Review paper

Usefulness of bioelectrical impedance analysis in assessment and monitoring of nutrition status of chronic heart failure patients

Przydatność pomiaru impedancji bioelektrycznej w ocenie i monitorowaniu stanu odżywienia chorych z przewlekłą niewydolnością serca

Grzegorz Sobieszek[1], Aneta Skwarek-Dziekanowska[1], Agata Kot[2], Mansur Rahnama-Hezavah[3], Tomasz Powrózek[4], Teresa Małecka-Massalska[4]

[1]Department of Cardiology, 1st Military Clinical Hospital with the Outpatient Clinic, Lublin, Poland
[2]Care and Treatment Facility, Cardinal Wyszynski Voivodeship Specialist Hospital, Lublin, Poland
[3]Chair and Department of Oral Surgery, Medical University of Lublin, Lublin, Poland
[4]Department of Human Physiology, Medical University of Lublin, Lublin, Poland

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Słowa kluczowe: przewlekła niewydolność serca, pomiar impedancji bioelektrycznej, niedożywienie, kacheksja.

Abstract

In chronic heart failure (CHF) patients malnutrition and/or cachexia are frequently observed syndromes that negatively affect the quality of life and survival of patients. That makes it necessary to investigate reliable methods of assessment of body composition which can facilitate appropriate clinical decisions on patients' treatment. Bioelectrical impedance analysis (BIA) is a reliable and non-invasive method to test body composition in patients suffering from various chronic diseases, including CHF. The aim of the review was to summarize recent findings on BIA assessment for nutritional and clinical management of CHF. Although BIA is a known technique used for body composition assessment, the number of papers analyzing its utility in cardiovascular diseases is still limited, particularly with a combination of molecular markers. Electrical parameters obtained in BIA in conjunction with biochemical determinations and molecular factors can improve selection of patients at risk of malnutrition and unfavorable prognosis related to nutritional deficits.

Streszczenie

U chorych na przewleką niewydolność serca (PNS) często stwierdza się obecność niedożywienia i/lub kacheksji, które mają niekorzystny wpływ na jakość i czas życia pacjentów. Konieczne jest poszukiwanie obiektywnych metod służących ocenie stanu odżywienia chorych, które mogą ułatwić podjęcie decyzji terapeutycznych. Pomiar impedancji bioelektrycznej (BIA) jest obiektywną i bezinwazyjną metodą pomiaru składu ciała u pacjentów cierpiących z powodu różnych chorób przewlekłych, w tym PNS. Celem niniejszej pracy było podsumowanie aktualnego stanu wiedzy na temat zastosowania BIA do oceny stanu odżywienia i monitorowania chorych na PNS. Na podstawie analizy danych z piśmiennictwa stwierdzono, że chociaż BIA jest znaną techniką, to liczba artykułów dotyczących jej wykorzystania u pacjentów z chorobami układu sercowo-naczyniowego jest ograniczona, szczególnie biorąc pod uwagę połączenie tej techniki z markerami molekularnymi. Parametry elektryczne uzyskane w analizie BIA w połączeniu z markerami biochemicznymi i molekularnymi mogą ułatwić selekcję chorych z ryzkiem rozwoju niedożywienia oraz niekorzystnym rokowaniem związanym z zaburzeniami stanu odżywienia.

Introduction

In recent decades, chronic heart failure (CHF) has become an increasing epidemiological, social and economic challenge. CHF is not only a progressive process but is often a consequence of different heart disorders. It is characterized by high morbidity and mortality and frequent exacerbations requiring hospitalization. CHF is a chronic disease with poor prognosis which is comparable to neoplastic diseases. It is a health problem that affects not only patients but also their families and the healthcare system [1–3]. The highest costs are generated by hospitalizations related to exacerbations and subsequent visits to health care facilities, which affect almost half of patients. Prognosis in CHF is often connected with complications and comorbidities, among other nutritional disorders such as sarcopenia and cachexia. They affect from 15% to as many as 50% of patients with CHF and significantly worsen the prognosis and functional

condition of patients [4–7]. However, we are still looking for markers to identify the early stage of excessive overhydration and nutritional disorders in CHF patients. It can be a critical factor in the improvement of prognosis. Presently, either sarcopenia or cachexia is often completely not treated, or even diagnosed in a late stage, when the treatment options are limited and the disease prognosis is unfavorable.

