Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis

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Background. Evaluation of dialysis adequacy has focused on parameters of solute (principally urea) clearance. Relatively little attention has been paid to the adequacy of ultrafiltration. At a given phase angle, the bioimpedance vector length reflects the degree of tissue hydration, as the vector lengthens with ultrafiltration.

Methods. We determined the relative risk of death associated with different bioimpedance vector lengths in a 3009 patient hemodialysis cohort using proportional hazards regression.

Results. The mean phase angle was 4.8°, and the mean vector length 300 ± 70 ohm/m (range 140 to 630 ohm/m). Vector length was much longer in women than men (mean 340 vs. 270 ohm/m) and significantly longer in African Americans and patients without diabetes. Adjusted for the effects of age, gender, race, diabetes, vintage, weight, albumin, prealbumin, creatinine, hemoglobin, ferritin, and dialysis dose, the relative risk (RR) of death was 0.75 (95% CI 0.57 to 0.88) per 100 ohm/m decrease in vector length. The effect of vector length on RR was somewhat more pronounced among men (vector length × gender interaction, P = 0.07). Considering vector length of 300 to 350 ohm/m as the referent category, the RRs of death were 1.54 (95% CI 1.08 to 2.21) and 2.83 (95% CI 1.55 to 5.14) for patients with vector length 200 to 250 and < 200 ohm/m, respectively.

Conclusion. Shorter predialysis bioimpedance vectors, indicating greater soft tissue hydration, were associated with diminished survival in hemodialysis patients. These findings validate clinical observations linking longevity to maintenance of dry body weight.

The evaluation of hemodialysis adequacy has focused on parameters of solute (principally urea) clearance.

Key words: ultrafiltration, hemodialysis, adequacy of dialysis, body fluid volume, bioimpedance, diabetes, phase angle.

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Lower volume normalized clearance × time products (Kt/V) have generally been associated with higher mortality rates in observational studies of maintenance hemodialysis patients [1], although the recently completed HEMO Study suggested that higher rates of urea clearance might not be of benefit [2]. In contrast to solute kinetics, relatively little attention has been paid to evaluation of the adequacy of ultrafiltration. Fluid removal is integral to dialysis since over- and underhydration have been linked with intradialytic morbidity and long-term cardiovascular complications. To date, the optimal post-dialysis (dry) weight is determined clinically, generally as the lowest weight a patient can tolerate without intradialytic symptoms or hypotension. This rather crude trial-and-error method does not account for changes in lean body mass, fat mass, or inflammatory or nutritional status over time.

Bioelectrical impedance analysis (BIA) is a practical, portable, relatively inexpensive and reliable bedside tool to aid the evaluation of body composition. Briefly, impedance is a measurable property of electrical ionic conduction of soft tissue, particularly lean tissue, since fat and bone are poor conductors [3, 4]. An impedance vector (Z) is the sum of resistance (R) and reactance (Xc). Alternatively, the impedance can be expressed as a vector with a magnitude |Z| = \sqrt{(R^2 + Xc^2)} and phase angle (arc tan Xc/R). In principle, at low frequencies (< 5 kHz) current would pass through the extracellular fluid while at higher frequencies (> 100 kHz) it would penetrate all fluid compartments. In practice, a variable amount of current can cross muscle cells even at very low frequencies, particularly when the current’s path is parallel to the fiber [5].

Estimation of total body water (TBW) with the conventional BIA approach assumes the body to be an isotropic...
of a given length [height (H)] and constant cross-sectional area, and uses regression equations based on \( H^2/R \) and other variables, including age, gender, body weight, and reactance. BIA estimation of masses and volumes of body compartments are accurate in healthy adults, although with 95% prediction intervals >3 kg [6–9]. In order to increase accuracy of TBW and body cell mass estimation from BIA, specific prediction equations have been developed for hemodialysis patients. Unfortunately these equations result in a bias in the order of 4 to 5 kg with respect to reference methods [8–10].

Some of the important limitations of conventional BIA can be overcome by direct evaluation of impedance vector readings. A graphic approach for monitoring relative changes in TBW based on single-frequency impedance analysis has been termed the resistance-reactance graph (RXc graph) [11]. This approach makes no assumptions about body geometry, hydration status, or the electric model of cell membranes. Rather, an individual's height-adjusted resistance (R/H) and reactance (Xc/H) are employed, yielding a phase angle and vector magnitude unaffected by the oblate errors of regression adjustment. The individual impedance vector plotted as a point on the R-Xc plane can be compared with normative data derived from a representative sample of healthy individuals of the same gender and race or ethnicity to evaluate the relative hydration status of the individual and can be followed over time. Referent, bivariate tolerance intervals were derived that included 50%, 75%, and 95% of healthy subjects from different races [12]. Gender, race, or ethnicity, body mass index (BMI), and age, in decreasing order, influenced the vector distribution pattern [13].

