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Future uses of vectorial bioimpedance (BIVA) in nephrology

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FUNDAMENTALS OF BIOELECTRICAL IMPEDANCE

Because of its biological implications, body composition (BC) is a measurement of the utmost importance both in healthy and diseased subjects, and progress has been made in recent decades in this field, allowing the measurement of body mass components that range from the simple two-category model (lean mass vs fat mass) to more sophisticated multi-component systems (molecular tests, body quantifications such as nitrogen, potassium, calcium, phosphorous, etc.)

The analysis of BC is limited to the measurement of total body water, lean mass, fat mass, and bone mass using bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DEXA), mainly because other techniques are still too complicated or expensive to be used, or are simply inaccurate.¹

Bioelectrical impedance analysis (BIA), in its different modalities [multi-frequency (MF-BIA), spectroscopic (SBI), and vectorial (BIVA)], is widely used throughout the scientific community as a diagnostic tool for changes in BC. Described and validated by Kushner in 1986,² the major advantages of this system are based on its non-invasiveness, economic viability, proven effectiveness, and ease of use, as compared to other reference techniques such as bone scans (DEXA), or the use of isotopes³ such as deuterium and ⁴⁰K.

The basis of BIVA was explained in this journal in 2002, establishing BC through a number of graphic vectors derived from resistance-reactance (R/Xc) with no equations.⁴⁻⁷ It detects changes in tissue hydration as low as 500ml, and its

standard error is 2%. The value is considered to be adequate when the vector is situated between the 50th and 75th percentiles (Figure 1).⁵

The Spanish health technology assessment agency (avalia-t) evaluated BIVA and found it to be an emergent, consolidated tool with no ethical repercussions, and very useful in the assessment of BC in patients with chronic kidney disease.⁸

The three parameters of clinical importance derived from BIVA are phase angle (PA), cellular Na-K exchange, and cell mass (CM).

PA (Figure 2) assesses the integrity of cell membranes and the relationship between the extracellular and intracellular

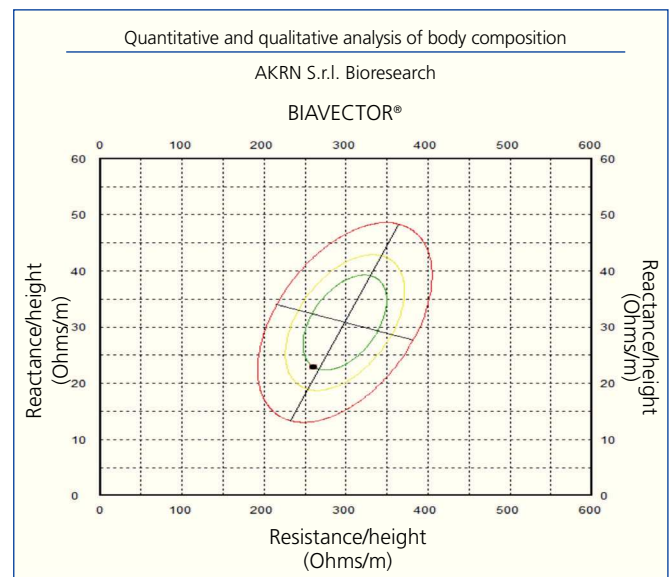


Figure 1. Nomogram for normal body composition between 50th and 75th percentiles

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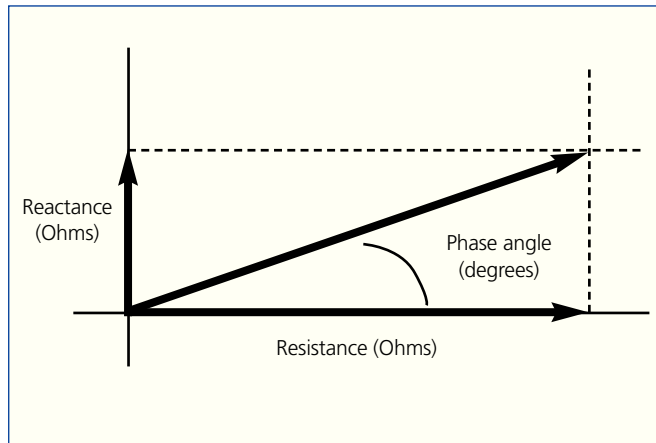


