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Accuracy of bioimpedance vector analysis and brain natriuretic peptide in detection of peripheral edema in acute and chronic heart failure

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ABSTRACT

Objective: To evaluate the role of bioelectrical impedance vector analysis (BIVA) and brain natriuretic peptide (BNP) in detecting peripheral congestion in heart failure (HF).
Background: BIVA/BNP are biomarkers for congestion in acute (ADHF) and chronic HF.
Methods: 487 ADHF and 413 chronic HF patients underwent BIVA and BNP tests.
Results: BIVA was more accurate than BNP in detecting peripheral congestion both in ADHF (AUC 0.88 vs 0.57 respectively; $p < 0.001$) and chronic HF patients (AUC 0.89 vs 0.68, respectively; $p < 0.001$). In ADHF patients, the optimal BNP cut-off for discriminating presence or absence of edema was >870 pg/mL (PPV = 48% and NPV = 58%) whereas in chronic HF it was >216 pg/mL (PPV = 18% and NPV = 95%). The BIVA detected edema when the vector fell into the lower pole of 75th percentile tolerance ellipse (PPV = 84% and NPV = 78%) in ADHF, the lower pole of 50% (PPV = 68% and NPV = 95%) in chronic HF.
Conclusions: In HF patients, BIVA is an easy, fast technique to assess peripheral congestion, and is even more accurate than BNP.

Introduction

Clinical congestion plays a key role in the diagnosis, prognosis and guide of therapies in patients affected by heart failure (HF).[1] Most patients with acute decompensated HF (ADHF) present with fluid overload. In chronic HF, i.e. when a stable chronic condition has been reached, the congestion can persist, leading to rehospitalization and death.[2–4]

Of the signs and symptoms associated with fluid accumulation, lower limb edema is the most accurate clinical parameter for a reproducible assessment of peripheral congestion as it occurs in about 60% of patients with ADHF and in 20% with chronic HF.[3–7]

Hemodynamic congestion also increases brain natriuretic peptide (BNP) serum levels[8–10] which can decrease when excess fluid is removed.[11,12] BNP is considered a biomarker of congestion and is

Abbreviations: ADHF, acute decompensated heart failure; AUC, area under the curve; BIA, bioelectrical impedance analysis; BIVA, bioelectrical vector analysis; BNP, brain natriuretic peptide; CHF, chronic heart failure; eCrCl, creatinine clearance; H, height; HF, heart failure; IQR, interquartile range; LR, likelihood ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NPV, negative predictive value; PPV, positive predictive value; R, resistance; SD, standard deviation; Xc, reactance.

The authors accept responsibility for all aspects of data reliability and freedom from bias and their discussed interpretation.

Conflict of interest: None declared.

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included in a combination of available measurements of clinical congestion that quantify fluid overload.[13] However, in a recent study, BNP did not seem to correlate with the presence or extent of lower extremity edema in ADHF, suggesting that it is not an appropriate biomarker for peripheral congestion.[14]

Recently, whole-body bioelectrical impedance analysis (BIA) has been proposed as a new technique for fluid status detection in HF,[15] on the basis of the theory that fluid accumulation improves the conductivity of an electrical current passing through the body. It was demonstrated that BIA correlates with BNP and hemodynamic congestion,[16–19] and contributes to the diagnosis and prognosis[18,20–23] and decision-making process for tailoring ADHF therapies.[24–27]

In particular, bioelectrical impedance vector analysis (BIVA) provides a quick, immediate and easy semi-quantitative evaluation of fluid status without using specific equations and models required for conventional BIA. As already described by Piccoli et al in 1994,[28] the conductivity of an electrical current passing through the body is described by two fundamental parameters: resistance (R, in Ohm) and reactance (Xc, in Ohm). These parameters are normalized by the subject's height (H) and then plotted in a nomogram as a bivariate vector (see also Fig. 1A). The final bivariate vector is included into one of three probability tolerance ellipses which, respectively, represent the 50th, 75th and 95th percentile of a normal distribution of bivariate vectors resulting from the analysis of a healthy reference population, normalized for gender. The final evaluation of the bivariate vector can be read at two different levels, taking into account the displacement of the vector from the major axis: 1) the displacement above or below the major axis will indicate, respectively, the dehydration or hyperhydration of the patient 2) the displacement toward the left or right side of the longitudinal major axis will give information on an increased or decreased cell mass, respectively.[15]

Therefore, vectors projecting into the lower poles are associated with increased tissue fluid volume (i.e. BIVA wet); conversely, those projecting into the 50th percentile or the upper poles of the ellipses indicate normal or decreased tissue fluid volume, respectively (i.e. BIVA dry) (Fig. 1A). The lower pole of the 75th percentile tolerance ellipse is the threshold for clinical edema, as outlined in studies involving patients suffering from kidney failure.[27–29] More recently, in ADHF patients, pitting edema was detected when a single vector was close to the lower pole of the 95th percentile tolerance ellipse.[20]

Although the above mentioned evidence suggests that BIVA and BNP can be useful and promising biomarkers for congestion,[30] their clinical usefulness in detecting peripheral congestion in HF has not been fully explored. Therefore, the objective of this study was to assess and compare their accuracy in detecting peripheral congestion in a large population of ADHF and chronic HF patients.

