs were in slight abduction to avoid contact between the extremities and other parts of the body. Catheter tubes were drained before measurements.

BIA measures resistance (*R*) and reactance (Xc) and calculates phase angle as the arctangent of Xc/*R*. Resistance, reactance, and phase angle were measured at 50 kHz. The Akern device is phase sensitive allowing a direct measurement of resistance, reactance, and phase angle, obviating the use of multifrequency measurements. Impedance is calculated as $\sqrt{R^2 + \mathrm{Xc}^2}$. Height was entered to standardize resistance, reactance, and impedance to resistance/*m* (*R*/*m*), reactance/*m* (Xc/*m*), and vector length which is height-normalized impedance (*Z*) and is calculated as $\sqrt{R/m^2 + \mathrm{Xc}/m^2}$). These variables are independent of

body weight. Changes in hydration can also be visualized using the bioimpedance vector analysis (BIVA) plot. However, summarizing the change in these data points for a large group of patients is difficult. We indirectly used the BIVA plot by measuring its components, such as the phase angle and vector length. In addition, BIA computes TBW, FFM, hydration score (TBW/FFM × 100%), BCM, and MM using proprietary software (Bodygram PLUS, AKERN, Florence, Italy). These calculations require body weight and sex.

To quantify hydration, we used the body weight independent variables: $TBW_{Biasioli}$ and cumulative fluid balance (CFB). $TBW_{Biasioli}$ is calculated as $(height(cm)^2/R) \times 0.713$ [25, 26]. This equation is derived from Nyboer's equation $Z = \frac{\rho L^2}{V}$ where Z is impedance in ohm, ρ is volume resistivity in ohm cm, L is conductor length in cm, and V is volume in liter. Nyboer's equation demonstrates that impedance is inversely related to biological volume, as are resistance and reactance [26, 27]. Lukaski et al. [27] demonstrated a strong correlation between $TBW_{Biasioli}$ and TBW determined by D_2O dilution ($r = 0.95$, $p < 0.0001$). Although not perfect, we chose $TBW_{Biasioli}$ because this estimation of TBW is independent of body weight, has a biophysical base, lacks reliance on regression models, and correlated best with TBW in humans ($r = 0.95$) [27].

Body weight dependent markers of hydration were calculated by the Bodygram PLUS software, which enhances conventional body compartment assessment by an innovative analysis of BiaVector powered by artificial intelligence. Bodygram PLUS presents TBW and hydration score. Hydration score is calculated as: (TBW/FFM) × 100%. Normal hydration score values are given as 72.7 and 74.3% [28]. Up to now, the Bodygram PLUS equations are not released. Since the body weight dependent variables are more prone to measurement errors due to unreliable body weight, we chose to report most of these results separately in e-Supplements.

CFB was acquired from the patient data management systems EPIC® and Metavision® and consists of the algebraic sum of daily fluid intake and output. CFB were retrieved at the time point of each BIA measurement.

Statistical analysis

The number of BIA measurements required to determine the relation between Δphase angle and Δreactance/m, using a two-tailed α of 0.05 and a power of 0.80, is 343.

Results are presented for body weight independent and body weight dependent variables separately. Continuous variables were tested for normality with the Kolmogorov–Smirnov test, histograms, and normal-quantile plots. Data are presented as means ± standard deviations when normally distributed, medians and interquartile ranges when non-normally distributed, or numbers (percent) when categorical. Two-tailed paired t-tests and ANOVA's for repeated measures were used as appropriate to determine differences between days. We use Δ to describe the change in time. Univariate analysis was used to determine the relation between Δphase angle and Δvector length between days 1 and 3 on the one hand, and concomitant changes in resistance (R/m), cellular mass and integrity (Xc/m), and markers of hydration on the other. To determine whether and to what extent the association between Δphase angle and Δvector length with ΔXc/m was additionally determined by changes in hydration, multivariable regression analysis was performed with $\Delta TBW_{Biasioli}$ and ΔCFB added as determinants. Multicollinearity and interactions were tested. Regression analyses were also conducted with Δphase angle and Δvector length in relation to body weight dependent markers of hydration. Since these variables require a reliable body weight, which is often not reliable in the ICU setting, we chose to present these results in Supplementary 1.

