Reviews in Endocrine and Metabolic Disorders
https://doi.org/10.1007/s11154-022-09757-2

The role of bioelectrical phase angle in patients with heart failure

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Accepted: 19 September 2022
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Abstract

The most challenging feature of heart failure (HF) still remains the evaluation of congestion. Residual congestion at discharge and the difficulties in perfectly dosing therapies in order to balance the hydration status of the patient are the most worrisome issues when dealing with HF.

The use of bioimpedance vector analysis (BIVA) might promote a different approach in the general management of patients with HF. BIVA is a reliable, fast, bedside tool able to assess the congestion status. It proved to be helpful to physicians for diagnosing congestive status, managing therapies, and providing prognostic information in the setting of HF.

Bioelectrical Phase Angle (PhA) – as derived from equations related to the parameters of BIVA – recently surged as a possible biomarker for patients with HF. Studies provided data about the application of PhA in the clinical management and in the overall risk stratification of HF patients.

Basically, the use of PhA might be considered as a holistic evaluation of patients with HF which includes the need for a multiparametric approach able to effectively depict the clinical status of patients. There is no definite biomarker able to comprehensively describe and identify all the features of HF patient, but scores based on molecules/techniques able to explore the different pathogenetic mechanisms of HF are desirable.

The aim of this review was to provide a comprehensive evaluation of literature related to PhA role in HF and the impact of this biomarker on clinical management and risk stratification of HF patients.

Keywords Bioimpendace vector analysis · Phase angle · Heart failure · Clinical management · Prognosis

Abbreviations

ADHF	acute decompensated heart failure.
AHF	acute heart failure.
AUC	area-under-the-curve.
BCM	body cellular mass.
BIVA	Bioimpendance vector analysis.
BMI	body mass index.
BNP	brain natriuretic peptide.
BUN	blood urea nitrogen.
CHF	chronic heart failure.
CV	cardiovascular.
CVD	cardiovascular disease.
ED	emergency department.
Gal-3	galectin-3.
GNRI	Geriatric Nutritional Risk Index.
HF	heart failure;
ECW	intracellular water.
ICW	intracellular water.
MACE	major adverse cardiac events.
NYHA	New York Heart Association.
PaO_2	partial pressure of arterial oxygen.
PhA	Bioelectrical Phase Angle.
R	resistance.
ROC	receiver operating characteristic.
Xc	reactance.

1 Introduction

Heart failufre (HF) is a complex clinical syndrome characterized by signs and symptoms which are related to the cardiac impairment in keeping adequate intracardiac pressures and/or cardiac output, thus promoting alterations in body

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Published online: 25 October 2022

composition [1]. Congestion is the natural consequence although its evaluation is still challenging.

Bioimpendance vector analysis (BIVA) has been recently considered as a technique able to provide information about general assessment, management, and prognostic evaluation of patients with HF [2–6]. BIVA derives from the application of low voltage alternating electric current running through the body; dedicated software analyses provide the corresponding bioelectrical parameters – namely resistance (R, in Ohm) and reactance (Xc, in Ohm) – which are normalized for subject's heights and plotted into a dedicated nomogram [2]. This nomogram – the BIVA scheme – allows the representation of hydration status of the patient and gives information about qualitative fluid and cell components of an individual [7].

Indeed, components of the BIVA scheme had been proved to give information about clinical management and prognosis of patients with specific diseases such as cancer and malnutrition [8–10].

Bioelectrical Phase Angle (PhA) is a specific biomarker which is derived from BIVA measurements of R and Xc using a 50 kHz phase-sensitive bioimpedance instrument [11]. Studies outlined the impact of PhA in the general assessment of healthy and unhealthy individuals, allowing the depiction of information about the clinical conditions of muscle mass of patients, cancer evolution and impact of chemotherapies, or even prognostic implication during COVID-19 infection [12–15].

Nevertheless, data on cardiovascular diseases are scant, while even more rare is information about the clinical and prognostic impact of PhA within HF. Queiroz et al. [16] outlined the role of PhA in predicting hospital length-of-stay in patients with acute myocardial infarction rather than foreseeing major adverse cardiac events (MACE). In patients with HF, PhA might be considered as a reliable tool for physicians who are involved in the daily management of this pathology [17–19].

The aim of this narrative review was to provide a comprehensive overview about the role and the impact of PhA in the general management and risk stratification of patients with HF.

2 Bioelectrical phase angle: definition and characteristics

PhA acts as a possible, reliable clinical and prognostic biomarker in the setting of HF [17, 18]. It is derived from the reciprocal between Xc and R and directly calculated as its arc tangent: (Xc/R) x 180°/π (Fig. 1) [11].

Specifically, cellular membranes act as capacitors surrounding intracellular fluids when alternating current passes through them. The delay that occurs between the time that electricity takes for passing through membranes and the time the voltage takes to change can be measured in degrees: this is the PhA [20, 21]. As a general rule, higher PhA values are related to healthier cell membranes. Normal values range between 5° and 7° [22], although values higher than 9.5° might be observed in healthy athletes [23].

