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Serum biochemical determinants of peripheral congestion assessed by bioimpedance vector analysis in acute heart failure

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ABSTRACT

Background: The pathophysiology of peripheral congestion is poorly investigated in patients with acute heart failure (AHF).
Objectives: to evaluate the relative contribution of serum colloid osmotic pressure (COP), relative plasma volume status (PVS), biomarkers of renal function, electrolytes, haemoglobin, and brain natriuretic peptide (BNP) in peripheral fluid overload using bioimpedance vector analysis (BIVA).
Methods: We retrospectively analysed data from 485 patients with AHF. Hydration status was evaluated by semiquantitative and quantitative approach using BIVA (R/Xc graph) and Hydration Index (HI), respectively. COP was calculated from albumin and total protein concentration, while relative PVS was calculated from validated equations.
Results: Congestion assessed by BIVA was observed in 304 (63%) patients and classified as mild (30%), moderate (42%), and severe (28%). On univariate analysis, HI was inversely correlated with COP ($P < 0.01$), glomerular filtration rate ($P < 0.01$), and haemoglobin ($P < 0.01$), while positive correlations were found for relative PVS ($P < 0.05$), BNP ($P < 0.01$), and blood urea nitrogen (BUN; $P < 0.01$). On stepwise multivariate analysis, COP explained 12% of the total variability, while BUN, PVS, haemoglobin, and BNP added a further 6%, 4%, 2%, and 1%, respectively, to the final explanatory model.
Conclusions: COP was the major determinant of the presence and entity of peripheral congestion assessed by BIVA. BUN, PVS, haemoglobin, and BNP revealed reduced influence on congestion as compared with COP. Routine laboratory testing could be useful in peripheral fluid accumulation. Future studies should evaluate the relationship between COP and pharmacological target therapies for the fluid management of AHF patients.

Introduction

Acute heart failure (AHF) is characterized by neurohormonal activation, sodium and water retention, and final central and/or peripheral congestion.[1] Lower extremity edema is the overt expression of a gradually gross fluid retention that should be promptly removed.[2] The clinical evidence of peripheral oedema is the consequence of about a 30% increase in interstitial fluid volume (i.e., equal to about a 4–5 kg increase in body weight).[3] Nevertheless, this clinical sign occurs in half of AHF patients admitted to the emergency department (ED; "bloaters" patients) and is associated with the worst prognosis.[2,4–6] Others can show breathlessness in the absence of clear peripheral congestion ("vascular phenotype" or "puffers" patients).[2,4]

Multiple factors can influence interstitial fluid overload. According to Starling's law, low plasma colloidosmotic pressure (COP), mainly related to hypoalbuminemia and/or increase in intravascular hydrostatic pressure, induces a fluid shift from the intravascular to the interstitial space. Literature data pointed out that hypoalbuminemia, the main determinant of COP, can facilitate the onset of cardiogenic pulmonary oedema,[7] although it failed to become a reproducible determinant of lower extremity oedema.[5,8,9] Plasma volume status

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(PVS) has also been poorly investigated in the pathogenesis of peripheral congestion in AHF patients.[10] Studies involving parameters of renal function as the main determinants of fluid overload in AHF patients were also not fully conclusive.[11,12] A previous study reported that the presence and degree of peripheral oedema formation did not reflect left ventricular function as well as brain natriuretic peptide (BNP) plasma levels did,[8] although we found a direct relationship between BNP and peripheral oedema.[13] Severe anemia in patients without heart failure is often associated with peripheral oedema caused by salt and water retention,[14] but such a relationship has not yet been explored in AHF.

It has been demonstrated that bioimpedance vector analysis (BIVA) is a quantifiable and reliable technique for assessing peripheral oedema in heart failure.[13,15] In combination with BNP plasma levels, it offers reliable insights for the prompt diagnosis of AHF in the ED.[16,17] Furthermore, it contributes to prognostic stratification[18] and the decision-making process during AHF therapies.[19]

The aim of this study was to evaluate the relative contribution of serum COP, biomarkers of renal function, electrolytes, relative PVS, haemoglobin, and BNP in the pathogenesis of peripheral fluid overload evaluated by means of BIVA.