Material and methods

This is a retrospective study. We reviewed the clinical data of patients who had been admitted to the Cardiology Unit of Altamura Hospital – Bari (Italy) due to ADHF[1] and/or to the heart failure outpatients unit during chronic HF[1] routine follow-up between January 2009 and November 2013. Nine hundred patients were consecutively enrolled: 487 had been admitted for ADFH and 413 for chronic HF.

All medical records were reviewed by two of the authors (FM and MI). At the time of admission, the baseline characteristics, underlying disease, comorbidities, physical examination, functional clinical status evaluated by means of the New York Heart Association (NYHA) classification, blood chemistry data, left ventricular ejection fraction (LVEF), BIVA and drugs administered at hospital admission were considered. Preserved left ventricular ejection fraction was defined as LVEF >45%, evaluated by Simpon's biplane method.[31] The Cockroft-Gault equation was used to estimate creatinine clearance: eCrCl (mL/min) = [(140 – age) × (weight)]/(72 x serum creatinine) x 0.85 (if female).[32] All of these measurements were performed as a routine evaluation of the patients admitted to our department both in ward and ambulatory settings.

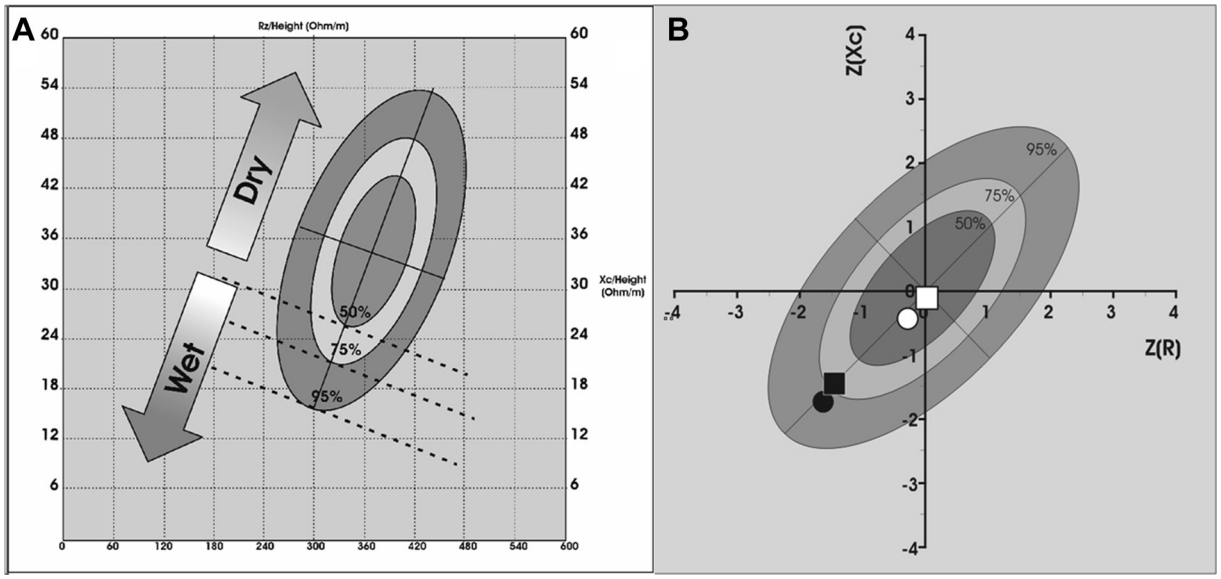

Fig. 1. A) The RXc graph shows three tolerance ellipses, plotting resistance (R) and reactance (Xc) standardized by height (H), and include 50th, 75th and 95th percentiles of healthy individual points, respectively. Vector displacements parallel to the major axis of tolerance ellipses indicate different soft tissue hydration. Vectors that project into lower poles are associated with increased hydration (BIVA wet), and conversely vectors that terminate in the upper and the lower pole of 50% of tolerance ellipse indicate normal or decreased hydration (BIVA dry). B) Mean impedance vectors with their SD plotted on the 3 tolerance ellipses (50th, 75th, 95th percentiles): ●) mean vector of ADHF patients with pitting edema; ○) mean vector of ADHF patients without pitting edema; ■) mean vector of CHF patients with pitting edema; and □) mean vector of CHF patients without pitting edema.