PhA might be adopted as a biomarker for the equilibrium between intra- and extra cellular volumes [11, 24]. This derives from the main sources of PhA: "R" is related to the amount of body fluids in the sum of intra- (ICW) and extracellular (ECW) water, while "Xc" is mainly linked to the inner characteristics of the cell membranes [20, 21, 25, 26]. Francisco et al. [27] found that PhA predicted ICW and the ratio between ECW and ICW; higher values in PhA are related to increased ICW pool and lower ECW/ICW ratio, independently from other confounding factors. Definitely, PhA is positively related to body cellular mass (BCM), while a negative relationship could be observed for ECW/ICW ratio [28–30]. Therefore, the shift of fluids from the ICW to ECW might be the expression of oedema or malnutrition [28–30].

Indeed, PhA should be associated to the evaluation of the vector length [31]. The analysis of the vectors should effectively take into account both PhA and vector length as for a given PhA value different vector lengths could exist (Fig. 1); this represents the different body composition status [32]. Therefore, the interpretation of PhA value in relation to vector length should be considered as the premix for a comprehensive evaluation of body composition of patients who undergo bioimpedance analysis.

The main determinants of PhA are age, sex, and body mass index (BMI) as men and younger individuals might demonstrate higher values in PhA [33–35]. Differences in the distribution of body fluids and variations in free-fat mass as well as weight explain the impact of the above-mentioned characteristics on the evaluation of PhA. Furthermore, Massari et al. [36] reported a higher PhA value (about 0.1° higher) when measurements were performed at the right side of the body rather than the left of patients with HF. Interestingly, some concerns may come from taking into account the technical error of measurement of PhA. Tables 1 and 2 pointed out the mean differences in PhA between groups of each study. Difference values ranged from 0.1° to 1.5°. Despite the small differences among groups, it has been calculated a mean technical error in bioimpedance analysis of about 1% [36]. Similar data are for the accuracy in PhA evaluation (approximately 0.01°, thus about 1%) [37]. Therefore, it might be assumed that the disease effect is much greater than the variability of the measurements, thus allowing the possibility to repeat PhA evaluation in daily clinical practice with a minimum risk for reproducibility performances.