Materials and methods

Study populations

This was a retrospective study. We consecutively enrolled all patients admitted to the Cardiology Department, because of AHF[1] between January 2010 and November 2014. At the time of admission, the baseline physical and clinical characteristics, comorbidities, blood chemistry data, left ventricular ejection fraction (LVEF), BIVA, and drugs adopted at hospital admission were considered. All of the interventions were made in agreement with standard care and in line with international guidelines. Exclusion criteria were age <18 years, chronic haemodialysis, oedema secondary to vein disorders, or lymphedema. Two authors reviewed the clinical data of the records (FM and PS).

The study was approved by the local Institutional Review Board and was in agreement with the Helsinki Declaration. All patients gave written informed consent before enrolment.

Biochemistry

Renal function was assessed by considering the serum creatinine, blood urea nitrogen (BUN), the estimated glomerular filtration rate, and BUN to creatinine ratio (BUN/Cr). This ratio is considered an index of disproportionate tubular reabsorption of the BUN as compared with creatinine.[12] The Cockroft-Gault equation was used to estimate creatinine clearance: eCrCl (mL/min) = [(140 − age) × (weight)]/(72 × serum creatinine) × 0.85 (if female).

COP was calculated using the formula of Landis-Pappenheimer.[19] Total serum proteins (TP) were measured using the Biuret method (normal range: 6.6–8.3 g/dL) and albumin (A) using the immunoturbidimetry method (normal range: 3.5–5.2 g/dL). Given "G" as the serum globulin concentration derived by the difference between TP and A ($G = TP - A$), COP can be obtained by the following formula: $A/TP \times (2.8 \times TP + 0.18 \times TP^2 + 0.012 \times TP^3) + G/TP \times (1.6 \times TP + 0.15 \times TP^2 + 0.006 \times TP^3)$.[20] COP normal values are 25 ± 2 mmHg.[7]

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

Finally, we calculated PVS by the following equation, which was previously validated in heart failure patients: actual PVS = (1 − haematocrit) × [a + (b × body weight in kg)] (a = 1530 in males and a = 864 in females, b = 41.0 in males and b = 47.9 in females), ideal PVS = c × body weight in kg (c = 39 in males and c = 40 in females), and relative PVS = [(actual plasma volume − ideal plasma volume)/(ideal plasma volume] × 100 (%)]. Relative PVS is the index for the deviation of patients from their ideal plasma volume.[10]

Echocardiography

LVEF was evaluated by means of Simpon's biplane method in relation to current guidelines.[21] We classified patients into three groups in agreement with recent guidelines: reduced LVEF ($<40\%$), mid-range LVEF (between 40% and 49%), and preserved LVEF ($\geq 50\%$).[1]

BIVA

BIVA was assessed on the right body side as previously reported.[22] The patients were in a semiorthopneic or supine position. Four electrodes were used during the performance of the BIVA: two of them served as "detecting" electrodes and were placed on the dorsal surface of the wrist and anterior surface of the ipsilateral ankle; the other two served as "inductor" for the electrical signal and were positioned on the dorsal surface of the hand and foot. We adopted a tetrapolar impedance plethysmograph which is able to emit a 50-kHz alternating sinusoidal current (CardioEFG, Akern RJL Systems, Florence, Italy).

We calibrated this instrument each morning using a standard resistor supplied by the manufacturer (R = 380 ohms, Xc = 47 ohms, 1% error).

The two vector components R and Xc of BIVA were recorded and divided by the subject's height (R/Xc graph).[23] The subject was defined as "wet" if his/her vector was at the lower pole of the 50th percentile vector tolerance of the referral intervals related to sex and Italian standards. "Severe congestion" was if vector was out of the lower pole of the 95th percentile, "moderate congestion" between the 95th and 75th percentiles, and "middle congestion" between the 75th and 50th percentiles (i.e., subclinical congestion). 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".[13,16,23] In addition, we used dedicated software (Bodygram 1.4, Akern RJL Systems, Florence, Italy) to estimate body hydration as well as the percentage of fat-free mass (Hydration Index; HI).[13,17,24]

Statistical analysis

Categorical variables are expressed as counts (percentages), and continuous variables are expressed mean value ± standard deviation (SD).

The natural logarithm was used to obtain an optimal residual analysis because the distribution of BNP levels had a skewed distribution. Between-group comparisons were performed using analysis of variance (ANOVA) followed by the Newman-Keuls test for multiple comparisons. Test for trend after one-way ANOVA was performed by involving the BIVA congestion groups (dry, mild, moderate, or severe wet). The correlation of the studied variables was assessed using Pearson's coefficient. Then, we included only the variables with a significant value at univariate analyses in the stepwise multivariate linear regression analyses. The coefficient of determination (R^2) was used to measure the proportion of variability of the dependent variable that is attributable to the independent variables. To avoid multicollinearity, redundant variables were dropped from the multivariate regression models (i.e., creatinine and albumin). In model 1, we included all significant variables, and in model 2, we exclude BUN to evaluate the effect of BUN and eCrCl. P values below 0.05 were defined as statistically significant. The analyses were made using STATA software, version 12 (StataCorp, College Station, Tex).