Figure 2. Relationship between resistance (R), reactance (Xc), and phase angle ($^{\circ}$)

space. By definition, PA is positively related with reactance (IW) and negatively with resistance (EW).⁹ This value is a prognostic tool for survival in several pathologies such as chronic kidney disease (CKD), heart disease, and cancer.¹⁰⁻¹³ In this issue, Caravaca, et al and Abad et al discuss their experience with advanced chronic kidney disease (ACKD) and patients on dialysis, pointing out the importance of PA as a parameter for survival.^{14,15}

Cellular Na-K exchange is an emergent parameter of great clinical relevance in monitoring inflammatory states. It is correlated with inflammation, malnutrition, and cardiovascular risk parameters.^{16,17}

As regards the cellular bioelectrical properties, NA/K act as true condensers, storing electricity on both sides of the membrane, therefore, NA-K exchange determines the level of damage to the cell membrane.

CM assesses the cell components involved in biochemical processes and energy metabolism. Nutritional state, level of activity, and pathological processes all alter CM, making this a useful biological marker. The equation [total body potassium (TBK) (in mmol) = cell mass \times 108.6] is derived from MC, which corresponds to total K content and is important for nutritional evaluations, especially for sarcopenia in elderly patients.¹⁸⁻²⁰

BIOELECTRICAL IMPEDANCE IN CHRONIC KIDNEY DISEASE

Several important advancements were made in 2010 in the management of CKD for slowing the progression of kidney disease and to reduce associated cardiovascular risk.²¹

Caravaca et al¹⁴ clearly showed the usefulness of SBI in evaluating the hydration state of ACKD patients, and established that a value of PA of 5.3° has prognostic value for survival along with the relationship between volume overload and increased blood pressure and cardiovascular risk factors. They also provided important information regarding the role of hyperaldosteronism, relating increased EW to a low urinary excretion rate of Na/K. Additionally, this study showed the relationship between hydration, nutrition, and inflammation, aiding in the decision-making process regarding the use of drugs and non-pharmacological treatments.

The cardiovascular effects and changes in BC are manifested in the initial stages of CKD, increasing TW at the expense of EW with decreased PA, which is associated with cardiac remodelling and left ventricular hypertrophy.²² PA was 22% lower than in control patients, and diabetic patients particularly suffered these changes, with a level of excess volume evidenced by increased TW and EW, and reduced CM.²³

Differences between sexes in BC, regardless of physiological and cultural function, are due to differences in diet, with nutrients that have estrogenic activity, providing a different perspective on cardiovascular risk.²⁴

Maintaining muscle mass is essential for preventing malnutrition.²⁵ Along with anthropometrics, BIVA evaluates muscle mass once the patient reaches a proper level of hydration. This, together with dynamometry, allows for estimating muscle strength and muscle mass. For each 0.5kg of force, the reactance/height ratio increases by 10hm/m, and each decrease of 10hm/m in the resistance/height ratio means a 0.063kg decrease in force.²⁶ At our centre, we analysed 519 patients with stage 2-5 chronic kidney disease using BIVA and dynamometry, observing that dominant and non-dominant arm strengths were significantly negatively correlated with age ($P < .001$), exchangeable Na-K ($P < .001$), and C-reactive protein ($P < .040$), and positively correlated with lean mass ($P < .001$), body muscle percentage ($P < .001$), PA ($P < .001$), serum albumin ($P < .001$), prealbumin ($P < .001$), nPNA ($P < .001$), urinary albumin/creatinine ratio ($P < .021$), and testosterone ($P < .001$).²⁷ In our study sample, for each kg of force, muscle mass changed by 0.659kg, or 4.4%. Additionally, the BIVA parameters were correlated with serum markers of nutrition and inflammation.

The estimation of glomerular filtration rate using MDRD and CKD-EPI does not consider BC. However, both muscle mass and CM influence glomerular filtration rates. Based on the validation studies performed by Donadio using CM, we evaluated 353 patients with stage 1-5 CKD and observed a significant correlation with current methods; a new method for evaluating glomerular filtration rate is available, although more studies are needed.^{28,29}

Overweight/obesity is a serious health problem, and is also associated with the development and progression of CKD, as well as the development of diabetes and cardiovascular events.³⁰

The use of the body mass index (BMI) as an indicator for overweight/obesity is questioned because of its high rate of error and lack of accuracy, whereas BIVA is a relevant option due to its reliability. It has demonstrated a specificity of 86%, a positive predictive value of 98%, and a negative predictive value of 20%. The error rate for the technique with elevated adipose levels is 9%.³¹