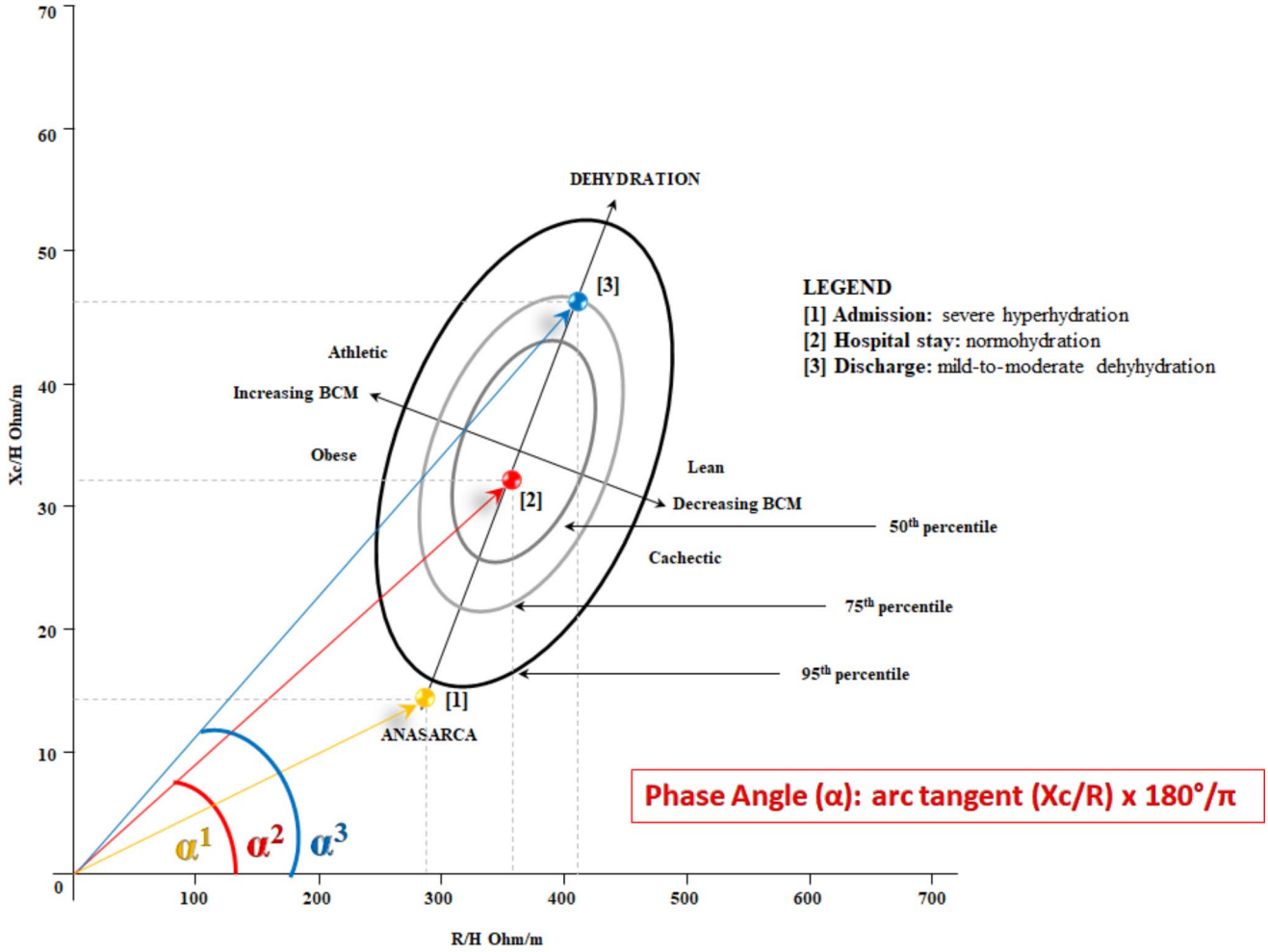

Fig. 1 Schematic representation of the bioimpedance vector analysis (BIVA) and the derivation of Phase Angle (PhA). The figure represents the variations of PhA and vector length in relation to the different stages of hospital stay due to acute decompensation of heart failure: PhA values (α° 1, 2, and 3) tended to increase while the patient lost his/her fluids
Abbreviations: H: height; **R**: resistance; **Xc**: reactance.

It is also encouraging that measurements from bioimpedance analysis demonstrated higher test-retest reliability, i.e. an excellent reproducibility of the technique in HF patients [36].

Paying attention to determinants, PhA might be considered as a general tool for comprehensively evaluating patients, particularly those suffering from HF.

3 Clinical and diagnostic value in congestion status

The assessment of congestion in the setting of HF is challenging and often underestimated. International guidelines [1] provided indications for general assessment of overt signs and symptoms of congestion – namely, peripheral oedema, rales, jugular veins distension, etc. – but physicians should be aware about residual congestion which often passes under-recognized [38–41]. A prevalence ranging from 40 to 77% in residual congestion has been observed in literature [38, 40], thus dramatically impacting on adverse outcomes of patients with HF such as re-hospitalization for HF and all-cause death [38–41].

The application of PhA might provide useful insights when approaching the evaluation of congestion in patients with HF (Table 1). BIVA already demonstrated to act as a reliable tool for the detection of peripheral oedema in acute and chronic heart failure alone or in agreement with further biomarkers of congestions [3, 6]. PhA could effectively detect the changes in fluid overload of patients with acute decompensated HF (ADHF, i.e. those with overt symptoms - breathlessness, ankle swelling, and fatigue – or signs - elevated jugular venous pressure, pulmonary crackles, and peripheral oedema of acute decompensation

Table 1 Clinical and diagnostic value of Phase Angle in the assessment of congestion in patients with heart failure

Study	N. of patients	Type of patients	Study design	BIA device	Follow-up	Results	ΔPhA
Alves et al. 2015 [42]	57	ADHF	Prospective	Biodynamics 450 tetrapolar system (Biodynamics Corp., Seattle, Washington, USA) 50 kHz frequency and 800 microA current	3 months	During hospitalization phase angle increased: from 5.3 ± 1.6° to 6 ± 1.6°, P = 0.007. PhA remained stable at 3-month f.u.	0.7°
De Ieso et al. 2021 [43]	142	ADHF	Observational	Multi-frequency medical whole-body composition analyser (Seca® mBCA 515, Hamburg, Germany)	N/A	Mean phase angle increased from 3.61 ± 0.82° to 3.83 ± 0.74° from admission to discharge	0.22°
Gastelurrutia et al. 2011[44]	54	Stable and unstable HF	Observational	Imp DF50 (ImpediMed, Queensland, Australia). 50 kHz frequency and 800 microA current	N/A	Male: PhA: Stable HF 4.5 ± 0.8° vs. unstable HF 3.8 ± 0.7°, p = 0.02 Female: PhA: Stable HF 3.9 ± 0.8° vs. unstable HF 3.9 ± 0.9°, p = 0.96	Male 0.7° Female 0°
Massari et al. 2016 [6]	900	487 ADHF and 413 CHF	Retrospective	CardioEFG, Akern RJL Systems, Florence, Italy Tetrapolar impedance plethysmograph, 50 kHz alternating sinusoidal current	N/A	Phase Angle ADHF 4.7 ± 1.2° vs. CHF 5.5 ± 1.3° ADHF Phase Angle With peripheral edema: 4.2 ± 1.0° vs. without peripheral edema: 5.1 ± 1.2, p < 0.01 CHF Phase Angle With peripheral edema: 4.5 ± 1.0° vs. without peripheral edema: 5.6 ± 1.2, p < 0.01	ADHF vs. CHF 0.8° ADHF 0.9° CHF 1.1°
Castillo Martínez et al. 2007 [45]	243	140 (101 in NYHA I–II and 39 in III–IV) with HFrEF 103 (67 in NYHA I–II and 36 in II–IV) with HFpEF.	Cross-sectional	Tetrapolar and multiple-frequency equipment (BodyStat QuadScan 4000, Bodystat Ltd.; Isle of Man, UK). Frequencies of 5, 50, 100, and 200 kHz.	N/A	HFrEF (P between NYHA groups: 0.04) *Men* NYHA class I-II: 5.7 ± 1.2° vs. NYHA class III-IV: 4.9 ± 0.9° *Women* NYHA class I-II: 5.1 ± 0.7° vs. NYHA class III-IV: 4.2 ± 1.9° HFpEF (P between NYHA groups: 0.01) *Men* NYHA class I-II: 5.8 ± 1.1° vs. NYHA class III-IV: 4.8 ± 1.1° *Women* NYHA class I-II: 4.9 ± 1.3° vs. NYHA class III-IV: 4.2 ± 1.0°	HFrEF *Men* 0.8° *Women* 0.9° HFpEF *Men* 1.0° *Women* 0.7°
Sobieszek et al. 2019 [46]	100	52 NYHA class I-II 48 NYHA class III-IV	Cross-sectional	ImpediMed bioimpedance analysis SFB7 BioImp v1.55 (PinkenbaQld 4008, Australia).	N/A	PhA NYHA class I-II 4.49° (2.80° – 7.19°) vs. NYHA class III-IV 2.95° (1.50° – 6.65°), p = 0.01	1.54°