The inclusion criteria were: a diagnosis of ADHF or CHF; age >18 years. Patients were excluded if they were under 18 years, on chronic hemodialysis or if they had edema secondary to vein disorders or limphedema.

The study was approved by the local Institutional Review Board and was in agreement with the Helsinki declaration.

Peripheral congestion assessment

Peripheral congestion assessment was performed by digital manipulation, as a clinical method for edema detection, by applying thumb pressure on different anatomical locations of the patient's leg (ankles, below and above the knees, perimalleolar zones). In particular, pitting edema was assessed by the physician who pressed and held their finger into the swollen tissue over a bony area for 5 s. Edema was confirmed if the indentation in the tissue remained after thumb removal.

BIVA

BIVA was assessed on the right body side as previously reported.[33] The measurements were obtained in a semiorthopneic or a supine position using a tetrapolar impedance plethysmograph that emitted 50 kHz alternating sinusoidal current (CardioEFG, Akern RJL Systems, Florence, Italy). This was calibrated each morning using a standard resistor supplied by the manufacturer (R = 380 Ω, Xc = 47 Ω, 1% error). One measurement electrode was positioned on the dorsal surface of the wrist and the second on the anterior surface of the ipsilateral ankle; one drive electrode was positioned on the dorsal surface of the hand and the other on the dorsal surface of the foot. The alternating current was applied using distal electrodes on the hand and foot, and the drop in voltage was detected by the proximal electrodes. The analysis of the alternating current through the body provided the measurements of resistance (R, in Ohm) and reactance (Xc, in Ohm), terms deriving from the physics of electricity. These values were divided by the subject's height. Both parameters were plotted on a dedicated graph and identified a final vector from the interaction between the two values (see Fig. 1A). The vector obtained fell into "ellipses": these are areas in which the values of BIVA from a healthy, general population are distributed, thus representing the normal distribution of vectors in a normal healthy population. Therefore, three kinds of ellipses can be considered: the 50th, 75th and 95th percentile of the vector distributions in a normal population. The final vector obtained from the patient analysis will fall into one percentile area, according to which the individual can be considered differently.

More specifically, when the individual vector fell into the lower pole of the 50th percentile vector tolerance, of the sex-specific reference intervals for the healthy Italian population, the subject was defined as "Wet." On the contrary, when the patient fell into the 50th percentile vector tolerance, or the upper pole of the ellipse, the subject was considered "Dry."[15] In order to define sets of tolerance ellipses (50th, 75th and 95th) independently of gender, the values of R/H and Xc/H were transformed into bivariate *Z*-scores using the mean and the SD of the sex-specific reference healthy population: $Z(R) = (R/H - 371.9)/49$, if female and $(R/H - 298.6)/43.2$, if male and $Z(Xc) = (Xc/H - 30.8)/7.7$, if female and $(Xc/H - 30.8)/7.2$, if male (20). In addition, we considered phase angle (degrees) [i.e. $\arctan(R/Xc) \times (180/\pi)$] and used dedicated software (Bodygram 1.4, Akern RJL Systems, Florence, Italy) in order to estimate body hydration as well as the percentage of fat free mass (Hydration Index; HI).[18,21]

BNP

BNP was measured using microparticle enzyme immunoassay (Architect, Abbott Park, IL, USA). The assay range was from 10 to 5000 pg/mL. The intra- and interassay variability coefficient ranged from 0.9% to 5.6% and 1.7% to 6.7%, respectively.

Statistical analysis

Categorical variables are expressed as counts (percentages), and continuous variables are expressed as values ± standard deviation (SD). The unpaired Student *t* test, χ^2 test, and one-way ANOVA were used as appropriate.

As the distribution of BNP levels was positively skewed, the values were expressed as median (interquartile range [IQR]). BNP log transformed was used for all the analyses unless otherwise specified. The areas under the receiver-operating characteristic (ROC) curves were used to evaluate the diagnostic performance of BIVA and BNP as well as corresponding specificity, sensitivity, accuracy and positive and negative predictive value (PPV and NPV, respectively). The optimal cut-off was obtained from the greatest sum of sensitivity and specificity. We also estimated the positive and negative likelihood ratio (LR+ and LR−) to provide additional diagnostics.

The LR+ is an estimate of how much more likely a positive test result is among those with a condition, in relation to those without

Table 1
Study population according to ADHF or chronic HF diagnosis.