The aim of the review was to summarize available literature data considering the utility of bioelectrical impedance analysis (BIA) assessment in CHF patients. The utility of the selected BIA parameters is discussed in the context of CHF, and utility of this method for patients' prognosis and nutritional screening is summarized. Recently, some authors have placed particular attention on BIA in combination with other methods for CHF management, including molecular markers.

Data on BIA assessment in CHF were derived from literature reports available in Scopus, PubMed and Google databases. The data screening was performed until August, 2023. The following terms and combinations of them were used for the literature screening: "Chronic heart failure", "CHF", "Bioelectrical Impedance Analysis", "BIA", "Phase angle", "prognosis", "outcome" and "monitoring". Based on the above terms, we built the search query, as follows: (BIA OR Bioelectrical Impedance Analysis OR Phase angle) AND (Chronic heart failure OR CHF) AND (prognosis OR outcome OR monitoring). For the Google search we added terms with the full query, such as: "BIA in CHF prognosis", "BIA and chronic heart failure", etc. Afterward, duplicates obtained from the screening of databases were removed and the abstracts selected for further analysis. If appropriate original full-papers were reviewed in order to derive data for the review. Exclusion criteria were as follows: a) papers on acute heart failure, b) papers not written in English, c) papers that do not refer to assessment of BIA parameters, d) papers that do not analyze BIA in the context of CHF, e) review papers or meta-analyses.

Results

Nutritional assessment of CHF patients

When assessing the irrigation and nutritional status of patients, including CHF, we focus on the assessment of clinical and anthropometric parameters. Clinical and anthropometric parameters are currently insufficient for the correct and reliable assessment of the nutritional status and body condition of people suffering from various chronic diseases, including CHF [8–11]. The most common method of detecting impending hyperhydration in CHF patients is regular body weight (BW) measurements. In the event of unexpected weight gain of more than 2 kg within 3 days, guidelines recommend increasing the dose of diuretics and contacting a doctor [12]. The sensitivity of this method in detecting CHF decompensation is low [13]. The anthropometric tests used to assess the nutritional status include: body mass index (BMI), waist to hip ratio (WHR), arm circumference, measurement of skin and fat folds measured in appropriate places, i.e. most often above the biceps, triceps, under the scapula and above the hip [11]. First, they do not directly reflect the state of the organism at the tissue and cellular level and often provide false-positive or negative results, as their measurement results may be masked by related conditions, e.g. improper water management in the body or kidney failure. All the methods of assessment used are aimed at making a diagnosis of the nutritional status, but they differ in the reproducibility of the results, and the basic limitation for most of them is the cost and availability of specialist equipment. However, anthropometric methods are burdened with a high risk of measurement errors, so it is worth supplementing them with more accurate methods, the repeatability of which is higher [11]. Based on the above observations, it seems justified to look for more objective methods that would allow us to determine both the condition of the organism at the cellular level and facilitate making appropriate therapeutic decisions. Additionally, it serves for monitoring patients with CHF.

Bioimpedance analysis in CHF patients

The goal of advancing CHF research is to get ahead of this stage and capture patients at risk of exacerbation before symptoms appear. The main task in the treatment of CHF is most importantly to reduce mortality, avoid hospitalization and shorten hospitalizations. What is more, it improves the clinical condition, exercise capacity, as well as the quality of life. The increased fluid retention changes the electrical properties of cells. These changes can be monitored with the help of BIA. Using this knowledge, the electrical properties of the tissues of patients with CHF were examined and the obtained data were correlated with the clinical condition of patients in terms of parameters reflecting the body composition and the severity of the underlying disease. BIA consists in measuring the total resultant electrical resistance of the body, which is a derivative of resistance (R) and reactance (Xc), using a set of surface electrodes connected to a computer analyzer and using a current of a given frequency and intensity [8, 9]. Using BIA, we are able to measure the amount of total body water (TBW), intracellular body water (ICW) and extracellular body water (ECW), as well as body cell mass (BCM), fat mass (FM) and fat-free body mass (FFM) [9]. Body composition assessment provides insight into the nutritional status of the patient, as well as the information on the performance of internal organs. The wide spectrum of the parameters obtained justifies the use of BIA in various disease entities (Figure 1).