Similar univariate and multivariable analyses were performed for ΔBCM and ΔMM as dependent variables. Again, these data are prone to measurement error due to unreliable body weight and the fact that the Bodygram PLUS equations are not validated for the ICU population. Since these data might still be of interest, the results are presented in Supplementary 2. Another Supplement is available showing the relation between changes in Xc/m, phase angle, vector length, BCM, and MM in relation to severity of disease scores (Supplementary 3). The collected data were analyzed using SPSS IBM 25 (SPSS Inc, Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 156 patients were enrolled in the study (consort diagram in Supplementary 4), 87 patients from the Amsterdam University Medical Center, location VUmc and 69 patients from the University Medical Center Groningen. Reasons for exclusion were admission to the ICU > 24 h before screening, an expected LOS < 72 h, BMI ≥ 35, and admission during weekends or during absence of the operators. Three patients declined participation.

The baseline characteristics of the study population are shown in Table 1. Mean age was 62.5 ± 14.5 years, 67% of the patients were male. The most frequent reasons for ICU admission were cardiovascular disease (28%), respiratory failure (17%), and trauma (15%).

Table 1 Baseline characteristics of patients.

Patient characteristics	Days 1 and 3 ($n = 156$)[a]	Day 7 ($n = 71$)
Age, year	62.5 ± 14.5	64.8 ± 12.6
Gender		
Male, *n* (%)	104 (67)	44 (62)
Female, *n* (%)	52 (33)	27 (38)
Pre-ICU LOS at general ward, days	0 [0–1]	0 [0–2]
ICU LOS, days	8 (4–15)	14 (9–27)
Height, cm	176 ± 9.7	174 ± 9.7
Weight, kg	82.4 ± 15.9	84.6 ± 19.4
BMI, kg/m^2	26.6 ± 4.5	27.9 ± 5.6
APACHE II score	21.8 ± 8.1 ($n = 87$)	23.1 ± 8.4 ($n = 44$)
APACHE IV score	79.3 ± 27.3 ($n = 69$)	74.2 ± 22.8 ($n = 27$)
Admission SOFA score	8.0 ± 3.2	8.3 ± 3.6
Admission diagnosis, *n* (%)		
Postoperative	18 (12)	10 (14)
Trauma	23 (15)	13 (18)
Neurologic	20 (13)	12 (17)
Respiratory	27 (17)	14 (20)
Cardiovascular/vascular	43 (28)	9 (13)
Gastrointestinal	7 (4)	6 (8)
Sepsis/SIRS	8 (5)	4 (6)
Other	10 (6)	3 (4)
Admission type, *n* (%)		
Medical	84 (54)	41 (58)
Surgical	72 (46)	30 (42)

Data are shown as mean ± SD, median [IQR] or *n* (%) when appropriate. APACHE scores are divided in APACHE II, which is measured in the Amsterdam University Medical Center, location VUmc, and APACHE IV which is measured in the University Medical Center Groningen.

APACHE acute physiology and chronic health evaluation as assessed 24 h after ICU admission, *BMI* body mass index, *ICU* intensive care unit, *LOS* length of stay, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment.

[a]Characteristics of the patients present on days 1 and 3.

Course of bioelectrical impedance analysis and fluid balance

A total of 383 BIA measurements were performed. BIA results, hydration parameters, and fluid balance on days 1, 3, and 7 are shown in Table 2.