	ADHF ($n = 487$)	Chronic HF ($n = 413$)
Age, yrs	78 ± 10	74 ± 10
Male (%)	50	59
BMI, kg/m^2	28 ± 5	28 ± 5
Medical history, %		
Coronary artery disease	38	44
Diabetes	28	24
Atrial fibrillation	54	41
ICD	11	13
De novo	34	–
NYHA class I/II/III/IV, %	0/7/15/78	2/70/28/0
LVEF	41 ± 12	44 ± 12
Preserved LVEF, %	41	47
Laboratory values		
Hemoglobin, g/dL	12 ± 2	13 ± 2
Hemoglobin <12 g/dL, %	53	28
Albumin, g/dL	3.2 ± 0.5	3.4 ± 0.5
Sodium, mEq/L	139 ± 4	139 ± 8
Potassium, mEq/L	4.0 ± 0.6	4.1 ± 0.6
Urea nitrogen, mg/dL	76 ± 45	60 ± 38
Creatinine, mg/dL	1.5 ± 0.9	1.2 ± 0.8
Creatinine 1.5 > mg/dL, %	35	18
eCrCl, mL/min per 1.73 m^2	44 ± 25	59 ± 29
eCrCl, <60 mL/min per 1.73 m^2, %	78	57
eCrCl, <30 mL/min per 1.73 m^2, %	33	14
Troponin >0.15 ng/mL, %	30	17
Therapies, %		
Furosemide	97	86
Beta-blockers	57	71
ACE inhibitors	34	44
ARBs	17	20
Digitalis	20	17
Calcium sntagonists	0	2
IV inotropes	14	3
Ultrafiltration	6	0

ACE: angiotensin-converting enzyme; ADHF: acute decompensated heart failure; ARB: angiotensin receptor blocker; BMI: body mass index; eCrCl: estimated creatinine clearance; HF: heart failure; ICD: implanted cardioverter/defibrillator; IV: intravenous; LVEF: left ventricular ejection fraction.
Values are expressed as mean ± standard deviation or percentages. Medical histories or therapies are not mutually exclusive categories.

Table 2
Peripheral congestion, BNP and BIVA data in ADHF and chronic HF patients.

	ADHF	Chronic HF
Lower extremity edema, %	49	13
BNP, pg/mL (median [IQR])	1030 [617–2135]	300 [143–660]
BIVA, (mean ± SD)		
R/H, Ohm/m	289 ± 73	318 ± 65
Xc/H, Ohm/m	24 ± 8.1	30 ± 7.5
Angle phase, °	4.7 ± 1.2	5.5 ± 1.3
Z (R) ± SD	−0.99 ± 1.5	−0.24 ± 1.3
Z (Xc) ± SD	−1.2 ± 1.1	−0.29 ± 1.0
Hydration index (%)	78.5 ± 6.1	74.5 ± 3.4

ADHF: acute decompensated heart failure; BNP: brain natriuretic peptide; BIVA: bioelectrical impedance vector analysis; H: height; HF: heart failure; R: resistance; SD: standard deviation; Xc: reactance; Z: *Z* score; Z (R): resistance transformed into bivariate Z-scores; Z (Xc): reactance transformed into bivariate *Z*-scores.

(e.g., LR+ = 5 means that a positive test result is 5× more likely to be true positive than false positive); the LR− is an estimate of how much less likely a negative test result is among those with the condition relative to those without (e.g., LR− = 0.20 means that a negative test is 80% less likely to be false negative than true negative).[34] The statistical significance of area under the curve (AUC) differences between BIVA and BNP findings for each comparison was also computed by comparing AUC values and the SE using Wald tests. *p*-values below 0.05 were defined as statistically significant. The analyses were made using STATA software, version 12 (StataCorp, College Station, Tex).

Results

Table 1 shows the characteristics of the study population according to ADHF and chronic HF diagnosis.

As expected, compared to the chronic HF group, ADHF presents a higher prevalence of peripheral congestion, higher BNP values, and lower values of BIVA parameters, indicating higher hydration (Table 2).

In both subgroups of patients with edema, BNP values were significantly higher, BIVA parameters significantly lower and the Hydration Index higher (Table 3) compared to the values of patients with no sign of peripheral edema. The mean vector was displaced between the lower poles of the 95th and 75th percentile tolerance ellipse in the ADHF group with edema, and close to the lower pole of the 75th percentile tolerance ellipse in the chronic HF group with edema (Fig. 1B).

When grading fluid status from the highest to the lowest level of "BIVA wet" (<95th, between 95th and 75th, and between 75th and 50th percentile of the lower poles of tolerance ellipses) till "BIVA dry" condition, the percentage of patients with peripheral edema and the BNP values significantly increases with decreasing BIVA vectors (Fig. 2A and B).

The diagnostic performances of BIVA and BNP in detecting peripheral edema are reported in Table 4. In ADHF, the optimal cut-off point for peripheral edema detection in BNP was >870 pg/mL; neither the LR+ nor the LR− was consistent with any clinical utility for ruling peripheral edema in or out. In contrast, the optimal cut-off point of 216 pg/mL had limited clinical utility for ruling peripheral edema out (LR− = 0.3). BNP accuracy did not change when the analysis was performed in patients with preserved renal function (eCrCl > 30 mL/min): 0.58 ± 0.03 and 0.74 ± 0.02 AUC in ADHF and chronic HF patients, respectively.

