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REPORTS OF ORIGINAL INVESTIGATIONS

Bioimpedance-measured volume overload predicts longer duration of mechanical ventilation in intensive care unit patients

Une surcharge volémique telle que mesurée par bio-impédance prédit une durée prolongée de la ventilation mécanique chez les patients à l'unité de soins intensifs

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Abstract

Purpose *Bioelectrical impedance analysis (BIA) is a technology that provides a rapid, non-invasive measurement of volume in body compartments and may aid the physician in the assessment of volume status. We sought to investigate the effect of BIA-measured volume status on duration of mechanical ventilation, 28-day mortality, and acute kidney injury requiring renal replacement therapy in a population of medical/surgical patients admitted to the intensive care unit (ICU).*

Methods *Prospective observational study of adult patients who required mechanical ventilation within 24 hr of admission to ICU. Bioelectrical impedance analysis measured extracellular water (ECW) and total body water (TBW) and these measurements were recorded on days 1, 3, 5, and 7.*

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Results *A total of 36 patients were enrolled. Mean (standard deviation) age was 61.8 (21.3) years and 31% of patients were female. The majority were admitted from the emergency department or operating room. The most common diagnosis was sepsis. At 28 days, eight patients (22%) had died. There was no association between ECW/TBW ratio at day 1 and 28-day mortality (odds ratio, 1.2; 95% confidence interval [CI], 0.6 to 2.3) after adjusting for age, sex, and Acute Physiology and Chronic Health Evaluation II score. The median [interquartile range] number of ventilator days was 5 [2.5–7.5]. On day 1, for each 1% increase in the ECW/TBW ratio, there was a 1.2-fold increase in ventilator days (95% CI, 1.003 to 1.4; P = 0.05). It is notable that 20% of eligible patients could not be enrolled because medical equipment interfered with correct electrode placement.*

Conclusion *Bioimpedance-measured ECW/TBW on day 1 of admission to the ICU is associated with time on the ventilator. While this technology may be a useful adjunct to the clinical assessment of volume status, there are technical barriers to its routine use in a general ICU population.*

Résumé

Objectif *L'analyse de l'impédance bioélectrique (AIB) est une technologie qui offre une mesure rapide et non invasive du volume dans les compartiments corporels et qui pourrait aider le médecin à évaluer la volémie d'un patient. Nous avons voulu étudier l'effet d'une volémie mesurée par AIB sur la durée de la ventilation mécanique, la mortalité à 28 jours, et l'insuffisance rénale aiguë nécessitant un traitement substitutif de l'insuffisance rénale dans une population de patients médicaux / chirurgicaux admis à l'unité de soins intensifs (USI).*

Méthode *Étude observationnelle prospective auprès de patients adultes nécessitant une ventilation mécanique dans les 24 h suivant leur admission à l'USI. L'analyse par impédance bioélectrique a mesuré la quantité d'eau extracellulaire et la quantité d'eau corporelle totale; ces mesures ont été enregistrées aux jours 1, 3, 5 et 7.*

Résultats *Au total, 36 patients ont été recrutés. L'âge moyen (écart type) était de 61,8 (21,3) ans et 31% des patients étaient des femmes. La majorité des patients avaient été admis du département de l'urgence ou de la salle d'opération. Le diagnostic le plus répandu était un sepsis. À 28 jours, huit patients (22%) étaient décédés. Aucune association n'a été observée entre le rapport d'eau extracellulaire / eau corporelle totale au jour 1 et la mortalité à 28 jours (rapport de cotes, 1,2; intervalle de confiance [IC] 95%, 0,6 à 2,3) après avoir tenu compte de l'âge, du sexe et du score APACHE-II (Acute Physiology and Chronic Health Evaluation II). Le nombre médian [écart interquartile] de jours sur ventilateur était de 5 [2,5–7,5]. Au jour 1, pour chaque augmentation de 1% du rapport d'eau extracellulaire / eau corporelle totale, on a observé une augmentation de l'ordre de 1,2 fois dans le nombre de jours sous ventilation (IC 95%, 1,003 à 1,4; P = 0,05). Il faut souligner que 20% des patients éligibles n'ont pas pu être recrutés parce que les équipements médicaux ont entravé le positionnement adéquat des électrodes.*