of HF [1]) during hospitalization course, thus allowing the evaluation of their re-compensation process [42]. Alves et al. [42] observed statistically significant lower PhA values at admission as compared to discharge, while they started to increase again at 3-month follow-up during outpatient evaluation. Such dynamic change might reflect that related to the congestion status of HF patients during their clinical in-hospital and out-of-hospital course. Similar results were from De Ieso et al. [43] in patients with ADHF: improvement in PhA was observed during the hospital stay after intensified diuretic therapy.

Gastelurrutia et al. [44] found lower PhA values in both stable and unstable patients with HF: nevertheless, unstable male patients showed even lower values than their stable counterparts, while no significant differences were according to females. Similar results were from Massari et al. [6]

Table 1 (continued)

Study	N. of patients	Type of patients	Study design	BIA device	Follow-up	Results	ΔPhA
Scicchitano et al. 2020 [18]	900	ADHF and CHF patients	Retrospective	CardioEFG, Akern RJL Systems, Florence, Italy Tetrapolar impedance plethysmograph, 50 kHz alternating sinusoidal current	N/A	Congestion biomarkers explained the 34% of PhA variability: 20% by PVS, 10% by peripheral congestion; 2% by BNP, respectively Age, GNRI, and only explained 6%, 0.5%, and 0.5% of PhA variability, respectively	
González-Islas et al. 2020 [51]	288	Stable HF patients	Prospective cohort	Tetrapolar and multifrequency equipment (Body Stat Quad Scan 4000). 50 kHz alternating sinusoidal current	N/A	Phase Angle RV dysfunction 5.5 ± 1.3° vs. without RV dysfunction 5.5 ± 1.3°, p = 0.808	0°

Abbreviations: ADHF: acute decompensated heart failure; **BIA**: bioimpedance analysis; **BNP**: brain natriuretic peptide; **CHF**: chronic heart failure; **f.u.**: follow-up; **GNRI**: geriatric nutritional risk index; **H.F.**: heart failure; **HFrEF**: heart failure with reduced ejection fraction; **HFpEF**: heart failure with preserved ejection fraction; **N/A**: not applicable; **NYHA**: New York Heart Association; **PhA**: phase angle; **PVS**: plasma volume status; **RV**: right ventricle

who found PhA values statistically significantly reduced in ADHF patients as compared to chronic HF (CHF) ones. Indeed, Massari et al. more specifically outlined the direct relationship between PhA and peripheral oedema: patients with peripheral oedema were more prone to lower PhA values as compared to those without, independently from their stable or unstable HF condition [6].

Patients suffering from CHF demonstrated lower PhA values when New York Heart Association (NYHA) class was higher (III-IV): such relationship was independent from sex and type of HF (systolic vs. diastolic HF), thus reflecting changes in body composition in relation to the progression of HF [45, 46].

Indeed, patients with HF are predisposed to cachexia – defined as an involuntary weight loss of at least 5% - and muscle wasting, which in turn might occur earlier than the former in patients with HF [47, 48]. BIVA notably allows the evaluation of cachexia in patients with HF [49], but this might impact on the evaluation of congestion. PhA might be used to further stratify the evaluation of these patients: lower PhA values are effectively related to overhydration status but the association with nutrition status and BCM should be weighted in relation to the vector length and the position in the vectorial graph. Actually, no direct comparison or study has been performed in order to fully address such issue. Scicchitano et al. [18] demonstrated that congestion biomarkers better impacted on the variability of PhA in patients with both acute HF (AHF) and CHF (about 34%), while the impact of nutritional status as assessed via the Geriatric Nutritional Risk Index (GNRI) was marginally able to explain the PhA variability (about 0.5%) as well as age (6%) and gender (0.5%). This was in line with the recent findings from Rinaldi et al. [50] who pointed out the low grade of evidence quality of studies trying to assess the influence of nutrition on PhA which prevented physicians to consider PhA as an accurate predictor of malnutrition. Further studies are needed in order to better address such a challenging issue.

Finally, PhA does not allow to distinguish between the dysfunctional cardiac chambers. PhA values seemed not to differ between patients with left ventricular dysfunction and those with alterations in right ventricular function [51].

4 Bioelectrical phase angle in HF: prognostic impact

The role of PhA in assessing the prognosis of patients with HF is an intriguing issue for attempting a comprehensive evaluation of these individuals.

A recent Danish study [52] found that lower PhA values in apparently healthy individuals was related to a 1.33-fold and 1.22-fold increase in the risk of cardiovascular disease (CVD) in women and men, respectively. Similarly, Portugal et al. [53] observed that higher PhA values were related to lower incidence of first cardiovascular (CV) event.