In ADHF and chronic HF patients the optimal threshold for edema detection in BIVA was the lower pole of the 75th and 50th percentile of tolerance ellipses. Considering the lower pole of the 95th percentile of tolerance ellipse as a threshold, the PPV was 95% in the ADHF group and 100% in the chronic HF group. Conversely, the lower pole of the 50th percentile of tolerance ellipse had a NPV of 91% in the ADHF group and 98% in the chronic HF group.

The optimal cut-off for the Hydration Index for detection of apparent edema was 76.9% and 73.8%, for ADHF and chronic HF groups, respectively.

The curve (AUC) differences between BIVA and BNP findings for each group are significant (Fig. 3).

Discussion

Our study demonstrated the reliability of BIVA evaluation in detecting peripheral congestion in both ADHF and chronic HF patients compared to plasma concentrations of BNP and clinical identification of peripheral edema. The AUC revealed a good performance of this instrumental evaluation in both clinical settings.

To the best of our knowledge, this is the first study which evaluates the clinical utility of BIVA and BNP to detect peripheral congestion in a large population of HF patients. Genot et al[35] attempted to evaluate the predictive value of BIVA in heart failure, however, while the results reported optimal diagnostic performance of BIVA in ADHF, the study population was small,. Better results in chronic HF were obtained by Alves et al[36] and Weyer et al[37] although, once again, the small sample size of the population limited the significance of the final results.

The clinical characteristics of our unselected patients are similar to IN-HF Outcome registry and ESC-HF Pilot Survey patients.[2,6,7] The study was performed in a representative western country population.

Patients with ADHF present a variety of clinical manifestations. About 90% of patients show signs and symptoms of congestion.[2,4,7] Some may manifest only central congestion or only peripheral congestion while others may present with both central and

Table 3
BNP and BIVA parameters according peripheral congestion in ADHF and chronic HF.

	ADHF		Chronic HF	
	With edema (n = 237)	Without edema (n = 250)	With edema (n = 54)	Without edema (n = 359)
BNP, pg/mL (median [IQR])	1167 [683–2563]	918 [569–1886][a]	561 [243–1333]	278 [129–583][a]
BIVA, (mean ± SD)				
R/H, Ohm/m	256 ± 64	319 ± 67[a]	270 ± 54	325 ± 64[a]
Xc/H, Ohm/m	19 ± 5.7	29 ± 7.1[a]	21 ± 6.1	31 ± 6.6[a]
Angle phase, °	4.2 ± 1.0	5.1 ± 1.2[a]	4.5 ± 1.0	5.6 ± 1.2[a]
Z (R), SD	−1.7 ± 1.3	−0.27 ± 1.4[a]	−1.5 ± 1.1	−0.04 ± 1.2[a]
Z (Xc), SD	−1.9 ± 0.7	−0.52 ± 1.0[a]	−1.6 ± 0.8	−0.10 ± 0.9[a]
Hydration index (%)	82.3 ± 6.2	74.8 ± 3.2[a]	79.3 ± 5.7	73.7 ± 1.9[a]

ADHF: acute decompensated heart failure; BNP: brain natriuretic peptide; BIVA: bioelectrical impedance vector analysis; H: height; HF: heart failure; R: resistance; SD: standard deviation; Xc: reactance; Z: *Z* score; Z (R): resistance transformed into bivariate *Z*-scores; Z (Xc): reactance transformed into bivariate Z-scores.
[a] $p < 0.01$ with vs without edema.

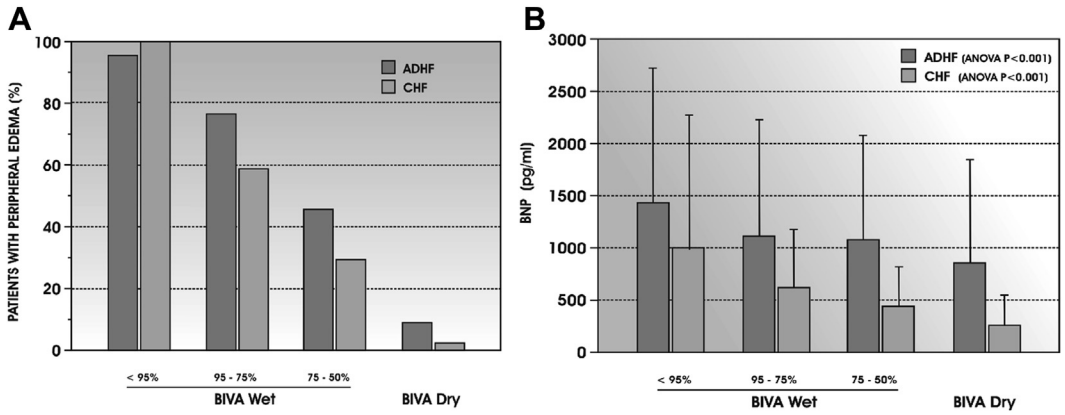

Fig. 2. A) Comparison between number of ADHF patients with peripheral edema and BIVA evaluation (p-anova < 0.001) and between chronic heart failure patients with peripheral edema and BIVA evaluation (p-anova < 0.001). B) Comparison between BNP values (expressed as median and interquartile range) in ADHF patients and BIVA evaluation (p-anova < 0.001) and between BNP values in chronic heart failure patients and BIVA evaluation (p-anova < 0.001).