Following clinical validation studies, normal hydration was defined as the range of impedance vectors falling within the reference 75% tolerance interval.

In hemodialysis patients, the thrice weekly wet-dry weight cycling parallels the cyclic backward-forward displacement of the impedance vector over definite elliptical areas on the R-Xc plane with vector displacement parallel to the major axis of the reference tolerance ellipses [14]. About 50% of patients undergoing maintenance hemodialysis cycle within the third quartile of impedance vector distribution of the healthy population, which allowed the identification of patients with full versus intermittent versus no restoration of normal tissue electrical conductivity.

In a previous study, we demonstrated that phase angle was directly correlated with several parameters of nutritional status and independently associated with survival in hemodialysis patients [15]. However, two persons at a given phase angle may be widely disparate in body composition and volume status, based on the vector magnitude. Given that ultrafiltration lengthens the impedance vector, we hypothesized that shorter vector length (i.e., inadequate ultrafiltration) would be associated with increased mortality, even after accounting for phase angle and other confounding variables. This observation would be consistent with our clinical impression that hemodialysis patients who achieve postdialysis weights at or near target experience more favorable outcomes.

### METHODS

Study subjects were 3009 prevalent adult hemodialysis patients from 101 free-standing Fresenius Medical Care North America (FMCNA) dialysis units across the United States. Inclusion criteria included age ≥18 years and thrice weekly in-center hemodialysis for ≥3 months. Patients with an amputation above the transmetatarsal site were excluded from participation. BIA Quantum (RJL Systems, Inc., Clinton Twp., MI, USA) was performed before a midweek dialysis session during the first 6 months of 1995. Briefly, an inner electrode was attached to the dorsal surface of the wrist on the arm without an arteriovenous fistula or graft. An outer electrode was placed on the dorsal surface of the third metacarpal bone. A second pair of electrodes was positioned on the anterior surface of the ipsilateral ankle and the dorsal surface of the third metatarsal bone [6]. A single frequency low-amplitude imperceptible current (800 \( \mu \)A at 50 kHz) was introduced via the electrodes on the hand and foot. The electrodes at the wrist and ankle detected the voltage decrease. The resistance and reactance in ohms was obtained directly from the device and normalized by the subject's height in meters and expressed as R/H and Xc/H in ohm/m according to the vector BIA (RXc graph) methodology [11]. Phase angle (the arc tangent of the reactance to resistance ratio) was calculated in radians, and multiplied by \( 180/\pi \) (∼3.14159265) to covert radians to degrees. Reactance, resistance, phase angle, and the derived estimates of total body water were merged with the Patient Statistical Profile, a database with selected demographic, historic, and laboratory information on patients cared for at FMCNA-affiliated dialysis facilities. Laboratory values were means of the three months proceeding BIA testing. All patients were followed for at least 1 year from the time of BIA testing or the point of censoring. Duration of follow-up ranged from 2 days to 18 months. Patients whose survival time was unknown or uninterpretable (\( N = 19 \)) (0.6%) were excluded from the analysis.

### Statistical analysis (general)

Continuous variables were described as mean ± standard deviation or median and interquartile range, and compared using Student t test, analysis of variance or non-parametric tests, where appropriate. Linear regression was used to determine independent correlates of vector length. Categorical variables were described as proportions. Height normalized impedance vector magnitude
\[ |Z/H| = \sqrt{[(R/H)^2 + (Xc/H)^2]} \] in ohm/m was evaluated as a continuous variable in the primary analysis. The association between vector length and patient survival was explored using proportional hazards (“Cox”) regression, with vector length expressed as a continuous variable [16]. In this case, the relative risk (RR) represents the expected change in risk per 100 ohm/m change in vector length. Companion analyses were performed using vector length categories (six predefined categories, namely <200, 200 to 250, 250 to 300, 300 to 350, 350 to 400, and ≥400 ohm/m) obviating the linearity assumption. Analyses were adjusted for case mix (age, gender, race, diabetes, and vintage (time since initiation of dialysis), and for case mix plus nutrition- and inflammation-related variables significantly associated with survival on univariate analysis. Unadjusted, case mix-adjusted, and multivariable-adjusted hazard ratios with 95% CI were calculated based on model parameter coefficients and standard errors, respectively. Factors not included in multivariable regression models were re-entered individually to evaluate for residual confounding (>5% change in vector length or phase angle parameter estimate). Multiplicative interaction terms with vector length were tested to explore for effect modification by other model covariates. Plots of log (−log [survival rate]) against log (survival time) were performed to establish the validity of the proportionality assumption [17]. Subjects who underwent kidney transplantation (N = 82) (2.7%), recovered renal function (N = 18) (0.6%), transferred dialysis facilities (N = 287) (9.7%), withdrew from dialysis (N = 42) (1.3%), or were lost to follow-up for unknown reasons (N = 8) (0.3%) were censored. Two-tailed P values less than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS version 6.08 (SAS Institute, Cary, NC, USA).