Body weight independent variables

By day 3, *R*/*m*, Xc/*m*, phase angle, and vector length significantly decreased (−12.0 Ω, $p < 0.01$; −2.6 Ω, $p < 0.01$; −0.4°, $p < 0.01$; −12.2 Ω/m, $p < 0.01$), while $TBW_{Biasioli}$ and CFB showed a significant increase (3.8 L, $p < 0.01$; 2.1 L, $p < 0.01$). By day 7, Xc/*m* and phase angle decreased further (−1.8 Ω, $p = 0.04$; −0.4°; $p < 0.01$), while CFB increased (3.5 L, $p < 0.01$). *R*/*m*, vector length, and $TBW_{Biasioli}$ were not significantly different between days 1 and 7.

Body weight dependent variables

By day 3, calculated MM and BCM showed a significant decrease (−1.1 kg, $p = 0.02$; −1.3 kg, $p < 0.01$), while $TBW_{Bodygram}$ and hydration score significantly increased (2.1 L, $p < 0.01$; 2.2%, $p < 0.01$). By day 7, BCM was also significantly decreased (−1.5 kg, $p = 0.03$). $TBW_{Bodygram}$ and hydration score showed a significant increase (2.4 L, $p = 0.02$; 1.7%, $p < 0.01$). MM was not significantly different between days 1 and 7.

Figure 1 shows box plots of percentage change of Δ*R*/*m*, ΔXc/*m*, Δphase angle, Δvector length, $\Delta TBW_{Biasioli}$, $\Delta TBW_{Bodygram}$, Δhydration score, ΔBCM, and ΔMM between days 1–3 and days 1–7. Due to its large variation, ΔCFB was not plotted but shown in the table below the box plots.

To determine the relation between changes in phase angle and vector length on the one hand and changes in Xc/*m*, fluid balance, and body hydration on the other, we focused on changes between days 1 and 3 because these were most significant. Matrices of these correlations are shown in Fig. 2.

Relation between changes in bioelectrical impedance markers and markers of hydration

Δphase angle was positively related to ΔXc/*m* ($r^2 = 0.55$, $p < 0.01$), while inversely related to ΔCFB ($r^2 = 0.08$, $p < 0.01$; Table 3). On univariate analysis, no significant relation was seen between Δphase angle and $\Delta TBW_{Biasioli}$ or Δ*R*/*m*. Δvector length showed a positive relation with ΔXc/*m* ($r^2 = 0.38$, $p < 0.01$) and Δ*R*/*m* ($r^2 = 1.00$, $p < 0.01$). Δvector length was inversely related to ΔCFB ($r^2 = 0.28$, $p < 0.01$) and $\Delta TBW_{Biasioli}$ ($r^2 = 0.70$, $p < 0.01$).

To determine whether and to what extent the association between Δphase angle and Δvector length with ΔXc/*m* was additionally determined by changes in markers of hydration, $\Delta TBW_{Biasioli}$ and ΔCFB were added as determinants to the regression analysis. The results for changes between days 1 and 3 are presented in Table 4a for Δphase angle as dependent variable and in Table 4b for Δvector length as dependent variable. The association between Δphase angle and ΔXc/*m* improved when adding $\Delta TBW_{Biasioli}$ to the model ($r^2 = 0.73$, $p < 0.01$). Including ΔCFB only improved the explanation further with 2% ($r^2 = 0.75$, $p < 0.01$). There was no multicollinearity and interactions were not significant.

Table 2 Course of fluid balance, hydration, and BIA-derived parameters.