Conclusion *Le rapport eau extracellulaire / eau corporelle totale, tel que mesuré par bio-impédance au premier jour d'admission à l'USI, est associé au temps passé sous ventilation mécanique. Bien que cette technologie puisse être un ajout utile à l'évaluation clinique de la volémie, il existe plusieurs obstacles techniques à son utilisation de routine chez une population générale à l'USI.*

Volume expansion with intravenous fluids is a critical step in the resuscitation of a majority of patients admitted to the intensive care unit (ICU). While this practice is beneficial in the appropriate context, indiscriminate fluid administration can lead to various degrees of volume overload (hypervolemia) that may be deleterious to recovery and lead to poor clinical outcomes. Hypervolemic ICU patients spend more time on mechanical ventilation and have higher rates of mortality compared with euvolemic controls.[1,2] Furthermore, a decrease in ventilator days and ICU stay has been observed in patients treated with a fluid restrictive strategy and a negative fluid balance is independently associated with weaning success in mechanically ventilated patients.[2]

Unfortunately, the clinical assessment of volume status by clinicians is poor with high inter-observer variability. Traditional measures such as the physical examination (blood pressure, heart rate, body weight, jugular venous pressure, lung auscultation, limb edema), laboratory testing (arterial blood gas, B-type natriuretic peptide), imaging (chest radiograph, inferior vena cava ultrasound), cumulative fluid balance, and invasive measurements to determine filling pressures (central venous pressure [CVP] via central venous catheter or pulmonary capillary wedge pressure) all have limitations.[3]

Bioelectrical impedance analysis (BIA) provides a rapid, non-invasive, point-of-care measurement of total body water (TBW), extracellular water (ECW), and intracellular water (ICW) and may aid the physician in the clinical assessment of volume status. Bioelectrical impedance analysis measurements correlate with gold standard techniques such as dual-energy x-ray absorptiometry[4] and isotope dilution.[5] Using this technology, the physician can obtain an objective measure of volume status to rationally guide clinical management and possibly reduce morbidity and mortality in patients admitted to the ICU.

The aim of this study was to assess the predictive value of BIA-measured volume status (defined as the ratio of ECW/TBW) to ventilator days, incidence of acute kidney injury (AKI) requiring renal replacement therapy (RRT), and mortality in critically ill patients.

Methods

Design, setting, and patients

We performed a prospective, observational pilot study at the Montreal General Hospital ICU between February 2016 and January 2017. This is a mixed medical and surgical 22-bed ICU in a level 1 trauma hospital. We included a convenience sample of adults > 18 years of age who required mechanical ventilation within 24 hours of ICU admission. We excluded patients with limb amputations, cardiac pacemakers, or implantable cardiac defibrillators and end-stage kidney disease on RRT. Informed consent was obtained from each patient or their substitute decision maker. The period of observation commenced within 24 hours of admission and continued for up to seven days as long as the patient remained in the ICU. This study was approved by the Research Ethics Board of the McGill University Health Centre.

Data collection and management

Baseline demographic and anthropometric data, comorbidities, and reason for admission were recorded for each patient into study-specific case report forms and an electronic database. Patient weight was measured using the hospital bed. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was determined during the first 24 hours of ICU admission. Additional variables including laboratory data and details of hospital course (e.g. use of vasopressor agents, need for mechanical ventilation, and initiation of RRT) were recorded at admission and every two days during the observation period. Cumulative fluid balance was recorded as the difference between fluid intake and output per day, not including insensible losses.

The BIA assessment of volume status was performed using a multi-frequency electrical impedance analyser (InBody, Seoul, South Korea) within the first 24 hours of admission, following initial fluid resuscitation, and subsequently every 48 hours for a period of up to seven days. Bioelectrical impedance analysis measurements were performed by four trained operators. For each measurement, the patient was placed in the supine position with the head of the bed elevated to 30°. The angles between upper limbs and trunk and between the legs were 30° and 45°, respectively, according to the manufacturer's recommendations. The skin was cleaned with alcohol before the application of four electrodes to both hands and feet. The BIA parameters of ECW and TBW were measured by an alternating electric flow of 300 microA and an operating frequency of 50 kHz. Volume status was defined as the ratio of ECW/TBW, the normal range being 36–39% as per the manufacturer's specifications. Thus, volume overload was defined as an ECW/TBW ratio > 39%.