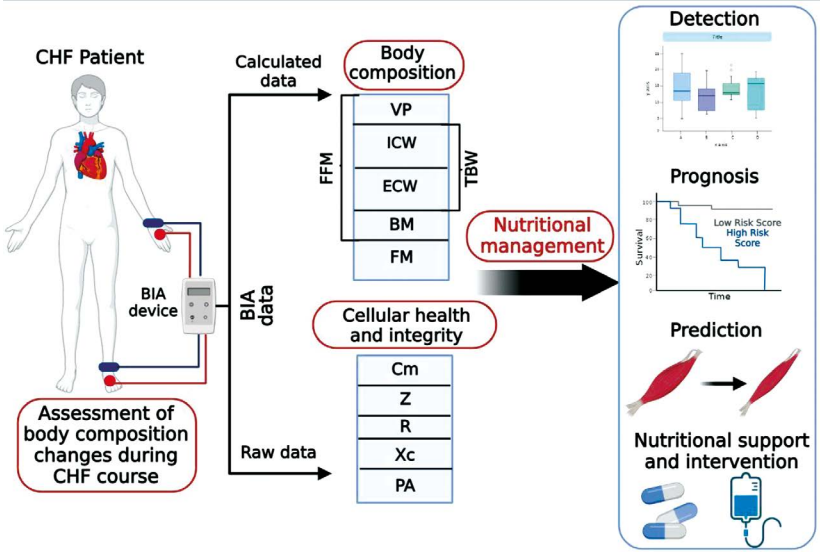

Figure 1. Prospective application of BIA parameters in monitoring the clinical and nutritional status of CHF patients. Nutritional management refers to detection of nutritional deficiencies, prognosis of malnourished/cachectic individuals, prediction of body composition changes with corresponding loss of tissue mass as well as nutritional intervention in malnourished ones (raw data from BIA: Cm – membrane capacitance, Z – impedance, R – resistance, Xc – reactance, PA – phase angle and calculated data from BIA: VP – visceral protein, ICW – intracellular body water, ECW – extracellular body water, TBW – total body water, BM – bone mass, FM – fat mass; FFM – fat-free mass)

BIA assessment in patients with CHF provides an objective assessment of hydration and body composition [2]. Due to its non-invasive nature and reliability, it can be an attractive alternative to other methods for assessment of FM and FFM content in CHF patients. CHF, like other chronic diseases, is a catabolic state of the body, and elevated FM may serve as a necessary energy reserve in this patient population. Cardiac cachexia, a syndrome involving progressive weight loss and changes in body composition, has a devastating effect on the course of CHF. There are studies showing the protective effect of adipose tissue in the context of CHF, and the loss of adipose tissue. BIA is a safe and convenient way to measure FM and FFM [14]. We have found limited examples of the use of BIA exclusively in CHF in the available literature reports. They are briefly summarized in Table I and discussed in detail in this and the following subsection.