	Day 1 ($n = 156$)	Day 3 ($n = 156$)	Day 7 ($n = 71$)	p value t-test days 1–3	p value t-test days 1–7	p value ANOVA
Body weight independent variables						
R/m, Ω	255.1 ± 69.4	243.4 ± 76.8	243.8 ± 80.9	<0.01*	0.35	0.20
Xc/m, Ω	21.9 ± 8.4	19.4 ± 8.8	18.9 ± 9.8	<0.01*	0.04*	0.01*
Phase angle, °	4.9 ± 1.3	4.5 ± 1.3	4.3 ± 1.6	<0.01*	<0.01*	<0.01*
Vector length, Ω/m	256.1 ± 69.6	243.9 ± 77.1	244.6 ± 81.3	<0.01*	0.35	0.20
$TBW_{Biasioli}$, L	52.8 ± 15.7	56.6 ± 18.6	56.7 ± 20.6	<0.01*	0.05	0.05
CFB, L	1.1 [0.0–3.2]	3.3 [0.9–6.1]	4.2 [1.2–10.0]	<0.01*	<0.01*	<0.01*
Body weight dependent variables						
$TBW_{Bodygram}$, L	48.5 ± 10.9	50.6 ± 12.4	50.7 ± 14.0	<0.01*	0.02*	0.04*
Hydration score[a], %	78.9 ± 6.2	81.1 ± 6.7	81.5 ± 7.1	<0.01*	0.01*	<0.01*
Overhydrated, n (%)	83 (53)	102 (65)	48 (68)			
Normohydrated, n (%)	71 (46)	50 (32)	20 (28)			
Dehydrated, n (%)	2 (1)	4 (3)	3 (4)			
MM, kg	36.3 ± 9.4	35.2 ± 9.7	33.6 ± 10.2	0.02*	0.09	0.02*
BCM, kg	28.6 ± 8.2	27.3 ± 8.4	25.7 ± 9.1	<0.01*	0.03*	<0.01*
FFM, kg	61.1 ± 11.6	62.0 ± 12.9	61.4 ± 15.3	0.03*	0.13	0.32

Data are shown as mean ± SD or median [IQR] when appropriate. An ANOVA was performed when data of days 1, 3, and 7 were present. Vector length was calculated as height-normalized impedance (Z). Δ indicates the change between days 1–3 and 1–7, respectively.

ANOVA analysis of variance, *BCM* body cell mass, *CFB* cumulative fluid balance, *FFM* fat-free mass, *MM* muscle mass, *R* resistance, *TBW* total body water, *Xc* reactance.

*$p < 0.05$.

[a]Normal values are between 72.7 and 74.3%.

The association between Δvector length and ΔXc/m improved when adding $\Delta TBW_{Biasioli}$ to the model ($r^2 = 0.77$, $p < 0.01$). ΔCFB did not improve the prediction further ($r^2 = 0.77$, $p = 0.48$).

Discussion

The present prospective study in critically ill patients shows that phase angle and vector length decreased during the first three days of ICU admission, while markers of hydration and CFB increased. On univariate analysis, changes in phase angle were largely explained by changes in reactance (a marker of cellular mass and integrity), while the change in resistance was not significantly contributing. The opposite was seen for changes in vector length. Changes in vector length could be nearly completely explained by changes in resistance and less by changes in reactance. When exploring the contribution of hydration as quantified by the body weight independent variables, we found that about half of the change in phase angle could be explained by changes in reactance, while the change in TBW ($TBW_{Biasioli}$) improved the explanation for the change in phase angle to about three quarters. Furthermore, the change in vector length was explained by the change in reactance for 38%. This increased to 77% when adding $\Delta TBW_{Biasioli}$ to the equation. Thus, changes in phase angle and vector length during the first three days of ICU admission could significantly be explained by changes in body hydration as quantified by variables independent of body weight.

In critically ill patients, an early decline in phase angle may represent a decline in BCM due to inflammation-induced catabolism; a decline in membrane integrity; fluid overload; and/or a shift of water from the intracellular to the extracellular compartment, which leads to a decrease in BCM [29]. These effects are strongly reflected by our results. The interrelation of these factors is complex and influenced by the severity of inflammation and fluid management and balance in the ICU. We found that altered hydration was a significant determinant of changes in phase angle, which should be accounted for during the course of ICU admission. The present findings suggest that fluid overload significantly influences phase angle. However, a causal relation can only be hypothesized. The use of phase angle as a biomarker in restrictive fluid trials could be an interesting way to examine this hypothesis.