Statistical analysis

Descriptive and outcome statistics for the study subjects are presented as count and percentage for categorical variables and as mean (standard deviation [SD]) for continuous variables when there is evidence of normality of distribution. Otherwise, data are presented as median [interquartile range (IQR)].

Multiple logistic regression analysis was used to investigate the effect of the ECW/TBW ratio at day 1 on the risk of in-hospital mortality at 28 days, adjusting for age, sex, and APACHE II score. ECW/TBW ratio at day 1, age, and APACHE II score were modelled as continuous variables. The assumption of linearity in the logit for all continuous variables in the model was assessed by the Box–Tidwell test.[6] Multicollinearity was assessed using the Pearson correlation coefficient statistic and by checking the variance inflation factor on a multiple regression model with the same dependent and independent variables.[7] The –2 log-likelihood ratio test was used to test the overall significance of the model. The fit of the model was assessed by the Hosmer–Lemeshow goodness-of-fit Chi square test.[8] To adjust for bias due to sparse data, we used a Firth regression correction.[9] Results are reported as odds ratios (OR) for 28-day mortality. Patients discharged home before 28 days were assumed to be alive.

To investigate the marginal effect of the ECW/TBW ratio at day 1 on ventilator days, we used a multiple linear regression model. Ventilator days were log-transformed (natural logarithm) to stabilize their variance and normalize their distribution. The covariates of interest were the same as those used in the logistic regression for 28-day mortality. Results are reported as the relative change in ventilator days for every 1% change in the ECW/TBW ratio at day 1.

In both models, to assess outliers and to detect influential observations, regression diagnostics were performed by plotting several diagnostic statistics against the predicted values, using estimated values and Pearson and Deviance residuals for the logistic regression[8] and studentized residuals for the linear regression.[10]

All hypotheses were two-sided and statistical tests were performed at a significance level of 0.05. Estimated parameters are reported with 95% confidence interval (CI). All analyses were done using SAS, version 9.4 (SAS Institute, Inc. Cary, NC, USA).

Results

Thirty-six patients were enrolled. The baseline demographics are shown in Table 1. Mean (SD) age was 61.8 (21.3) years and more than two-thirds of study

Table 1 Demographics of study population (n = 36)

Age (years), mean (SD)	61.8 (21.3)
Sex (female), n (%)	11 (31)
APACHE II, mean (SD)	18.7 (5.9)
Diabetes, n (%)	4 (11)
Coronary artery disease, n (%)	5 (14)
Cancer, n (%)	8 (22)
Location before admission, n (%)	
Operating room	15 (42)
Emergency department	13 (36)
In-patient ward	8 (22)
Reason for admission, n (%)	
Sepsis	9 (25)
Trauma	6 (17)
GI hemorrhage	2 (6)
Neurosurgical	7 (19)
GI perforation/obstruction	4 (11)
Other	8 (22)

APACHE = Acute Physiology, Age, Chronic Health Evaluation; GI = gastrointestinal; SD = standard deviation

Table 2 Serial measurements

	Day 1 ($n = 36$)	Day 3 ($n = 24$)	Day 5 ($n = 13$)	Day 7 ($n = 5$)
Weight (kg), mean (SD)	76.2 (19.9)	83.2 (17.3)	85.9 (18.5)	74.5 (21.0)
Fluid balance (L), median [IQR]	0.6 [-0.03–1.8]	3.3 [1.5–6.8]	3.4 [-0.3–8.9]	0.8 [-3.1–10.8]
CVP (mmHg), mean (SD)	11.3 (5.5)	10.5 (5.0)	11.6 (2.1)	8.8 (3.8)
Vasopressors, *n* (%)	11 (31%)	5 (21%)	2 (17%)	0
ECW/TBW ratio (%), mean (SD)	40.6 (1.7)	41.2 (1.7)	41.4 (1.8)	41.1 (1.9)