The authors of the study described below also analyzed BIA parameters in the clinical assessment of patients with CHF. They found that patients with a more severe course of CHF (New York Heart Association [NYHA] grades III and IV) have abnormal BIA parameters that reflect abnormalities in the morphology and functioning of the organism at the cellular level. In this group, lower values of the phase angle (PA) at 50 kHz were found (median PA: 2.95° and 4.49°; $p = 0.010$), the electric capacity of the cell membrane (Cm) (median Cm: 0.92 nF and 1.57 nF; $p = 0.020$), Xc at 50 kHz (median Xc: 23.17 and 39.0; $p < 0.01$) and a higher impedance ratio at 200 kHz and 5 kHz (Z200/Z5) (median Z200/Z5: 0.89 and 0.83; $p < 0.01$) than in patients classified as NYHA I–II [9]. Thomas *et al.* found significantly better survival of individuals in the group with high FM compared to people with low FM (90.2% vs. 80.1%, $p = 0.008$). They also noted an improvement in 5-year survival in patients with high FFM compared to patients with low FFM (89.3% vs. 80.9%, $p = 0.036$). Comparing the body composition categories, patients with high FFM and FM had the best prognosis, and the worst prognosis was in the group with low FFM and low FM [15]. The effectiveness of BIA in the assessment of FM, FFM and bone mass (BM) compared to dual energy X-ray absorptiometry (DEXA) is considered the gold standard in body composition analysis, which was assessed by Shah *et al.* Compared to DEXA, BIA gave higher FFM and BM values, but lower FM values. The correlation between DEXA and BIA was close for both FFM and FM (FFM: $p < 0.001$; FM: $p < 0.001$), but less for BM ($p < 0.001$). FM, FFM, and BM measurements made in the bioelectric impedance analysis correlated well with other body size measurements (BMI, waist circumference and hip circumference) [16]. Castillo-Martinez *et al.* studied 243 patients with CHF, including 140 with heart failure with a reduced ejection fraction (HFrEF) and 103 with heart failure with a preserved ejection fraction (HFpEF). In the study, they assessed the dependence of BIA parameters such as impedance (Z), PA and Xc on the (NYHA) class of heart efficiency. In both CHF categories, Xc and PA were much lower, the Z ratio of 200 kHz to 5 kHz (Z200/Z5) was higher, and the Z vector was much shorter and downsloping in the NYHA III–IV group compared to the NYHA

Table 1. Summary of studies investigating raw and calculated parameters of BIA and studies combining BIA with other tools for clinical and nutritional management of CHF (studies limited only to CHF)

Studied parameters	Study group	Major findings	Citation
BIA parameters only:			
PA Z200/Z5 Cm	100 CHF patients Median age: 73 years	Low PA, and Cm values and higher values of the Z200/Z5 ratio are observed in patients with severe CHF (NYHA III–IV). In men Cm negatively correlated with CRP level	[9]
FM FFM	359 CHF patients Mean age: 56 years	Higher FM and FFM are associated with improved outcomes in CHF regarding patient's w5-year survival	[15]
Xc PA Z200/Z5	346 CHF patients Mean age: 64 years	Xc and PA are significantly lower and the impedance ratio Z200/Z5 is higher in the patients with severe CHF (NYHA III–IV)	[17]
PA	389 CHF patients Mean age: 61 years	Low PA is associated with malnutrition markers – decreased body mass index, handgrip strength, and hemoglobin and with a poorer NYHA functional class	[18]
BIA parameters combined with other methods:			
EI + NTpro-BNP, CRP	170 CHF patients Mean age: 34 years	EI combined with NTpro-BNP and CRP could be a useful marker for CHF severity and could predict future CHF-related admissions	[20]
Cm + irisin, CRP, albumin	66 female CHF patients Mean age: 77 years	Combination of Cm with irisin, CRP and albumin demonstrated sensitivity of 93.3% and specificity of 85.3% for distinguishing between cachectic and non-cachectic CHF patients	[22]
PA + sST2	91 male CHF patients Mean age: 69.5 years	PA combined with sST2 demonstrated potential utility in male patients with CHF under cachexia condition in death rate prediction	[24]
PA + rs767455 TNFRSF1A	142 CHF patients Mean age: 77 years	TT genotype carriers had significantly lower PA values compared to other genotype carriers and can be considered as an unfavorable factor related to a higher risk of cachexia in CHF patients	[25]
PA + rs7193943 ITGAM	154 CHF patients Mean age: 69.5 years	GG genotype correlates with low PA and susceptibility to cachexia development in CHF patients	[29]

CHF – chronic heart failure, Cm – capacitance of membrane, CRP – C-reactive protein, EI – edema index, FFM – fat-free mass, FM – fat mass, NYHA – New York Heart Association, PA – phase angle, Xc – reactance, Z – impedance.