Several recent studies demonstrated that low-phase angle on admission to the ICU is associated with higher ICU, hospital, and 90-day mortality, especially in combination with other predictors [17–20, 30]. In one study, BIA-derived parameters had a stronger predictive power than severity of disease scores such as APACHE II, SAPS III, and SOFA [18]. Thus, low-phase angle on admission seems an interesting biological risk factor. The present study shows that increased hydration is associated with a decline

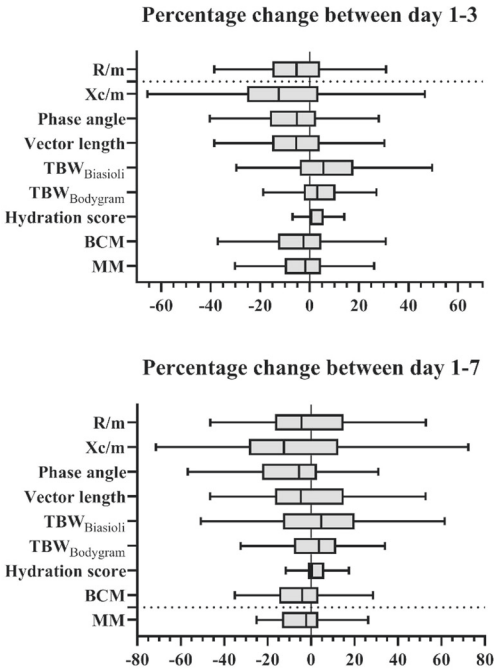

Fig. 1 Box plots of percentage change in *R*/*m*, Xc/*m*, phase angle, vector length, TBWBiasioli, TBWBodygram, hydration score, BCM, and MM between days 1 and 3. Data are shown as mean ± SD or median [IQR] when appropriate. BCM body cell mass, CFB cumulative fluid balance, MM muscle mass, *R* resistance, TBW total body water, Xc reactance. $^{*}p < 0.05$.

	Percentage change between day 1-3 (n=156)	Percentage change between day 1-7 (n=71)
R/m, Ω	-4.4 ± 16.2	-1.4 ± 26.4
Xc/m, Ω	-10.6 ± 24.6	-8.4 ± 35.5
Phase angle, °	-6.4 ± 21.5*	-8.2 ± 24.8*
Vector length, Ω/m	-4.5 ± 16.2*	-1.4 ± 26.4
$TBW_{Biasioli}$, L	7.6 ± 18.4*	8.3 ± 28.3
CFB, L	78.3 [-0.2 – 302.5]*	129.6 [-6.9 – 363.5]*
$TBW_{Bodygram}$, L	4.3 ± 10.7*	5.2 ± 17.1*
Hydration score, %	3.0 ± 6.4*	2.3 ± 7.4*
BCM, kg	-2.9 ± 21.7*	-5.5 ± 20.5*
MM, kg	-1.9 ± 17.6*	-3.3 ± 17.3*

in phase angle. Previous studies on the predictive capacity of phase angle on outcome did not analyze hydration as a determinant. To what extent low-phase angle on ICU admission was already influenced by fluid overload in these studies is therefore not known. Nevertheless, whether caused by low cell mass and integrity (reactance) or fluid overload, the finding that low-phase angle predicts poor outcome remains valid.

This study also shows that MM and BCM decreased over time, while hydration increased. This was contrary to what was expected, because we expected an overestimation of BCM and MM due to increased body hydration. This may indicate a real loss of lean body mass during the first days of ICU admission, or a shift of water from the intra- to the extracellular compartment with intracellular "dehydration." The Akern device enhances conventional body compartment assessment by an innovative analysis of BiaVector powered by artificial intelligence, which may indicate that altered hydration is incorporated in the assessment. However, because the equations of BCM and MM require an accurate body weight and fluid homeostasis, the reliability of these results can be questioned. Nevertheless, we considered reporting this data of interest.