BC varies with age and sex throughout a patient's lifetime. It has been observed using BIVA that, after the age of 50 years, changes in BC are produced in both sexes, i.e., increased percentage of fat, reduced muscle mass, increased TW and EW, and reduced PA, CM, IW, and baseline metabolism. This is probably related with the patient's habits, in which a sedentary lifestyle and diet play an important role.³²

When evaluating the changes produced by aging in our patients, BC values cannot be compared with younger populations and serious challenges must be addressed for their management, since sarcopenia is the primary change to the bodies of healthy elderly people, which is currently a focal point of medical research.³³

Sarcopenia in elderly people translates into changes to BC detected using BIVA, with reduced PA, CM, and TBK. PA has turned out to be a marker for mortality in hospitalised elderly patients; those with a PA of $4.3 \pm 1.1^\circ$ have a higher rate of survival.³⁴

BIOELECTRICAL IMPEDANCE VECTOR ANALYSIS IN DIALYSIS

Dialysis produces important changes in BC within a short time, and this is where BIVA has been most used for establishing proper BC and controlling morbidity and mortality factors, such as malnutrition, inflammation, and cardiovascular risk. It has established in recent years as a tool that aids in decision making both in haemodialysis (HD) and peritoneal dialysis (PD) patients.³⁵ BIVA has evolved the concept of "dry weight" into a more physiological and less arbitrary situation as appropriate weight, or "appropriate BC."

By evaluating extracellular volume, BIVA facilitates the prevention of cardiovascular events and loss of residual renal function. In all of its modalities, dialysis controls volume based on EW, and maintaining patients in a euvolemic state is a challenge for nephrologists.^{36,37}

Individualised ultrafiltration, within the concept of individualisation of dialysis prescription, and the use of TW

as a parameter that must be included in the adjustment of dialysis regimens makes prescriptions more efficient and effective.³⁸

V is a component of Kt/V . Compared with different anthropometric formulae (Watson, Hume, Randall, Tzamaloucas, and Chertow) and the urea kinetic model, TW estimated using BIVA resulted to be the most reliable method.^{39,40}

An evaluation of BC in both dialysis techniques shows that patients on PD have a significantly higher percentage of TW than patients on HD. The prevalence of volume-dependent hypertension is higher in PD patients, but not significantly.⁴¹ Using the EW/TW ratio, it was recently suggested that BC was similar between predialysis HD and PD patients. Atrial natriuretic peptide (ANP) values were similar in PD and HD patients after dialysis, in spite of improved EW/TW indices, which suggests that volume compartmentalisation was different between the two techniques.⁴² With the introduction of icodextrin and the expanded use of ambulatory peritoneal dialysis (APD), especially with high transporters, hydration state was shown to be the same in the two techniques, and an estimated 25% of PD and HD patients had volume excesses. BIVA has proven to be useful in establishing proper hydration in CAPD and HD. The vectors of oedema patients are short, falling below the 75th percentile.^{43,44}

Malnutrition is very prevalent both in PD and HD patients, with similar values between the two techniques, although some studies point towards a greater prevalence in PD, which is estimated at 34%. Moreover, anomalies in nutritional state have been shown using different methods of measurement.⁴⁵

Patients that start dialysis have improved nutritional state within the first six months of treatment, yet even so, 40% are malnourished. The serum albumin value is considered a mortality indicator, and patients with levels $<3.5\text{g/l}$ have twice the mortality rate than those with values $>4\text{g/l}$.⁴⁶ Hypoalbuminaemia has been associated with hydration state, both in PD and HD patients, as well as comorbidity factors, as measured by BIVA.⁴⁷ Prealbumin has a similar predictive value to albumin, and is not affected by hydration state.⁴⁸

BIVA provides an excellent correlation with albumin, nPNA, and Kt/V in both HD and PD, with PA and CM as prognostic markers for survival.^{49,50} Abad et al¹⁵ shared their new and interesting experience with controversial results as compared to other authors^{9,10} using MF-BIA; they observed that a PA of 8° was prognostic for survival in both HD and PD, with a better nutritional state in PD patients. The authors also observed a significant positive relationship between PA and interdialysis weight gain, EW, and IW, which suggests that the BC of these patients corresponds to long vectors above the 75th percentile.