I–II group by gender [17]. Colín-Ramírez *et al*. in a retrospective study examined 389 patients with CHF and the endpoint of the analysis was all-cause mortality. In the studied population, PA < 4.2° characterized patients with lower mean BMI, hand grip strength and hemoglobin value, as well as higher incidence of NYHA functional class III and renal failure. Adjusted for age, diabetes, and hemoglobin levels, PA < 4.2° was shown to be an independent predictor of all-cause mortality in CHF patients [18]. Beside the BIA, also bioimpedance spectroscopy (BIS) is considered as a non-invasive method to measure fluid volume in HF patients. Accardi *et el*. using this method compared fluid volumes between HF patients and healthy individuals – the extracellular fluid as a percentage of total body water (ECF%TBW) values were significantly higher in HF patients as compared to healthy ones. According to the authors ECF%TBW may aid in clinical risk stratification and fluid volume monitoring in HF patients [19].

Combination of BIA with other diagnostic parameters

BIA parameters are often combined with other factors, such as laboratory markers, biochemical and genetic tests. The correlation of BIA parameters with other markers looks very promising in obtaining values that are important in diagnosis, short- and long-term prognosis, as well as control during treatment.

Sato *et al*. correlated BIA with the level of brain natriuretic peptide (BNP). In a prospective single center

study, 170 patients with CHF due to congenital heart disease (CHD) were included. Among the BIA parameters, they assessed the edema index (EI, the ratio of extracellular water to total body water) and then compared the results to laboratory parameters. They also assessed the relationship between CHF-related admission rates and EI. Patients in NYHA functional classes III–IV had a higher EI than those in NYHA classes I–II ($p < 0.001$). EI was significantly correlated with the level of NTpro-BNP ($p < 0.001$). Higher EI values were significantly associated with a future increased risk of hospitalization due to HF (HR = 4.15, $p < 0.001$). The authors concluded that EI determined by BIA could be a useful indicator of the severity of HF and could also predict future CHF hospitalizations in adult CHD patients [20]. In the aforementioned analysis, at best, weak correlations between the BIA FM, FFM and BM measurements and the measures of CHF advancement, including echocardiographic severity of left ventricular dysfunction, NTpro-BNP, CRP, creatinine and age, were found. Moreover, the authors of the following study, in a group of men, found a close correlation between inflammation (represented by CRP concentration) and the values of PA, Cm, Xc and Z200/Z5 [16]. An extremely interesting use of BIA was proposed by Scicchitano *et al.* as a method for calculating the eGFR (Donadio formula). The work compared the use of various eGFR enumeration patterns (Donadio, Cockcroft-Gault, MDRD-4, CKD-EPI formula) for predicting all-cause mortality in CHF patients. Four hundred and thirty-six people with CHF were enrolled in the study, and the conclusions indicate that eGFR, calculated using the Donadio formula, was an independent predictor of mortality in patients with CHF, similar to the measures derived from the MDRD4 and CKD-EPI formulas, but less accurate than the Cockcroft-Gault formula [21].