peripheral congestion. Lower extremity edema is the only clinical sign of peripheral congestion that is detectable when the interstitial fluid volume rises to almost 30% above the normal (4–5 kg of body weight) range.[38] Therefore, this clinical sign is related to gross fluid retention that should be promptly removed using diuretics or mechanical tools.[39] Lower extremity edema is a common sign in ADHF patients who arrive at the emergency department (35–77%).[40] Nevertheless, about 23% of patients did not show any inferior limb edema at hospital admission and sometimes the reason for this is associated with significant care-seeking delays.[40] Our study population showed an edema occurrence in near half of ADHF patients which is a prevalence similar to the IN-HF Outcome registry but lower than the ESC-HF Pilot survey (56% and 65%, respectively).[4,7] At the time of discharge, the persistence of congestion affected 8.2–24% of patients[4,7] and increased the mortality and rehospitalization rate during 1-year follow-up.[4] In the EVEREST trial, this risk seems higher in patient with peripheral than in those with central congestion (1.98 and 1.38 hazard ratio, respectively).[41]

On the other hand, peripheral congestion affected a minority of patients with chronic HF and occurred in 13% of our population. This percentage was not evaluated in a recent Italian registry (IN-HF), while the CIBIS II trial reported a prevalence of 20%.[3] Despite the small percentages outlined in these studies, peripheral congestion in chronic HF and in ADHF patients, alone or in combination with other signs and symptoms of central congestion, seems independently associated with all cause deaths, hospitalization and deaths due to heart failure.[3] Therefore, peripheral fluid accumulation should be carefully assessed as its redistribution can induce pulmonary congestion and subsequent HF exacerbation without previous weight changes.[42]

These considerations emphasize the need for careful examination of HF patients in order to assess the presence of subclinical central and/or peripheral congestion using new and simple biomarkers to provide fast, quantitative and qualitative fluid estimation.

Bioelectrical impedance analysis is a non-invasive, fast, portable, reproducible,[33] safe[43] and low-cost technique that can be used at patients' bedside, independently of their collaboration. As body impedance is 90% generated by the soft tissues of limbs, and only 10% by the trunk, it is considered a reliable biomarker of peripheral congestion. The lower pole of the 50th percentile tolerance ellipse (i.e. BIVA vector below the − 1 SD of ZXc) is considered the threshold for the detection of fluid accumulation before manifestation of edema occurs (i.e. BIVA wet)[28] and is also adopted in emergency departments to discriminate between cardiac and non cardiac dyspnea (sensitivity: 69%; specificity: 79%).[20] Piccoli et al[29] observed 88% sensitivity and 87% specificity for edema detection in patients suffering from renal failure and showing vectors falling within the lower pole of the 75th percentile tolerance ellipse, also demonstrating higher reproducibility indexes in AHDF patients when the mean vector was close to the lower pole of the 95th percentile tolerance ellipse.[20] Di Somma et al[21] recently observed a mean vector displaced between the 75th and 95th percentile tolerance ellipses as being able to better evaluate the peripheral congestion of ADHF patients.

Our results were in line with the findings of Di Somma et al, demonstrating that the lower poles of the 75th and 95th

Table 4
Diagnostic accuracy on BNP and BIVA in detection of peripheral edema.

	Assay	AUC mean ± SE (95% C.I.)	p Value	Cut-off	Sensitivity %	Specificity %	PPV %	NPV %	LR+	LR−
ADHF	BNP	0.57 ± 0.02 (0.52–0.61)	0.007	>870 pg/mL	63	49	48	58	1.2	0.8
	BIVA	0.88 ± 0.01 (0.84–0.90)	0.0001	<95%	34	98	95	61	21.0	0.7
				<75%	75	86	84	78	5.5	0.3
				<50%	93	66	72	91	2.8	0.1
	Hydration index	0.87 ± 0.02 (0.83–0.90)	0.0001	76.9%	79	82	80	80	4.3	0.3
Chronic	BNP	0.68 ± 0.04 (0.63–0.72)	0.0001	>216 pg/mL	85	41	18	95	1.4	0.3
	BIVA	0.89 ± 0.02 (0.86–0.92)	0.0001	<95%	20	100	100	89	n.a.	0.8
				<75%	63	95	68	94	14.0	0.4
				<50%	85	87	50	98	6.7	0.2
	Hydration index	0.88 ± 0.02 (0.84–0.91)	0.0001	73.8%	85	80	40	97	4.3	0.2

ADHF: acute decompensated heart failure; AUC: area under curve; BNP: brain natriuretic peptide; BIVA: bioelectrical impedance vector analysis; HF: heart failure; LR+: likelihood ratio positive; LR−: likelihood ratio negative; n.a.: not available; NPV: negative predictive value; PPV: positive predictive value.