In the landmark study of Thibault et al. [20], phase angle was conceived as a marker of FFM. The authors suggested that phase angle would be less dependent on fluid variation than the standard body composition equations, although it was also suggested that rapid fluid shifts could contribute to

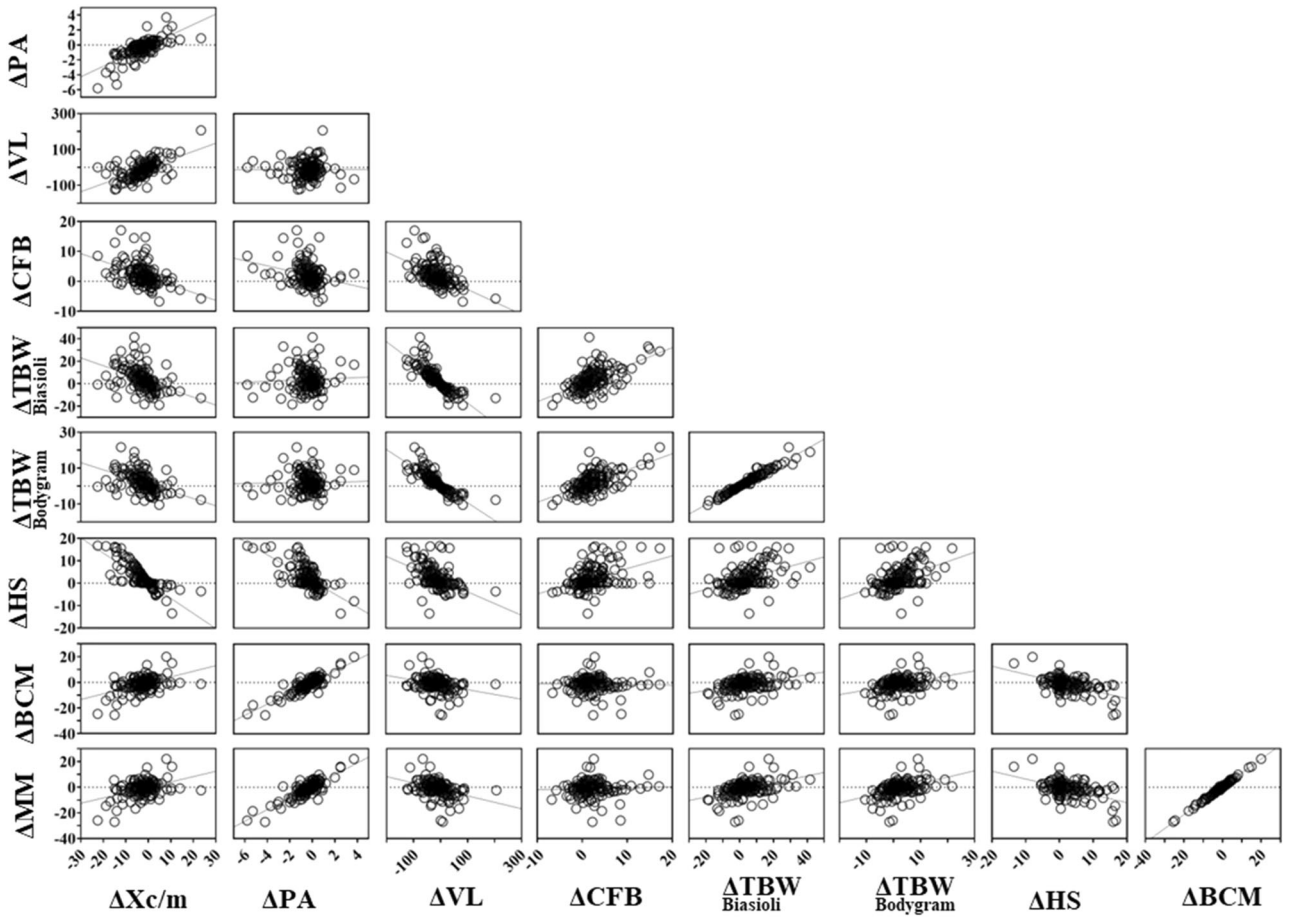

Fig. 2 Correlations between changes in Xc/*m*, phase angle, vector length, CFB, TBWBiasioli, TBWBodygram, hydration score, MM, and BCM between days 1 and 3. The dotted line indicates $Y = 0$. BCM body cell mass, CFB cumulative fluid balance, HS hydration score, MM muscle mass, PA phase angle, TBW total body water, VL vector length, Xc reactance. Δ indicates change between days 1 and 3.

Table 3 Univariate linear regression analyses between Δphase angle and Δvector length in relation to Δ*R*/*m*, ΔXc/*m*, ΔCFB, and $\Delta TBW_{Biasioli}$.

Dependent variables	Independent variables	r^2	B	β	95% CI	*p* value
Δphase angle	Δ*R*/*m*	0.00	0.00	−0.01	−0.00–0.00	0.93
	Δ*Xc*/*m*	0.55	0.14	0.74	0.12–0.16	<0.01*
	ΔCFB	0.08	−0.09	−0.28	−0.14 to −0.04	<0.01*
	$\Delta TBW_{Biasioli}$	0.00	0.01	0.05	−0.01–0.03	0.54
Δvector length	Δ*R*/*m*	1.00	1.00	1.00	1.00–1.01	<0.01*
	Δ*Xc*/*m*	0.38	4.5	0.61	3.58–5.42	<0.01*
	ΔCFB	0.28	−6.64	−0.53	−8.35 to −4.93	<0.01*
	$\Delta TBW_{Biasioli}$	0.70	−3.83	−0.84	−4.23 to −3.43	<0.01*

The analysis was performed for changes between days 1 and 3. Δ indicates change between days 1 and 3. *CFB* cumulative fluid balance, *CI* confidence interval, *R* resistance, *TBW* total body water, *Xc* reactance.