In a group of women, an attempt was made to correlate the BIA parameters with the concentration of circulating irisin [22]. Irisin is a hormone that regulates energy changes in the body and reflects the energy balance of the heart muscle [23]. In women with diagnosed cachexia, significant deterioration in the values of parameters reflecting the nutritional status and heart function was found, compared to non-exhausted patients. The mentioned differences were in body weight ($p = 0.010$), BMI ($p = 0.024$), adipose tissue ($p = 0.020$) and muscle mass ($p = 0.031$), albumin concentration ($p < 0.001$), SGA score ($p < 0.001$), hemoglobin ($p = 0.025$), CRP ($p = 0.005$), TNF-α ($p = 0.032$), NYHA grade ($p = 0.030$), EF% ($p = 0.039$) and NT-proBNP ($p < 0.001$). Moreover, in women with cachexia, a significantly lower concentration of circulating irisin was found (median concentration: 7.13 µg/ml and 7.62 µg/ml; $p = 0.022$) and lower values of parameters obtained from the measurement of bioimpedance – PA (mean value PA: 3.60 ±1.17° and 4.60 ±1.08°; $p = 0.005$) and Cm (median Cm: 0.860 nF and 1.280 nF; $p < 0.001$) compared to non-exhausted patients. In the study group, the level of circulating irisin was positively correlated, primarily with the weight of adipose tissue ($R = 0.408$; $p = 0.020$) and negatively with Cm ($R = –0.393$; $p = 0.005$). Interestingly, the Cm value was selected as an independent factor associated with an over 10 times greater chance (OR = 10.76; $p < 0.001$) of developing cachexia in women with CHF. Simultaneous assessment of albumin, CRP, irisin and Cm made it possible to distinguish women with cachexia from non-exhausted women with a sensitivity of 80% and a specificity of 97.1% (AUC = 0.949; $p < 0.001$). The results presented by the authors proved that BIA parameters, such as PA and Cm combined with irisin, can select patients with an unfavorable clinical picture and disease prognosis. Additionally, they can reflect the nutritional status of CHF patients and select those at a high risk of cachexia. Moreover, the assessment of irisin concentration and measurement of Cm can significantly improve the diagnosis of cachexia in patients with CHF, finding its place next to parameters such as CRP or albumin level [22].

Interesting conclusions can be drawn from the comparison of BIA results with the determination of ST2 concentration. ST2 is a receptor protein that comes in two forms: transmembrane (ST2L) and circulating in the blood (sST2) [24]. sST2 binds to IL-33, which is secreted by cardiomyocytes in response to mechanical stimulation or damage to them [21]. ST2 may be a potential diagnostic marker that characterizes the processes of myocardial remodeling and fibrosis and, above all, provides valuable prognostic information [24]. In this research patients with cachexia had a higher concentration of sST2 in the blood plasma (median sST2: 27.4 ng/ml and 20.62 ng/ml; $p < 0.001$) compared to non-debilitated patients. In addition, men with CHF presented significantly worse values of parameters reflecting the nutritional status (albumin, SGA score, PA, Cm) and a higher concentration of inflammatory markers in the blood (CRP and TNF-α) and lower hemoglobin level and EF% (all parameters $p < 0.05$) compared to patients without diagnosed cachexia. The level of plasma sST2 in patients with CHF significantly and positively correlated primarily with the level of CRP ($R = 0.524$; $p < 0.001$), NT-proBNP ($R = 0.438$; $p < 0.001$) and the SGA score ($R = 0.430$; $p < 0.001$) and negatively with the value of PA ($R = –0.513$; $p < 0.001$), Cm ($R = –0.421$; $p < 0.001$) and the weight of adipose tissue ($R = –0.301$; $p = 0.015$). During the observation, the value of PA < 3.06° (HR = 9.62; $p < 0.001$) and the concentration of sST2 in the blood plasma > 33.15 ng/ml (HR = 8.60; $p = 0.003$) were the most unfavorable factors influencing prognosis in CHF patients.

The latest studies indicate the possibility of combining BIA with the assessment of immunological parameters. Increased release of pro-inflammatory cytokines leads to the development of a generalized inflamma-

tory process and disturbances in the metabolic functions of the organism associated with increased catabolism of muscles and/or adipose tissue, which may result in the development of malnutrition and cachexia [25]. TNF-α appears to play an important role in this process in patients with CHF, which exhibits its activity by binding to TNFR types 1 and 2 on the surface of various cell types, including myocardial fibroblasts, stimulating their proliferation. The above observation seems to justify the role of TNF-α and its receptors not only in the development of inflammation but also in the process of heart remodeling [26]. TNF-type 1 receptor (TNFR1), encoded by the *TNFRSF1A* gene, plays an important role in regulating the intracellular response to TNF-α. In patients with CHF, the TT *TNFRSF1A* genotype seems to be especially unfavorable. In the group of patients studied by the authors of the following study, patients with TT genotype had significantly lower blood albumin levels ($p = 0.039$), higher CRP levels ($p = 0.012$), and NT-proBNP ($p = 0.015$) in the blood serum, a higher percentage of NYHA grade III and IV ($p = 0.006$) and a higher incidence of moderate and severe malnutrition on the SGA scale ($p = 0.022$) compared to carriers of other genotypes. When BIA was performed in this group of patients, it was noted that TT carriers had significantly lower PA values compared to other genotype carriers ($p = 0.035$ and $p = 0.032$ for men and women, respectively) [25].