Admission in intensive care unit might be related to worst prognosis in case of lower PhA values [54]. Non-survivors effectively showed significantly lower PhA measurements, while values < 4.6° increased the risk of 1-year all-cause mortality by 81%, even after adjusting for confounding factors [54].

Literature is scant about studies dealing with the prognostic role of PhA in HF (Table 2). Alves et al. [55] tried to evaluate the impact of PhA in the prognosis of ADHF. At 24-month follow-up, those who survived had higher PhA values than patients who died. Specifically, PhA was an independent predictor of death at multivariate regression analysis, thus demonstrating a 2.67-fold increase in all-cause mortality risk when it was lower than 4.8° [55]. Scicchitano et al. [17] identified the determinants of long-term mortality in patients with ADHF by considered congestion

Table 2 Prognostic role of Phase Angle in patients with heart failure

Study	N. of patients	Type of patients	Study design	BIA device	Follow-up	Results	ΔPhA
Langer et al. 2021 [52]	2601	Apparently healthy patients who underwent BIVA evaluation	Longitudinal population-based	RJL model 103 analyser (RJL Systems, Detroit) 50 kHz frequency and 400 microA current	24 years	*Women* PhA was lower in those who developed CVD than those who did not (6.3° vs. 6.0°, p < 0.001). HR: 1.33 (95% CI: 1.11–1.60) when PhA was at the 5th percentile *Men* PhA was not dissimilar in those who developed CVD than those who did not (7.1° vs. 7.0°, p = 0.246). HR: 1.22 (95% CI: 0.92–1.60) when PhA was at the 5th percentile	*Women* 0.3° *Men* 0.1°
Stellingwerf et al. 2022 [54]	1023	Consecutive patients, admitted to the ICU	Prospective observational	BIA 101 Anniversary Sport Edition analyzer, Akern Srl. Alternating current 400 mV and 50-kHz.	1 year	PhA significantly higher in survivors than in non-survivors [5.4° vs. 4.7°, p < 0.001. At multivariate analysis, low PhA was independent predictor of 1-year mortality (OR: 1.81; CI: 1.09e2.97; p = 0.02).	0.7°
Alves et al. 2016 [55]	71	ADHF patients with LVEF < 45%	Prospective observational	Biodynamics 450 tetrapolar system (Biodynamics Corp., Seattle, Washington, USA) 50 kHz frequency and 800 microA current	2 years	PhA non-survivors: 5.08° ± 1.9° vs. PhA surivivors: 6.3° ± 2.2°, p = 0.038 PhA < 4.8° HR: 2.67, 95% CI: 1.21–5.89, p = 0.015	1.22°
Scicchitano et al. 2022 [17]	252	ADHF patients	Retrospective	CardioEFG, Akern RJL Systems, Florence, Italy Tetrapolar impedance plethysmograph, 50 kHz alternating sinusoidal current	Median 447 days	At multivariate Cox regression analysis: PhA HR 0.72 (95% CI 0.57–0.91), p = 0.008 PhA ≤ 4.9° sensitivity = 75%, specificity = 44%, PPV = 40%, NPV = 84%, p < 0.0001 as 1-year mortality predictor	N/A
De Berardinis et al. 2014 [56]	205	ADHF patients admitted to the Emergency Department	Prospective observational	CardioEFG, Akern RJL Systems, Florence, Italy Tetrapolar impedance plethysmograph, 50 kHz alternating sinusoidal current	18 months	*Endpoint death + HF rehospitalization* PhA with endpoint: 4.3 ± 1.7° vs. PhA without endpoint: 4.7 ± 1.5°, p = 0.17 *Endpoint death* PhA with endpoint: 4.24 ± 2.09° vs. PhA without endpoint: 4.62 ± 1.48°, p = 0.79 **ROC curve analysis** Endpoint *HF rehospitalization*: 30 days: AUC 0.52, p = ns; ***60 days: AUC 0.54, p = 0.04***; 90 days: AUC 0.57, p = ns; 180 days: AUC 0.52, p = ns; 12 months: AUC 0.53, p = ns; 18 months: AUC: 0.52, p = ns. Endpoint *death*: ***30 days: AUC 0.64, p = 0.01; 60 days: AUC 0.68, p = 0.003; 90 days: AUC 0.58, p = 0.04; 180 days: AUC 0.79, p = 0.0001; 12 months: AUC 0.79, p = 0.0001; 18 months: AUC: 0.86, p = 0.0001.***	*Death + HF rehospitalization* 0.4 *Death* 0.38

Table 2 (continued)