Statistical analysis (bioimpedance vectors)

The parameters (slope and length of semiaxes) of the bivariate confidence and tolerance ellipses were calculated following methods described elsewhere. In the statistical analysis of mean vectors, separate 95% confidence and tolerance ellipses were calculated using methods described elsewhere. In the statistical analysis of mean vectors, separate 95% confidence and tolerance ellipses were calculated using methods described elsewhere.

RESULTS

The mean age was 60.5 ± 15.4 years, 47.2% were women, 46.9% black, 45.4% white, 6.5% Hispanic, and 1.2% of other races or ethnicities. Thirty-seven percent of patients had diabetes mellitus. The median dialysis vintage was 2.6 years (interquartile range 1.4 to 4.9 years). A detailed description of the distributions of R, Xc, and phase angle across the population has been previously reported [19].

Correlates of vector length

The mean phase angle was inversely correlated with age (r = −0.33, P < 0.0001) and vintage (r = −0.15, P < 0.0001). The mean phase angle was significantly wider in men than women (5.0° vs. 4.4°, P < 0.0001), blacks (5.3°) than whites (4.3°), Hispanics (4.7°), or persons of other races or ethnicities (4.6°) (P < 0.0001), and in patients without diabetes (4.9° vs. 4.5° in patients with diabetes, P < 0.0001) (Fig. 1). In contrast, age was directly correlated with vector length (r = 0.19, P < 0.0001) and vector length was substantially longer in women than men (337 vs. 270 ohm/m, P < 0.0001) (Fig. 1). Mean vector length was slightly shorter among patients with diabetes (Fig. 1). Linear regression showed significant associations among vector length and age, gender, race, or ethnicity, diabetes, and the diabetes × gender interaction, with these factors explaining 28% of the variation in vector length. Vector length was unrelated to vintage. Figure 2 shows the predialysis distribution by gender and race (95%, 75%, and 50% tolerance ellipses) for the nondiabetic patients classified as white or black, for comparison with other published data. These distributions can be utilized for comparison and for bedside identification of shorter and more down sloping vectors.

Vector length and mortality

The overall 1-year survival rate was 88%. Mortality was significantly associated with age [RR 1.04 (95% CI 1.03 to 1.05) per year increase], and race or ethnicity [RR 0.59 (95% CI 0.48 to 0.74) in blacks and RR 0.39 (95% CI 0.22 to 0.65) in Hispanics, compared with whites]. The proxies of nutritional status, serum albumin [RR 0.34 (95% CI 0.26 to 0.44) per g/dL increase] and creatinine [RR 0.87 (95% CI 0.84 to 0.90) per mg/dL increase] were inversely...
related to mortality. The relation between survival and unadjusted RR was curvilinear (reverse J-shaped). The unadjusted risk of death was increased among patients with diabetes, but not significantly so in multivariable analyses [RR 1.22 (95% CI 0.98 to 1.50)]. In this cohort, mortality was not significantly associated with gender or dialysis vintage.

There was a significant association between vector length and mortality [multivariable RR 0.75 (95% CI 0.57 to 0.88 per 100 ohm/m change in vector length)]. To test the linearity assumption, we fit companion models in which vector length was divided into six pre-defined categories (<200, 200 to 250, 250 to 300, 300 to 350, 350 to 400, and ≥400 ohm/m). Using 300 to 350 ohm/m as the referent vector length, the RR of death was 1.54 (95% CI 1.08 to 2.21) for vector length 200 to 250 ohm/m and 2.83 (95% CI 1.55 to 5.15) for vector length <200 ohm/m. The increase in RR with shorter vector length was independent of age, gender, race, diabetes, vintage, albumin, creatinine, hemoglobin, ferritin, and perhaps most important, phase angle. There was no interaction between phase angle and vector length. In other words, shorter vector lengths and narrower phase angles were independently associated with mortality. The association of vector length with mortality tended to be more pronounced among men (vector length × gender interaction, P = 0.07). Figure 3 shows the multivariable adjusted RR of death within the six predefined vector length categories plotted on the 50%, 75%, and 95% tolerance ellipses.