Inflammation modifies BC, reduces muscle mass, and increases EW and Na-K exchange, changes that are observed using BIVA in both types of dialysis, in comparison to healthy subjects.^{51,52}

The concept of malnutrition can be redefined including BIVA parameters such as PA, TBP, and CM, along with biochemical markers, which allows us to discriminate between malnutrition-inflammation and a state of volume overload due to other causes.⁵³

Obesity poses a risk of mortality in the general population; but observational studies of dialysis patients showed the opposite.⁵⁴ Adipose tissue is a complex organ with functions that go beyond energy storage. Researchers showed that the protective effect of a high BMI is provided by the quantity of muscle, not adipose tissue.⁵⁵ Recently, the same authors stressed the importance of distinguishing between the two components. In the BIVA, subjects with a higher proportion of muscle show higher CM, PA, IW, and baseline metabolism than those in which the amount of fatty tissue surpasses 35% of the total body composition. These variations are accompanied by increased energy intake and reduced protein consumption, which entails a higher risk of cardiovascular events.^{56,57}

The dialysis procedure also has important metabolic effects. HD impacts the body's metabolism by increasing protein catabolism, including a loss of amino-acids in the dialysis solution and from proteolysis induced by cytokines that are activated by non-ultrapure dialysis membranes and solutions. This results in increasing the energy expenditure by 10% and the rate of proteolysis of muscle proteins by 133%. The oxidation substrate becomes altered, carbohydrate levels decrease, and lipids and amino-acids are oxidised at an accelerated rate.^{58,59}

PD exerts its protein catabolic effects by protein and amino-acid loss through the peritoneal effluent.

Patients on HD have a higher nPNA on days in which they undergo a dialysis session. Since muscle is the energy source used by the organism in this case, its integrity must be prioritised, requiring a systematic evaluation and control of baseline metabolism in order to prevent protein-energy wasting.⁶⁰

Preventative measures, such as administering oral nutritional supplements and/or parenteral intra-dialysis nutrition are being used currently, with different results.⁶¹

Finally, the time and frequency of HD influences BC. Patients with 8-hour sessions have increased reactance and PA values, which is attributed to changes in body fluid levels that are less intense and more progressive under shorter dialysis sessions, which allows for a more efficient vascular filling.⁶²

BIOELECTRICAL IMPEDANCE IN KIDNEY TRANSPLANTS

Kidney transplantation is the treatment of choice for eligible CKD patients, but few studies have analysed the role of BC in this therapy.^{63,64} The majority of patients do not have bilateral functioning of native kidneys, and renal function progressively and slowly deteriorates towards ACKD in the majority of cases. The guidelines for nutritional management of transplant patients were published only recently.⁶⁵

Obesity also affects transplant patients (previously obese or not). This is a common and multifactorial issue (absence of physical activity, genetic predisposition, corrected uraemia, age, sex, and race) that is associated with important complications such as hypertension, type 2 diabetes, coronary disease, and dyslipidaemia, which increase post-transplant morbidity and mortality rates.⁶⁶ Contrary to the results observed with dialysis patients, a high BMI in these cases is directly associated with hospitalisations and high mortality rates, which appears to suggest that the recovery or loss of renal function has a different influence on how adipose tissue exerts its metabolic effects.⁶⁷

The analysis of BC using BIVA is attracting a growing interest in the importance of carefully selecting transplant candidates, patient evolution and pharmacological management.⁶⁸

Malnutrition-inflammation is associated with progressive loss of graft function, poor immune response to the transplant, and more rejection episodes. This syndrome recently was the subject of a protocol for a validated evaluation system similar to that of patients with CKD on dialysis, since it produces changes in BC, particularly in the form of loss of muscle mass.⁶⁹

A comparison using BIVA of the BC of patients undergoing transplants with values from a healthy reference population showed that patients with no initial deterioration of renal function (one month following transplantation) had a similar body composition to the reference population, whereas those that were in the initial stages of CKD (<75ml/min/1.73m²) had changes in BC values, with increased EW, decreased IW, lower PA, and increased exchangeable Na-K, similar findings to those observed in CKD patients.^{70,71}

Gender is also a source of variation, especially in the pre-transplant period, and influences patient evolution during the first three months following the procedure. Pre-transplant BC values in male transplant patients included higher resistance, reactance, and CM, and lower EW than in healthy controls, which is in accordance with a situation of depletion. However, three months after transplant, the only difference between the two study groups was a higher EW and TW as compared to controls. There were no differences in the group of transplanted female patients.⁷²

With the available data, the analysis of BC in transplant patients, risk stratification, and optimising patient health are challenges that can be more easily faced using BIVA.