Study	N. of patients	Type of patients	Study design	BIA device	Follow-up	Results	ΔPhA
Colín-Ramírez et al. 2012 [57]	389	CHF patients	Retrospective	RJL Systems analyzer (Quantum X, Clinton Township, MI, USA). Alternating electric currents of 800 mA at 50 kHz	3 years	PhA < 4.2°: RR 3.08 (95% CI 1.06–8.99)	N/A
de Borba et al. 2022 in press [58]	2164	Patients who underwent PhA evaluation	Systematic review and meta-analysis	N/A	N/A	Pts with CVD had significantly smaller PhA values as compared to controls, independently from gender. In women, PhA values were significantly different in the context of heart failure (P < 0.01).	N/A
Garlini et al. 2019 [59]	42 studies	Patients who underwent PhA evaluation	Systematic review	N/A	N/A	PhA predicted mortality risk in patients with kidney diseases and cancer. No definitive data are in HF patients.	N/A
Garlini et al. 2020 [60]	43	Patients with CIED	Prospective observational	Biodynamics 450 tetrapolar system (Biodynamics Corp., Seattle, Washington, USA). 50 kHz frequency and 800 microA current	N/A	PhA values before CIEDs implantation: 6.3° (5.6° – 7.0°) vs. PhA Values after CIEDs implantation: 5.9° (5.5° – 6.9°). p = 0.067	0.4°
González-Islas et al. 2020 [51]	288	Stable HF patients	Prospective	Tetrapolar and multi-frequency equipment (Body Stat Quad Scan 4000). 50 kHz alternating sinusoidal current	N/A	*Cardiac cachexia prediction*: Phase angle < 5°: univariate analysis: HR: 3.43, 95% CI 2.08–5.65, p < 0.001, multivariate analysis: HR: 2.11, 95% CI 1.05–4.25, p = 0.036	N/A

Abbreviations: ADHF: acute decompensated heart failure; **AUC**: area under the curve; **BIA**: bioimpedance analysis; **BIVA**: bioimpendance vector analysis; **CI**: confidential interval; **CIED**: cardiac implantable electronic device; **CVD**: cardiovascular diseases; **H.F.**: heart failure; **HR**: hazard ratio; **LVEF**: left ventricle ejection fraction; **N/A**: not applicable; **NPV**: negative predictive value; **OR**: odds ratio; **PhA**: phase angle; **PPV**: positive predictive value; **ROC**: receiver operating curve; **RR**: relative risk

parameters and arterial blood gas components. The receiver operating characteristic (ROC) curves analyses revealed that PhA ≤ 4.9° showed sensitivity 75%, specificity 44%, positive predictive value 40%, and negative predictive value 84% for all-cause mortality. More specifically, the combination of PhA, brain natriuretic peptide (BNP), blood urea nitrogen (BUN)/creatinine ratio, and partial pressure of arterial oxygen (PaO_2) explained 60% of the overall deaths within the study population [17].

Such results also pointed out the need for including BIVA in daily clinical practice since admission at the emergency department (ED) for a comprehensive stratification of the overall risk of the patients. De Berardinis et al. [56] effectively considered 202 patients who were admitted at the ED with signs and symptoms of ADHF. Hydration status was assessed via vector or BIVA-derived hydration percentage in order to better classify patients in relation to their volemic status. The hydrogram was created for each patient. PhA and hydration index (HI) were both assessed and computed in the final analysis. PhA was *per se* independent predictor for mortality at 18-month follow-up (area-under-the-curve [AUC] 0.86, p = 0.0001); indeed, PhA maintained its predictive value for the risk of re-hospitalization for HF at 60-day follow-up, while losing it at longer follow-ups [56]. The combination of PhA evaluation with galectin-3 (Gal-3) measurements dramatically ameliorated the prediction of all-cause death and/or hospitalization for HF till 18-month follow-up [56]. Nevertheless, authors did not provide data on body cell composition, thus considering PhA as a prognostic determinant of fluid overload rather than general indicator for nutritional status.