**DISCUSSION**

Inadequate fluid removal during hemodialysis can lead to hypertension, heart failure, and stroke, among the leading causes of death in dialysis patients. In contrast, excessive fluid removal can lead to hypotension, arrhythmias, muscle cramping, nausea, vomiting, and other adverse effects. Commonly, the rate of ultrafiltration exceeds the rate of vascular refill (especially with shorter dialysis sessions), leading to inadequate intradialytic fluid...
removal, hypervolemia, hypertension, the provision of antihypertensive therapy, and ultimately a vicious cycle, yielding a steady-state well above dry weight. Chronic hypervolemia can contribute to cardiomyopathy, pulmonary congestion, systemic and pulmonary hypertension, and potentially, an increased risk of ischemic coronary artery disease, stroke, and sudden death. Quantitative measures other than clinical symptoms and more specific parameters than changes in overall body weight would be valuable to guide prescription of dry weight and potentially, avoid intra- and interdialysis complications of cardiovascular disease.

BIA allows a specific assessment of the electric properties of tissues that depend on both tissue hydration and structure. With bioimpedance vector analysis (RXc graph), different patterns of the impedance vector distribution have been found to reflect different hydration and nutritional states independent of body weight [11–14]. Phase angle has been associated with mortality in patients with acquired immunodeficiency syndrome (AIDS) [20] and end-stage renal disease (ESRD) [15, 21] and has been directly correlated with other proxies of nutritional status in several diverse cohorts [22, 23]. Few studies have jointly considered phase angle and vector magnitude.

The findings by gender and race are consistent with reports in healthy adults from the Europe [12] and the United States [14]. An interesting parallel can be made with findings from a large Italian hemodialysis population in whom impedance measurements were performed pre- and postdialysis with the same device and method. In the Italian study, thrice weekly wet-dry weight cycling was linked to a cyclic backward-forward displacement of the impedance vector with displacement parallel to the major axis of the reference, gender-specific, tolerance ellipses from the healthy population [13]. Gender-specific tolerance ellipses of the Italian hemodialysis population were of the same shape as those of the healthy Italian population. The predialysis vector position in Italian hemodialysis patients (of whom the vast majority were Caucasian) was similar to that of the nondiabetic, white patients studied here.

In this study, we documented a significant association between shorter vector length and mortality. We could not demonstrate an association between longer vector lengths and decreased mortality. Whether this reflects a nonlinear relation between vector length and mortality or insufficient power to detect such an association is unknown. Interestingly, the relation between total body water and vector magnitude is asymmetric (a hyperbolic function), with a shortening of vectors outside of the lower poles of the 75% tolerance ellipses when tissue hydration increases.

We have previously shown an increase in the RR of death for hemodialysis patients with phase angles below 4°. Shorter vectors tend to be seen with narrower phase angles, due to the geometry of the bivariate distribution of vectors. The geometric link between phase angle and vector length could lead to errors in determining a patient’s nutrition and prognosis if one were to focus only on phase angle while neglecting vector magnitude. For example, wider phase angles with longer vectors are observed in states of dehydration (e.g., predialysis, cholera, prerenal azotemia), and narrower phase angles with shorter vectors are observed with fluid overload (e.g., predialysis, edema) independent of either nutritional status or prognosis [24].

There are several limitations to the analyses presented here. BIA was performed predialysis. Since interdialytic weight gain varies within and among individuals, there was more noise in the estimates of resistance and reactance than there might have been had BIA been obtained postdialysis. Therefore, it is even more noteworthy that a significant association between vector length (as a proxy for volume status) and mortality was demonstrated. We did not record direct physical examination findings (e.g., edema, pulmonary rates). These might have substantiated alterations in impedance parameters. Aside from height and weight, no other measures of body composition were obtained. Finally, the sample was restricted to maintenance hemodialysis patients; results may not be generalizable to peritoneal dialysis patients, persons with acute renal failure on hemodialysis, or persons with less severe degrees of chronic kidney disease.

**CONCLUSION**

In a large, nationally representative sample of hemodialysis patients, we demonstrated a significant association between vector length (a known proxy for volume status and ultrafiltration) and mortality. These findings were independent of case mix, confounding laboratory values, and phase angle. These findings validate the clinical observation linking longevity to maintenance of dry body weight. Since hemodialysis population norms of vector distribution, including length and phase angle, have been developed, bioelectrical impedance vector analysis may be used to evaluate the adequacy of ultrafiltration in hemodialysis. Prospective, serial determinations of phase angle and vector length will be required to determine the utility of bioelectrical impedance vector analysis in clinical practice.

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