Results

Four hundred eighty-five patients with AHF were included in this study. Table 1 summarizes the characteristics of the study population.

Peripheral oedema was present in 49% of patients. BIVA congestion ("wet") was found in 304 (63%) patients. They were classified as mild (30%), moderate (42%), and severe (28%), while 37% of the whole population was "dry."

As expected, HI significantly increased with the increase in congestion as assessed by BIVA: 73% ± 1% in "dry," 76% ± 2% in "mildly wet," 81% ± 4% in "moderately wet," and 88% ± 3.9% in "severely wet" ($P < 0.001$ for trend).

According to hydration status, as evaluated by BIVA, COP was significantly and inversely correlated to the presence and entity of congestion (Fig. 1). At univariate analysis, there was a significant correlation between hydration status and haemoglobin, total protein, albumin, BUN, creatinine, eCrCl, BNP levels, and relative PVS, whereas no significant associations were found for serum BUN/Cr, electrolytes, and LVEF (Tables 2 and 3). In particular, HI was 78% ± 6%, 78% ± 6%, and 79% ± 6% in reduced, mid-range, and preserved LVEF, respectively ($P = 0.09$). A strong relationship was found between serum albumin and COP ($r = 0.73$; $P < 0.001$).

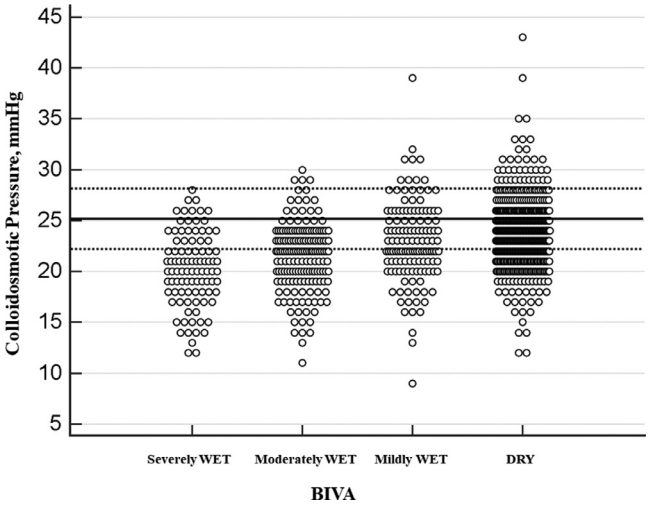

Fig. 1. Relationship between plasma colloidosmotic pressure (COP) and hydration status according to bioelectrical vector analysis (BIVA). Data are expressed as values (□) and standard deviation (SD) (lines).

ANOVA: $P < 0.01$. Student-Newman-Keuls post hoc tests between all groups, $P < 0.05$.

Table 1
Study population

	ADHF ($n = 485$)
Age, y	78 ± 10
Male (%)	50
BMI, kg/m²	28 ± 5
Medical history,%	
- Coronary artery disease	38
- Diabetes	28
- Atrial fibrillation	54
- ICD	11
- De novo	34
LVEF	41 ± 12
- Preserved LVEF,%	39
- Mid-range LVEF,%	18
- Reduced LVEF,%	43
Laboratory values	
- BNP, pg/mL	1518 ± 1258
- Haemoglobin, g/dL	12 ± 2
- Haemoglobin <12 g/dL,%	53
- Total protein, g/dl	6.2 ± 0.7
- Albumin, g/dL	3.2 ± 0.5
- Albumin, <3.2 g/dl%	44
- COP, mmHg	22 ± 4
- Sodium, mmol/L	139 ± 4
- Potassium, mmol/L	4.0 ± 0.6
- Chloride, mmol/L	101±6
- BUN, mg/dL	76 ± 45
- Creatinine, mg/dL	1.5 ± 0.9
- BUN/creatinine	53±18
- Creatinine 1.5 > mg/dL,%	35
- eCrCl, mL/min per 1.73 m²	44 ± 25
- eCrCl, <60 mL/min per 1.73 m²,%	78
- eCrCl, <30 mL/min per 1.73 m²,%	33
Therapies,%	
- Furosemide	97
- Beta-blockers	57
- ACE inhibitors	34
- ARBs	17
- MRAs	79
- Digitalis	20
- Calcium antagonists	0
- Ivabradine	6
- IV inotropes	14
- Ultrafiltration	6