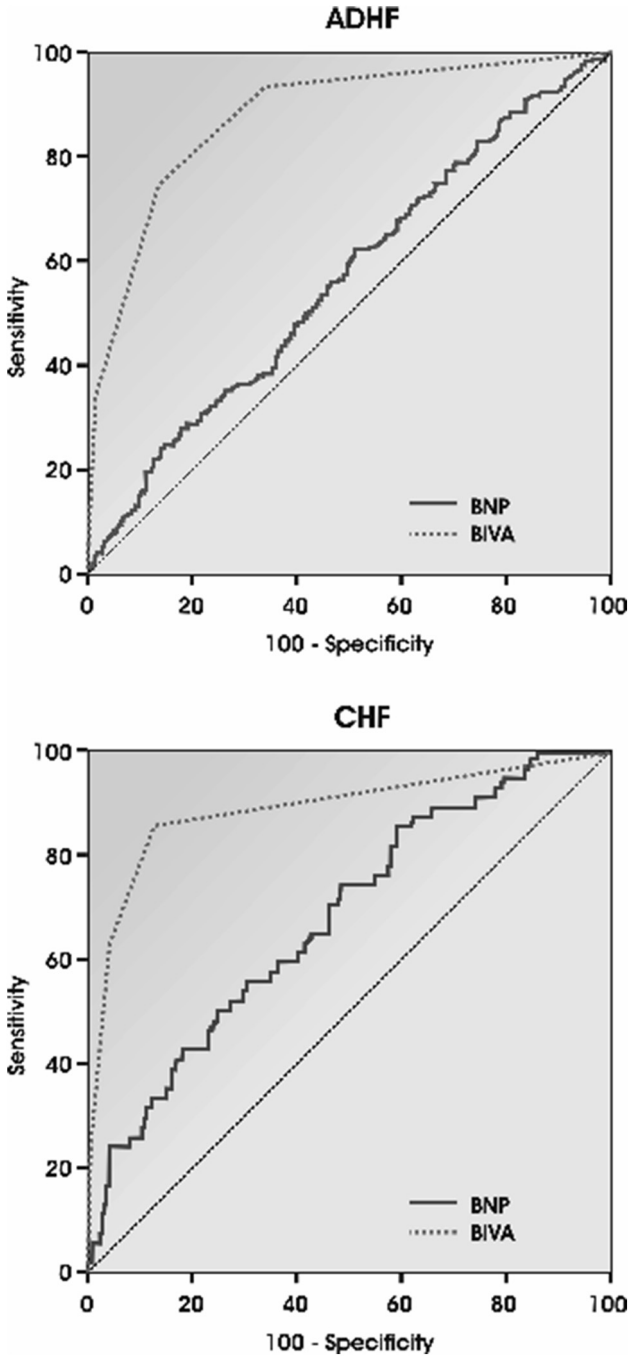

Fig. 3. Receiver operating characteristic curves for detection of pitting edema in ADHF and CHF for BIVA (dotted line) and BNP (continuous line).

percentiles of tolerance ellipse can identify peripheral congestion in ADHF patients (Fig. 1B). When considering chronic HF patients, our BIVA measurements displayed a mean vector close to the lower edge of the 75th percentile tolerance ellipse (Fig. 1B). Therefore, the optimal cut-offs for the detection of pitting edema were slightly different for ADHF and chronic HF patients (the lower pole of the 75th and 50th percentiles, respectively). This small difference between the two groups can be explained by the different degree of peripheral fluid retention. In fact, peripheral edema was associated with higher Hydration Index in ADHF compared to chronic HF patients (82.3% vs 79.3%, $p < 0.01$). BIVA could easily and correctly detect peripheral edema as demonstrated by its high PPV and positive/negative likelihood ratio which was positive when the individual vector fell within the lower level of the 95th percentile tolerance ellipse in both groups. Furthermore, the presence of edema was excluded by BIVA when values did not fall under the lower pole of the 50th percentile tolerance ellipse, as demonstrated by the high NPV and low likelihood ratio negative.