*$p < 0.05$.

cell damage and a decrease in phase angle. In our cohort, we found that the decline in phase angle was indeed related to the water content of the FFM (hydration score). FFM includes intracellular and extracellular water. While phase angle, BCM, and MM decreased, FFM and hydration score increased. This supports the suggestion that especially the extracellular compartment was fluid overloaded. Fluid overload could add to the inflammation-induced membrane injury and subsequently lead to an altered distribution of fluids. However, again, the reliability of these body weight dependent variables can be questioned where the use of phase angle remains valid.

Table 4 Multivariable stepwise regression analyses for Δphase angle (a) and Δvector length (b) between day 1 and 3 including body weight independent explanatory variables.

Variable	Model 1			Model 2			Model 3		
	B	SE B	β	B	SE B	β	B	SE B	β
Panel a									
ΔXc/*m*	0.14	0.01	0.74**	0.18	0.01	0.95**	0.17	0.01	0.90**
$\Delta TBW_{Biasioli}$				0.06	0.01	0.46**	0.07	0.01	0.56**
ΔCFB							−0.07	0.02	−0.20**
r^2			0.55			0.73			0.75
F for change in r^2			188.9			96.9			15.1
Panel b									
ΔXc/*m*	4.50	0.47	0.61**	2.25	0.31	0.31**	2.31	0.33	0.32**
$\Delta TBW_{Biasioli}$				−3.21	0.20	−0.70**	−3.29	0.23	−0.72**
ΔCFB							0.44	0.62	0.04
r^2			0.38			0.77			0.77
F for change in r^2			93.3			266.5			0.5

CFB cumulative fluid balance, *CI* confidence interval, *SE* standard error, *TBW* total body water, *Xc* reactance.