Values are expressed as mean ± standard deviation or percentages.
ACE: angiotensin-converting enzyme; **ADHF:** acute decompensated heart failure; **ARB:** angiotensin receptor blocker; **BMI:** body mass index; **BUN:** blood urea nitrogen; **COP:** serum colloid osmotic pressure; **eCrCl:** estimate creatinine clearance; **ICD:** implanted cardioverter/defibrillator; **IV:** intravenous; **LVEF:** left ventricular ejection fraction; **MRAs** mineralocorticoid receptor antagonists.

The stepwise multiple regression analysis containing COP, haemoglobin, BUN, eCrCl, BNP, and relative PVS as possible determinants of HI revealed that independent predictors were COP, BUN, relative PVS, haemoglobin, and BNP. All of these explained the 25% of the interindividual fluid variation (Table 4, model 1). COP emerged as the major determinant of hydration status (12% of variability) (Table 4). Interestingly, when BUN was removed from the multivariate analysis, the estimated glomerular filtration rate emerged as an independent predictor (Table 4, model 2).

Discussion

In this study, we examined the biochemical variables associated with the presence and degree of peripheral congestion assessed by BIVA in AHF patients. Four major findings emerge from our analysis. First, the imbalance between the two main Starling's opposing forces—COP and relative PVS—was involved in the pathogenesis of peripheral congestion. Second, among renal function biomarkers, BUN was superior to eCrCl in predicting peripheral congestion, while BUN/Cr and electrolytes were not significantly associated with congestion assessed by BIVA. Third, lower haemoglobin levels appeared to be associated with the magnitude of peripheral congestion. Fourth, BNP levels seemed to be weak and independent predictors of peripheral fluid accumulation.

Taken in aggregate, our data suggest that "bloater" compared with "puffer" patients generally have lower haemoglobin levels, COP, and plasma volume expansion and higher BNP levels and more severe renal dysfunction.

In the literature, a typical "bloater" is characterized by longer hospitals stays,[25,26] worse prognosis,[26,27] and greater response to diuretic and serelaxine therapies.[5,6] Therefore, useful information from laboratory testing can provide a good overview of the prognosis of the AHF patient.

The imbalance in Starling forces is underrecognized in AHF, and factors influencing peripheral oedema formation are incompletely understood. To our knowledge, we demonstrated for the first time that COP and relative PVS are the main determinants of the degree of

Table 2
Laboratory tests according to BIVA congestion

	BIVA DRY		BIVA WET		
	(*n* = 181)	Mild (*n* = 92)	Moderate (*n* = 127)	Severe (*n* = 85)	*P*-value for trend
Hemoglobin, g/dL	13 ± 2	12 ± 2	11 ± 2	11 ± 2	<0.001
Total protein, g/dl	6.4 ± 0.7	6.2 ± 0.7	6.0 ± 0.6	5.8 ± 0.7	<0.001
Albumin, g/dL	3.4 ± 0.4	3.3 ± 0.6	3.1 ± 0.5	3.0 ± 0.5	<0.001
Sodium, mmol/L	139 ± 4	140 ± 5	139 ± 4	139 ± 6	0.6
Potassium, mmol/L	4.0 ± 0.6	3.9 ± 0.6	3.9 ± 0.7	4.0 ± 0.6	0.6
Chloride, mmol/L	101 ± 5	101 ± 6	101 ± 6	101 ± 6	0.7
BUN, mg/dL	66 ± 32	76 ± 40	80 ± 44	91 ± 46	<0.001
Creatinine, mg/dL	1.3 ± 0.8	1.5 ± 0.9	1.6 ± 0.9	1.9 ± 1.2	<0.001
BUN/creatinine	54 ± 20	54 ± 18	52 ± 17	52 ± 18	0.7
eCrCl, mL/min per 1.73 m²	47 ± 22	44 ± 31	44 ± 25	38 ± 20	0.049
BNP, pg/mL	1301 ± 1150	1534 ± 1323	1564 ± 1221	1896 ±1378	<0.001
Relative PVS,%	- 2.7 ± 15	0.9 ± 14	2.8 ± 15	2.3 ± 12	<0.001
LVEF,%	43 ± 13	42 ± 13	42 ± 11	40 ± 12	0.09