In addition to semiquantative evaluation, BIVA can provide a quantitative assessment of fluid status by means of the Hydration Index. At the time of admission to the emergency department, patients suffering from ADHF showed a mean Hydration Index of 81%.[21] Our data showed a lower value for mean Hydration Index (78.5%) which could address the hospitalization of the patient to cardiology department after emergency department admission.

Another important finding of the present study is the relationship between peripheral fluid overload and a smaller angle phase. This impedance parameter seems to be an independent prognostic marker in several clinical conditions[44] and an independent predictor for mortality in chronic HF patients.[22] Its biological meaning is not well understood. In HF patients, we found that peripheral fluid accumulation significantly decreased the angle phase at 4.2° and 4.5°, for ADHF and chronic HF, respectively. Although a decrease in the angle phase can also be found in cases of malnutrition[44,45] and in chronic HF patients suffering from cachexia,[23] its evaluation can increase the prognostic value of BIVA in HF patients: the greater the decrease, the higher the risk of worsening cardiac failure.[46]

An important insight deriving from this research would be the evaluation of the number of patients suffering from right- or left-side HF. Unfortunately, we did not provide any differentiation in terms of right- or left-side HF when enrolling our patients. Although this can be considered as a limitation of this study, the aim of our research was only to provide a full evaluation of BIVA in assessing HF patients. Furthermore, prospective evaluations could be considered in order to implement such research.

Hemodynamic congestion in HF induces an increase in plasma BNP values. This mechanism could explain an indirect association between BNP and peripheral edema, although Breidthardt et al[14] failed to demonstrate a significant association between BNP values and presence and severity of lower limb edema in ADHF patients. Our study showed significant higher BNP values in both ADHF and chronic HF patients with pitting edema. These results, in line with the literature,[16,18,19] demonstrated the relationship between hemodynamic cardiac failure and peripheral fluid overload. Piccoli et al demonstrated that NT-proBNP was twice as high in ADHF patients with BIVA wet than in those with BIVA dry when evaluated in a subgroup of patients without lung congestion.[20] However, when considering the subgroup with lung congestion NT-proBNP values were at the highest limit of the normal range regardless of BIVA measurements.[20] Therefore, BNP seems mainly to reflect central rather than peripheral congestion.

Although we found a significant correlation between BNP and peripheral edema, the BNP is not clinically useful for peripheral edema detection in ADHF. Probably several other factors can influence the BNP levels and peripheral edema detection. In fact, BNP value can be altered by obesity, renal insufficiency and/or myocardial stress unrelated to volume status and persisting in some HF patients despite the reduction in hemodynamic congestion after treatment (so called “BNP memory” effect).[8] Furthermore, it is also known that the complex pathophysiology of edema should include other important determinants such as intravascular and extravascular oncotic pressures and permeability of the blood vessels. We found that the performance of BNP is independent of renal function and limited to ruling out peripheral congestion in chronic HF patients when its value is within the “grey zone” and lower than 216 pg/mL.

Recently, BNP has been included in a score system that can quantify the degree of congestion, which is helpful in the initiation and follow-up of the response to therapies in ADHF.[13] In this setting, our results did not find a significant correlation between BNP and peripheral congestion thus suggesting that high levels of BNP alone could not be associated to relevant fluid overload.

Despite all of these considerations and beyond the comparisons between our data and literature results, our study showed important clinical practice implications. First of all, we observed optimal performances of BIVA evaluation in the clinical setting of ADHF and chronic HF patient evaluation. BIVA can provide reproducible and more reliable data in the evaluation of peripheral congestion compared to both BNP plasma levels and clinical evaluation of peripheral edema. The data of our study corroborate a possible objective and quantitative evaluation of peripheral congestion in HF failure.

These considerations revealed intrinsic insight for future development of HF patient evaluation. In relation to reliability, the cost-effectiveness, the mathematical background of BIVA measurements and future research can effectively be oriented toward more home monitoring of HF instability. Many HF patients are not able to recognize the worsening of peripheral congestion. The periodical, home- or out-patient monitoring of BIVA variations can be an early and non-invasive tool for recognizing signs of HF worsening in patients, thus providing therapies at an earlier stage. Clearly, BIVA will not substitute the clinical assessment of HF patients but it will certainly help the physician to provide a complete and more reproducible evaluation of patients.

Conclusions

Peripheral congestion is a fundamental clinical sign in ADHF patients presenting at the emergency department and/or those suffering from chronic HF. However, its exact quantification and its relation to central congestion is still a question of debate. Our study suggests that BIVA and its association to BNP can provide a useful insight in the detection of peripheral congestion in patients suffering from chronic HF or ADHF. In particular, BIVA allowed a more accurate estimation of peripheral congestion than BNP which does not seem to be useful in ADHF.

Therefore, BIVA could be a fundamental tool to associate with physical examination in order to better stratify HF patients or favor a more reliable home monitoring of patients by specialized care givers in order to detect the onset of peripheral congestion earlier.

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