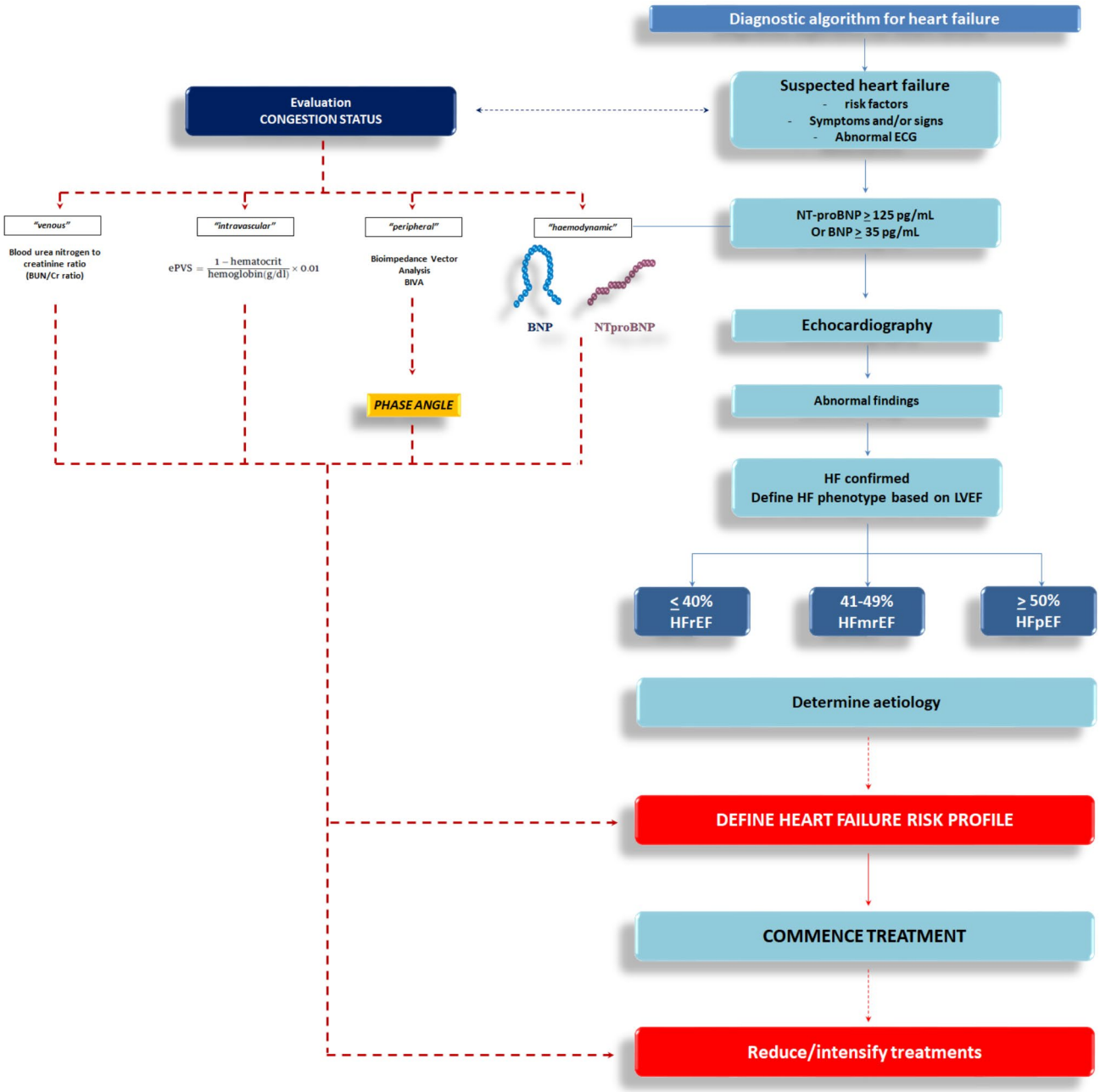

Fig. 2 Attempt for deriving a flow-chart to promote a comprehensive evaluation of patients with HF by including congestion biomarkers
Abbreviations: BIVA: bioimpedance vector analysis; **BNP**: brain natriuretic peptide; **BUN**: blood urea nitrogen; **Cr**: creatinine; **ECG**: electrocardiogram; **ePVS**: estimated plasma volume status (Strauss-Duarte formula); **HF**: heart failure; **HFmrEF**: heart failure with mildly reduced ejection fraction; **HFpEF**: heart failure with preserved ejection fraction; **HFrEF**: heart failure with reduced ejection fraction; **LVEF**: left ventricle ejection fraction; **NT-proBNP**: N-terminal pro-B-type natriuretic peptide.

Colín-Ramírez et al. [57] evaluated patients suffering with CHF by means of BIVA. PhA measurements were derived and computed for evaluating its prognostic impact on all-cause mortality after 3-year follow-up. PhA < 4.2° identified patients at risk for mortality with a relative risk equal to 3.08 at multivariate regression analysis. A recent meta-analysis from de Borba et al. [58] outlined that PhA was able to predict the occurrence of HF as its values were significantly different between those with and without such disease. Furthermore, the authors revealed that PhA predicted CVD in both male and female patients [58]. PhA might be effectively considered as a risk biomarker for mortality. Garlini et al. [59] performed a comprehensive systematic analysis on the impact of PhA on major outcomes.

PhA impacted on the mortality risk of patients with kidney diseases and cancer, while no definite indications could be suggested in HF patients due to paucity and heterogeneity of data [59].

Indeed, the adoption of BIVA is safe in patients with cardiac implantable electronic devices. Patients with HF often are implanted with devices for rhythm and arrhythmias control. Such devices demonstrated to be unaffected by the electric waves of BIVA as well as PhA which continued to act as a reproducible biomarker in CHF patients and showed no significant variations in values before and after implantation [60].

Finally, PhA might be used for predicting muscle waist and sarcopenia in patients with HF. Although the comprehensive evaluation of body cell composition via PhA could be considered challenging without integrative information derived by the hydrograph, PhA per se might be included in dedicated prognostic models and scores. A recent prospective cohort study from González-Islas et al. [51] evaluated 288 HF patients who underwent BIVA evaluation and were followed-up for 24 months. The R-Xc graphs were computed in order to classify the hydration status of patients and to evaluate their cachectic status. Authors identified a 2.11-fold increase in risk of cachexia in patients with HF and lower PhA values, independently from the cardiac dysfunctional chamber – right or left – or further confounding factors. Nevertheless, the results of González-Islas et al. [51] should be cautiously considered: (1) Body cell composition better derives from the analysis of the hydrograph as a whole; (2) PhA better represents the fluid overload rather than body cell composition, thus providing objectively limited indications in the assessment of HF cachexia; (3) Dedicated studies able to provide indications about the role of PhA in agreement with vector length would be advantageous for the sake of clarity in the context of HF cachexia.

5 Indications and future perspectives

The prevalence and the incidence of HF are still increasing [61]. Despite innovations in therapies, CV mortality, HF hospitalization, and all-cause death rates in patients with HF show percentages higher than 9% [62–64]. The need for a comprehensive evaluation and risk stratification of patients with HF is fundamental in order to understand the correct management, up-titration and maximization of therapies, and identification of subtle alterations which might predict early occurrence of adverse events.