Recent scientific reports described the use of *ITGAM* genetic analysis, but mainly in the pathogenesis of systemic lupus erythematosus (SLE) [27, 28]. The authors of these studies indicated the use of genetic methods in the assessment of CHF patients and their reference to laboratory tests and BIA. The *ITGAM* gene is critical in the activation, migration and adhesion of leukocytes, and its primary function is to encode the αMβ2 integrin chain [29, 30]. Inflammation is mediated by genes, including the ITGAM gene (also known as CD11b, Mac-1 integrin α chain, or the complement receptor) located on chromosome 6 16p11.2. Its protein product influences the functioning of the INF-γ receptor and the inflammatory mediator and secretion regulation [29]. The process described above is clearly marked in patients with CHF. In carriers of the GG genotype of the ITGAM gene, compared to other variants of the tested SNP (AA or GA, respectively), significantly higher values of body weight, LDL and diastolic blood pressure were observed. Moreover, in these patients, a significantly lower incidence of diabetes was observed. Lower, but only in women, parameter values derived from BIA: Cm (0.7 vs. 1.3 nF), PA (2.8° vs. 4.2°) and Z200/Z5 (1.1 vs. 1.2). However, the same patients achieved significantly higher values of creatinine, CRP, NT-proBNP and PASP.

Limitations of BIA

The results of the BIA test are influenced by variable factors, which depend on the correct operation of the device, as well as the proper preparation of the tested person. The main limitation of BIA is that it cannot be used in the decompensation of CHF [31]. This is because the torso contributes little to the total body impedance, as it is relatively short, has a large cross-section and has heterogeneity in the tissues. Therefore large changes in the volume of the torso may result in relatively small changes in the total body impedance. Additionally, the BIA results may not be reliable in obese patients (with BMI > 34 kg/m^2); they have a relatively high amount of ECW and TBW, which can overestimate FFM and underestimate FM values. Uniquely, in patients suffering from CHF, the contraindications for BIA assessment include implanted cardiac devices, such as a cardiac pacemaker, cardioverter-defibrillator or presence of metal implants. New equations are needed to validate BIA in specific conditions related to the clinical picture of CHF patients.

Conclusions

The use of bioimpedance measurements and the determination of the electrical properties of body tissues in patients with CHF may additionally allow one to determine the deterioration of the body condition even before the systemic manifestation of clinical symptoms, and also constitute a valuable tool for monitoring the treatment process. Electrical parameters obtained in BIA in conjunction with biochemical determinations and molecular factors objectively reflect the nutritional status of patients with CHF. Based on the results included in this study it has been confirmed that similarly as in other systemic diseases the PA is one of the most valuable parameters derived from BIA. It allows one to monitor malnourished patients, identify cachectic ones, and determine prognosis of the disease course. Complementing PA assessment with molecular testing improves the accuracy of nutritional screening and prognosis of CHF patients.

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Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Tomasz Powrózek PhD, Assoc. Prof.
Department of Human Physiology
Medical University of Lublin
ul. Radziwiłłowska 11
20-080 Lublin, Poland
Phone: +48 814486080
E-mail: tomaszpowrozek@gmail.com

Grzegorz Sobieszek PhD
Department of Cardiology
1st Military Clinical Hospital
with the Outpatient Clinic
al. Racławickie 23
20-048 Lublin, Poland
Phone: +48 261183614
E-mail: grzes.bies@interia.pl

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