BIOELECTRICAL IMPEDANCE IN HEART FAILURE AND CARDIORENAL SYNDROME

The prevalence of symptomatic chronic heart failure (HF) affects 2% of subjects older than 45 years, is the most important cause of hospitalisations in patients older than 65 years, and an important public health issue. The presence of renal disease in patients with normal or low ejection fractions is frequent, as well as in patients with or without symptoms. Altered renal function plays an important role in the progression of heart disease and is an independent risk factor of morbidity and mortality.⁷³ This relationship between kidneys and heart has been recently redefined as cardiorenal syndrome (CRS).⁷⁴ Although the mechanism is not well defined, it is known that heart function deterioration causes decreased perfusion in renal tissues, which explains some of the aspects involved in CRS.⁷⁵

Chronic HF is characterised by cyclic volume overload (pulmonary and peripheral) and overload elimination (diuretics, ultrafiltration). Despite a positive response, the high rate of rehospitalisations suggests that the discharge criteria are probably poorly correlated with clinical stability. The use of BIVA for evaluating heart failure has been examined in the context of measuring myocardial stress.⁷⁶ In a combined study using BIVA and BNP in 292 patients with dyspnoea, 58.2% had acute cardiac decompensations, with significantly higher BNP values and short BIVA vectors with isolated predictive values or values associated with BNP, as compared to those that did not suffer acute heart failure, proving that the combination of BIVA and BNP is useful in the management of these patients. This combination of BIVA and Pro-BNP discriminates between cardiac and non-cardiac dyspnoea, improving the speed and accuracy of diagnosis.⁷⁷

Outpatient follow-up of heart patients can benefit from the use of BIVA, with the objective of monitoring pharmacological treatment. This method can achieve a 35% reduction in rehospitalisations and treatment costs.^{14,78}

With the objective of maintaining haemodynamic stability and good volume control and nutritional state, the therapeutic alternatives with PD or HD in CRS open the door for the use of BIVA in evaluating BC along with cardiovascular risk factors.⁷⁹

BIOELECTRICAL IMPEDANCE IN CRITICAL PATIENTS

An exact quantification of body fluids in critical patients is neither practical nor possible. Central venous pressure is used to monitor solution infusions.

BIVA has been proven a useful tool as compared to central venous pressure. Both components of the vector are inversely correlated with central venous pressure values. Increases in central venous pressure corresponded to a short vector towards the lower part of the ellipse, below the 75th percentile. Situations of depletion are associated with long vectors, above the 75th percentile. A combination of BIVA and tissue hydration parameters yields a more precise quantification of fluids in critical patients, particularly in those with low central venous pressure.⁸⁰ It also allows for monitoring surgical patients under anaesthesia, facilitating fluid therapy and nutritional support.⁸¹

In multi-organ failure with continuous renal replacement therapy, BIVA in combination with serum markers facilitates proper management of BC, while monitoring nutritional state and hydration, especially with regard to the extracellular space.⁸² In the case of sepsis treated with drotrecogin alpha (Xigris®), Na-K exchange and PA are the predictive parameters for patient evolution during the first 24 hours. In several studies, including over 30 patients with sepsis, a PA>4° upon hospitalisation was significantly correlated with survival.⁸³ Additionally, this pathology is associated with a 15%-20% loss of muscle proteins and potassium, reducing IW and TBK and increasing TW and EW. BIVA facilitates the early detection of these changes, as well as the necessary nutritional support for preserving muscle tissue.⁸⁴ Lean mass, a primary component of metabolic activity, functions as a reservoir for amino-acids during the stress response. The loss of CM is correlated with altered physiological functioning and survival.⁸⁵ Monitoring CM is more precise than lean mass, since the latter includes EW, which fluctuates, especially in patients undergoing continuous dialysis sessions, whereas the former only considers IW. As such, the systematic evaluation of BC is clinically important in critical patients.