CVP = central venous pressure, $n = 23, 13, 3, 4$ at days 1, 3, 5, 7, respectively

IQR = interquartile range

Vasopressors, $n = 36, 24, 12, 7$ at days 1, 3, 5, 7, respectively

ECW/TBW ratio, $n = 36, 24, 13, 5$, at days 1, 3, 5, 7, respectively

ECW = extracellular water; SD = standard deviation; TBW = total body water

subjects were male. Mean (SD) APACHE II score was 18.7 (5.9). Forty-two percent of patients were admitted to the ICU after a surgical procedure, 36% from the emergency department and 22% from an in-patient ward. The most common reasons for admission were sepsis (25%), neurosurgical pathology including intracranial hemorrhage or traumatic brain injury (19%), and trauma (17%). Approximately 20% of eligible patients could not be enrolled because medical equipment such as casts, dressings, and vascular cannulas interfered with correct electrode placement.

Table 2 documents the trends in patient weight, cumulative fluid balance, need for vasopressors, CVP, and ECW/TBW ratio. There were 36 patient measurements on day 1, 24 measurements on day 3, 13 measurements on day 5, and five measurements on day 7. On day 1, 30 patients (83%) had ECW/TBW values > 39% and were thus volume overloaded as defined by the normal range of values for ECW/TBW ratio using this device (36–39%). Mean patient weight and cumulative fluid balance increased from day 1 to day 5, and by day 7 these parameters returned to baseline values in the five remaining patients. The ECW/TBW ratio remained elevated and relatively unchanged throughout the period of observation.

At 28 days, eight patients (22%) had died (Table 3). Logistic regression analysis showed no significant association between the ECW/TBW ratio at day 1 and mortality (OR, 1.2; 95% CI, 0.6 to 2.3; $P = 0.75$) after adjusting for age, sex, and APACHE II score. The median [IQR] number of ventilator days was 5 [2.5–7.5] (range 1–39). ECW/TBW ratio at day 1 was associated with the number of ventilator days. Results of the linear regression, after adjustment for age, sex, and APACHE II score, suggest that for each 1% increase in ECW/TBW ratio on day 1, there was a 1.2-fold increase in ventilator days (95% CI, 1.003 to 1.4; $P = 0.05$). That is, we expect to see a 20% increase in number of ventilator days for a 1% increase in ECW/TBW at day 1. During the study period, two patients (6%) developed AKI requiring RRT and this was not associated with ECW/TBW ratio at day 1 (results not shown).

Table 3 Clinical outcomes ($n = 36$)

28-day mortality, *n* (%)	8 (22)
Ventilator days, median [IQR]	5 [2.5–7.5]
AKI requiring RRT, *n* (%)	2 (6)

AKI = acute kidney injury; IQR = interquartile range; RRT = renal replacement therapy

Discussion

We studied a bioimpedance device that provides a quantitative determination of ECW/TBW to prospectively determine whether this parameter is associated with adverse outcomes in a heterogeneous medical and surgical ICU population. BIA devices measure the volume within body compartments and may help clinicians objectively determine the extracellular (intravascular and interstitial) volume of a patient.

We observed that the mean ECW/TBW ratio recorded within the first 24 hr of admission to the ICU was elevated in > 80% of patients despite the mean cumulative fluid balance being only 0.6 L positive at this time. This likely reflects the volume the patient received in the operating room or emergency department prior to their arrival in the ICU. At our centre, the fluid administered prior to ICU admission is not consistently accounted for in the cumulative fluid balance calculations. This highlights a potential advantage of BIA measurements, specifically to provide an objective point-of-care measurement of volume status, which may reduce dependence on recordings of fluid balance (or lack thereof) during transitions of care.