Several risk scores have been validated in the setting of HF for accurate risk of adverse events prediction [65–67]. The Seattle Heart Failure Model (SHFM) – one of the first validated score for the evaluation of the prognosis of patients with HF – included 20 items which are related to clinical data, main laboratory examinations, and drug treatments (except angiotensin receptor–neprilysin inhibitors [ARNIs]) [65–67]. Indeed, SHFM is not set for unstable patients and/or those who undergo clinical decompensation. Furthermore, no applicability is for the clinical management of HF patients and no congestion biomarkers have been included. Similar considerations are for the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC-HF) score [65–67]. Although MAGGIC-HF score includes clinical, instrumental, and biochemical variables, there is no inclusion of mineralocorticoid receptor antagonists (MRAs) or ARNIs or even biomarkers; no mention is for congestion assessment of HF patient. Although The PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure (PREDICT-HF) score and the Barcelona Bio-Heart Failure (BCN-Bio-HF) risk calculator do include ARNIs and some biomarkers (N-terminal pro.

B-type natriuretic peptide [NT-proBNP], high-sensitivity troponin T, and interleukin-1 receptor-like-1 for the BCN-Bio-HF risk score), there is not any referral to congestion assessment of HF patients [65–67].

Therefore, it is plausible that limitations like those previously outlined may account for the reduced performances of these risk scores as they provide over- or under-estimation of the overall mortality risk in HF patients [65–67]. Good reproducibility (i.e. AUC > 0.7, [65]), sometimes even higher (i.e. AUC > 0.80, [66]) might effectively derive from the use of each score, but it should be implement in order to better clinically evaluate HF.

Furthermore, the greatest limitation of risk scores in HF is related on the use of variables which are generic and unfocused on the main pathogenetic mechanisms of HF. The inclusion of circulating biomarkers might be able to improve risk stratification protocols when added on top of the best HF risk models, although little data are on the clinical management of HF patients [68].

Hydration status as assessed by BIVA demonstrated higher specificity and positive predictive value (PPV) in detecting peripheral oedema in ADHF and CHF [6]. BIVA also predicts length-of-stay and all-cause death in HF patients [3, 5]. These data outlined the need for including the evaluation of congestion in patients with HF for the overall risk stratification and therapeutic management of these patients [2]. Specifically, Scicchitano P et al. [17] recently observed that PhA – i.e. a biomarker derived from BIVA – modestly (AUC 0.68) identifies ADHF patients who are at risk for death. No data are in literature about patients with CHF.

Nevertheless, the potential role of PhA as able to predict peripheral oedema and, contextually, adverse events might be used in addiction to further parameters and biomarkers

for a reliable stratification of the risk of HF patients. Scicchitano P et al. [17] just reported the improvement in the overall risk stratification when PhA was added to other factors – namely BNP, BUN/creatinine ratio, and PaO_2. Specifically, higher values in BNP and BUN/creatinine ratio and lower values in PaO_2 increased the risk for death of 2%, 1%, and 2%, respectively, while reduced PhA values promoted a 28% increase in the risk of all-cause mortality in HF patients.

The derived suggestions were: (1) to include BIVA in the evaluation of patients with both ADHF and CHF; (2) to validate the daily clinical application of BIVA in HF setting; (3) to adopt PhA as a putative biomarker in those patients; and (4) to implement PhA in well-established risk scores for a better evaluation of the clinical profile of patients with HF.

Therefore, the first attempt should be directed to the identification of a possible reference value for PhA for the correct identification of patients with HF who are at risk for developing MACE. Nevertheless, as bioimpedance analysis per se did not measure PhA or R and Xc, the need for implementing vectorial analysis instead of BIA in clinical setting is fundamental for the sake of reproducibility and identification of cut-off values for PhA. Secondly, physicians should provide more data on the reproducibility of the PhA in the risk stratification of patients with CHF.

Researches should be based on large population studies and should aim at evaluating the impact of BIVA variables – and PhA in particular – on the daily clinical management and prognostic stratification of HF patients.

International guidelines on the management of HF consider at first the use of overt clinical signs and symptoms for suspecting the presence of HF, then echocardiography (Class of recommendation I, Level of evidence C) and laboratory assessment of natriuretic peptide (Class of recommendation I, Level of evidence B) for final diagnosis [1]. A position paper from Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) proposed the standard-of-care for the constitution of a cardiology network for outpatient HF care and define the structure and organization of outpatient clinics [69]. No mention is for bioimpedance analysis as there is paucity of data in literature.

We do believe that a multiparametric approach which includes PhA evaluation and biochemical/clinical biomarkers of HF might be considered and validated in the next future. As bioimpendance analysis is a fast and reliable tool to be applied in daily clinical practice and in the outpatient setting, it can be associated during the ward hospital stay or at each follow-up in outpatient visits. Figure 2 tried to describe a flow chart which includes PhA and congestion evaluation in the clinical management of patients with HF. Nevertheless, further researches are needed in order to finally approve these indications in the general management of patients with HF.

6 Conclusion

The application of PhA in clinical evaluation of patients with AHF and CHF might be a good option for the clinicians. Nevertheless, there is paucity of data in literature in the context of HF. Indeed, PhA *per se* cannot be considered as a comprehensive biomarker in HF: the inclusion of PhA into a validated multiparametric model for clinical and prognostic evaluation of HF should be preferred.

Further studies are necessary for the possible, definite adoption of BIVA – and PhA in particular – in the flow-chart evaluation of patients with HF.

Declarations

Competing Interests and Funding None declared.

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