BIOELECTRICAL IMPEDANCE IN HIGH-RISK PREGNANCY

A significant challenge lies in analysing changes to BC in physiological systems such as the menstrual cycle. Important fluctuations in BC and weight during the menstrual cycle have been the objective of two studies with BIVA in women that did not take oral contraceptives. These studies demonstrated variations in BC during the premenstrual period as high as two litres in TW.⁸⁶ Menstrual synchronisation has also been described in women that live or work together in their workplace or school, consisting of normalised cycles and simultaneous occurrence.⁸⁷

During pregnancy, BC suffers changes as the body adapts, especially evidenced by weight gain. The resulting BC is not completely understood, justifying its assessment using BIVA.

Pregnancy produces increased TW at the expense of EW, especially in the last two trimesters. IW increases, reaching a maximum peak during the end of the third trimester. These changes can be explained by water retention in certain tissues, such as the breasts and pelvis, with the objective of facilitating both labour and puerperium.

Monitoring BC during pregnancy provides relevant information regarding the quality of adaptation by the mother to the physiological situation. Body water content is related to plasma volume, and BIVA directly provides us with variations in BC at different stages (Figure 3).

Additionally, BIVA allows for detecting increases in TW and their distribution before they become clinically apparent. Increased IW and EW are observed in women that develop gestational hypertension, although these results are not conclusive.⁸⁸

Few studies have used BIVA in preeclampsia, an important cause of death in mothers. We followed 10 pregnancies at risk of preeclampsia, whether because they developed this condition in earlier pregnancies or had hypertension before pregnancy, and observed that once blood pressure was controlled, it produced changes in BC similar to those described by other authors, reducing resistance and reactance. After the sixth month of gestation, subjects approach baseline BC values with normal blood pressure and urine albumin/creatinine ratio (Cigarrán, unpublished data, Figure 3).

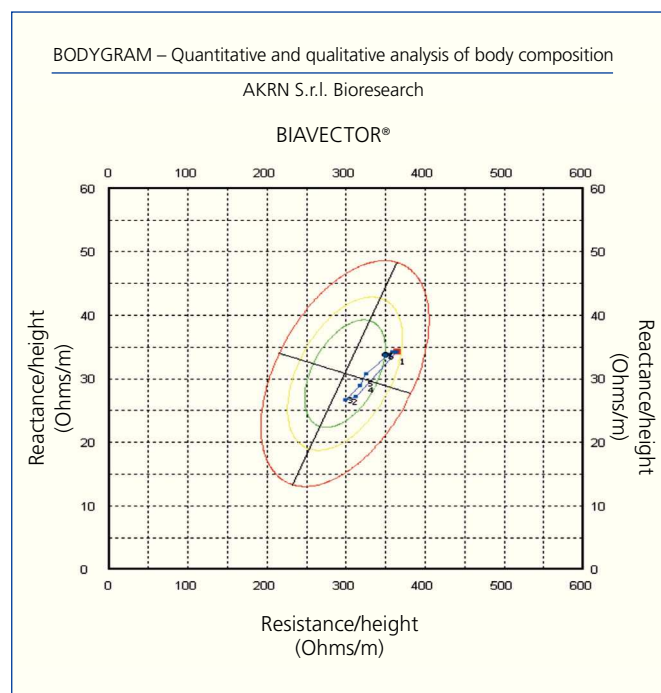


Figure 3. Monitoring body composition in high-risk pregnancy

A group from São Paulo, analysing the evolution of BC using BIVA in 23 pregnancies with preeclampsia and comparing them to 22 normal pregnancies with no pathology, observed an increase in TW and IW volume, and the resistance index (height [cm]²/resistance [Ohm]) in the group of patients with preeclampsia. The authors attributed these changes to water and sodium retention due to generalised vasoconstriction, increased capillary permeability, and reduced sodium excretion.⁸⁹

BIVA evaluates variations in BC during the menstrual cycle, normal pregnancy, and high-risk pregnancy.

CONCLUSIONS

1. BIVA is an extremely valuable tool for clinical use because of its safety, ease of use, low cost, and accuracy.
2. Monitoring body composition in CKD, dialysis, and kidney transplant patients allows for evaluating changes in nutritional state, inflammation, and cardiovascular risk.
3. Parameters derived from BIVA have proven their validity in predicting mortality; the most important is PA.
4. The concept of “dry weight” changes to appropriate or euvolemic body composition.
5. Future lines are being opened for the application of BIVA in fairly unfamiliar settings such as heart failure, cardiorenal syndrome, critical patients, and high-risk pregnancies.

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