The ECW/TBW ratio measurements remained elevated throughout the observation period despite an early rise and eventual fall in body weight and cumulative fluid balance. Although there were only a small number of patients measured at day 7, this observation may reflect the underlying pathophysiology of critical illness. It has been shown that ICU patients rapidly lose lean muscle mass, and thus their ICW becomes proportionally smaller and their ECW becomes larger. In this circumstance, the ECW accounts for a larger percentage of the TBW and this translates into a higher ECW/TBW ratio.[11] Thus in practice, as the patient is "de-resuscitated" to a normal volume status clinically, a persistent increase in ECW/TBW ratio may reflect loss of muscle mass. The other possibility is sub-clinical hypervolemia, which can be measured by bioimpedance but cannot be detected by clinical assessment.

Our data show that a higher ECW/TBW ratio on day 1 of admission to the ICU is associated with increased number of ventilator days independent of severity of illness as measured by the APACHE II score. This finding of "early" volume overload prolonging time on mechanical ventilation has been recently reported in critically ill children.[12] It is well documented that excess volume leads to interstitial tissue edema and organ dysfunction in critically ill patients.[13,14] In the kidney, interstitial tissue edema leads to impaired venous outflow (and eventually arterial inflow) causing renal ischemia.[13] We hypothesized that we would observe an increased incidence of AKI requiring RRT in those who were volume overloaded,[15,16] but event rates at the end of the study were too low to determine this.

While others have shown increased mortality in the setting of volume overload[8,17] the power of our small study was perhaps too low to detect any association between these variables. Samoni *et al*. studied 125 patients from a medical/surgical ICU and found a significant association between elevated bioimpedance vector analysis (BIVA) measurements and mortality.[18] Basso *et al*. studied 64 medical/surgical patients using BIVA and found, similar to our study, that most patients were hypervolemic on admission, and that this persisted during their ICU stay.[19] These investigators observed a significant correlation between maximum bioimpedance-measured hydration status and mortality. Yang *et al*. studied 140 medical patients and reported that bioimpedance-measured overhydration on the third admission day to ICU was an independent predictor of hospital death.[20]

A significant finding in our study pertains to the feasibility of performing BIA measurements in the critically ill population, thus far not discussed in any other published study using a bioimpedance device. We encountered many logistical barriers that interfered with the proper use of the BIA device at the bedside. The presence of medical equipment on patients' hands and lower extremities precluded BIA measurement in a significant number of patients and contributed to lower recruitment rates. In addition, all BIA devices require an accurate body weight, which changes daily in this patient population and is influenced by the presence of medical equipment on the patient's bed (tubing, drains, pillows, casts, etc.). If an accurate weight is not obtained, the accuracy of the BIA measurement is diminished.

Bioelectrical impedance analysis devices have other limitations, namely the inability to distinguish between intravascular and interstitial volume in the extracellular compartment. It is well known that in sepsis, the distribution of fluid in body compartments is altered, with capillary leak promoting fluid movement from the vascular into the interstitial space.[21] The inability to determine a patient's intravascular volume is a source of clinical uncertainty and our study does not address questions regarding the assessment of cardiac output, volume responsiveness, or organ perfusion in this population.

This study has many strengths, specifically its prospective nature, multiple BIA measurements over time, and the use of a novel technology to measure volume status in a critically ill population. Limitations include the small study size, which may have resulted in low statistical power to detect an association of the ECW/TBW ratio at day 1 with mortality, the heterogeneous mix of ICU patients, the challenges related to the logistics of performing measurements in all patients, and the lack of direct clinical applicability of the results.

Conclusions

A higher ECW/TBW ratio within 24 hr of admission is associated with an increase in number of ventilator days in mechanically ventilated patients. There are several logistical barriers that limit the routine use of this technology in all ICU patients.

Conflicts of interest None declared.

Editorial responsibility This submission was handled by Dr. Sangeeta Mehta, Associate Editor, *Canadian Journal of Anesthesia.*

Author contributions *Douglas Slobod* contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. *Catherine L. Weber* and *Dev Jayaraman* contributed to the conception and design of the study. *Han Yao*, *Joelle Mardini*, and *Justyna Natkaniec* contributed to the acquisition of data. *José A. Correa*, *Catherine L.*

Weber, and *Dev Jayaraman* contributed to the analysis and interpretation of data.

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