**$p < 0.01$.

Our study has several strengths. To our knowledge, this is the first study that focuses on the relation between changes in fluid balance and body hydration on changes in BIA-derived phase angle and vector length in critically ill patients. The study included a heterogeneous population of critically ill patients, who were included in two different centers. We were able to obtain BIA measurements over the course of 1 week, which allowed us to make comparisons between days 1, 3, and 7. Moreover, by incorporating multiple markers for body hydration and CFB we could include both a clinically applicable and scientifically relevant measurement of fluid status and make precise matches between hydration and BIA-derived phase angle and vector length.

Our study has several limitations. Most importantly, BIA requires body weight to calculate MM, BCM, FFM, and $TBW_{Bodygram}$, while the accuracy of body weight measurements of critically ill patients is poor and weighing was not always feasible [31]. Height is also an important variable for most of the prediction equations we used. Slight inaccuracies could have introduced additional error. However, in the ICU setting we could not do better. Furthermore, the Bodygram PLUS algorithms require fluid homeostasis. For this reason BCM, MM, $TBW_{Bodygram}$, and hydration score measurements may not be reliable. We chose to present the analyses with these markers mostly in e-Supplements. The measurements of *R*/*m*, Xc/*m*, phase angle, vector length, and $TBW_{Biasioli}$ are, however, independent of body weight and therefore suitable for the critically ill population. In some patients, a left-sided configuration was required (e.g., because of bandage material or wounds on the right side). Due to limb dominance and asymmetry of organs in the trunk this could have led to potential confounding of our BIA measurements. Furthermore, cardiorespiratory monitors may have affected the BIA measurements. We have been doing replicate measurements in the past and did not find interaction or noise. In the present study, only stable measurements were recorded. If present, infusions on the measured site were temporarily stopped to prevent this from influencing the BIA measurements. Finally, the CFB retrieved from our patient data management system does not take insensible perspiration into account. Thus, CFB does not necessarily reflect changes in total body hydration. We therefore used different hydration scores, among which $TBW_{Biasioli}$ seems the most interesting for the critically ill population, because this equation does not require body weight and only includes directly measurable parameters. Finally, since this study was observational, we do not know whether the reported relations are causal. Future studies are needed to show whether different strategies of fluid management are reflected in changes in phase angle and vector length and which strategy maintains phase angle best.

Conclusions

The present prospective two-center study demonstrates that phase angle, a BIA-derived marker of general health, reactance/*m*, and the length of the impedance vector decreased during the first three days of ICU admission, while markers of hydration and CFB increased. The decline in phase angle and vector length was not only related to a decline in reactance, reflecting cellular mass and integrity, but for a substantial part also by increased hydration. Because phase angle, vector length, and the Biasioli equation for TBW are independent of body weight, they seem

useful markers to monitor fluid status in the critically ill. Only after fluid homeostasis has been restored, phase angle can be used as a biomarker of cellular mass and integrity.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions ND is the main writer of the paper, collected the data for the Department of Adult Intensive Care Medicine, Amsterdam UMC, VU University Medical Center, analyzed, and interpreted the patient data. LH collected the data for the Department of Critical Care, University of Groningen, University Medical Centre Groningen, assisted with data analysis, and contributed to writing the paper. BB and JS contributed to collecting data for the Department of Adult Intensive Care Medicine, Amsterdam UMC, VU University Medical Center and to writing the paper. JG, SNS, and MWN contributed to writing the paper. HMOS participated in the design, the statistical analysis, interpretation of the data, and in the drafting and writing of the paper. All authors read and approved the final paper.

Compliance with ethical standards

Conflict of interest The bioelectrical impedance device was financed by an unrestricted research grant from Nutricia Medical Care.

Ethical approval The study protocol was approved by the local research ethics committee (VU University Medical Center, amendment to METc reference number 2013.318, UMC Groningen, METc 2016.691). Since all patient data were anonymized and BIA is non-invasive with a low patient burden the need for informed consent was waived.

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