BNP: brain natriuretic peptide; **BUN**: blood urea nitrogen; **COP**: serum colloid osmotic pressure**; eCrCl:** estimate creatinine clearance; **LVEF:** left ventricular ejection fraction; **PVS:** plasma volume status.

peripheral congestion. Arques et al. previously demonstrated the importance of COP as a determinant of presence and degree of pulmonary congestion.[7] Therefore, COP emerged as an important biochemical-derived variable to be considered when signs and symptoms of pulmonary and/or peripheral oedema are present in AHF patients. Physiologically, albumin accounts for 50% of the plasma protein mass and provides 70% to 80% of COP.[23] Forty-four percent of our AHF population showed hypoalbuminemia, which is in line with literature data.[28] Breidthartd et al. explored the relationship between serum albumin and leg oedema found no differences in serum albumin levels in patients with and without peripheral oedema. However, they found a weak association between low albumin level and more extensive leg oedema.[8] Grodin et al. found that lower albumin was associated with a trend toward increased peripheral oedema ($P = 0.09$) in 456 AHF subjects randomized in the DOSE-AHF and ROSE-AHF trials.[9] On the contrary, Giempelewicz et al. outlined significantly lower albumin levels in the subgroup with peripheral oedema of the RELAX-AHF trial.[5] We demonstrated a strong relationship between albumin levels and the presence and severity of peripheral congestion in a large population with AHF. The use of BIVA in our study overcame the limitation of physical examination of peripheral oedema typical of the studies mentioned above.[22] BIVA can better evaluate peripheral congestion, even during its subclinical expression.[15,16] In fact, between the 50th and 75th percentile, peripheral oedema can produces results that are phenotypically absent. In fact, in our study, BIVA "wet" was present in 63% of total patients, while peripheral oedema was detected in only 49% of patients. As consequence, 14% of patients showed subclinical congestion.

Table 3
Bivariate correlation with Hydration Index (%)

	R	*P*-value
COP, mmHg	−0.35	<0.001
Haemoglobin, g/dL	−0.26	<0.001
Total protein, g/dl	−0.30	<0.001
Albumin, g/dL	−0.32	<0.001
Sodium, mmol/L	0.06	0.2
Potassium, mmol/L	−0.01	0.8
Chloride, mmol/L	−0.05	0.3
BUN, mg/dl	0.25	<0.001
Creatinine, mg/dl	0.22	<0.001
BUN/creatinine	0.03	0.5
eCrCl, mL/min per 1.73 m²	−0.20	<0.001
Relative PVS,%	0.11	0.045
Ln BNP, pg/mL	0.18	<0.001
LVEF,%	0.05	0.3

Ln BNP: natural logarithm of brain natriuretic peptide; **BUN**: blood urea nitrogen; **COP**: serum colloid osmotic pressure**; eCrCl:** estimate creatinine clearance; **LVEF:** left ventricular ejection fraction; **PVS:** plasma volume status.

Our research also reinforced the concept that BUN and creatinine are "not married" in the setting of heart failure.[29] Surprisingly, we found that BUN is a stronger biomarker of peripheral congestion than estimated glomerular filtration rate. After removing BUN from the multivariate model, glomerular filtration rate emerged as a significant predictor of peripheral congestion. This observation is of particular interest and deserves some explanation. Serum creatinine is filtered at the glomerular level and then undergoes tubular secretion. On the contrary, urea is filtered, but the renal tubules reabsorb it. In particular, urea reabsorption in the proximal tubules is passively linked to the reabsorption of sodium and water, whereas it is mediated by the effect of arginine vasopressin in the collecting duct.[29] In heart failure, significant renal neurohormonal activation related to low cardiac output (i.e., increase in the sympathetic nervous system, renin-angiotensin-aldosterone axis, and vasopressin) causes an elevation in BUN levels that is not associated with a proportional rise in creatinine levels.[29] Thus, the rise in BUN can be considered an index of neurohormonal activation, venous congestion, and glomerular filtration variations.[12] Our results were partially in line with those from Parrinello et al., who found significantly higher BUN/Cr and BUN levels in patients with ultrasound caval congestion and chronic heart failure.[12] In contrast, we found a statistically significant relationship between peripheral congestion, BUN, and eCrCl but not with BUN/Cr. Furthermore, our data are in line with previous studies in AHF patients: the lower the glomerular filtration rate, the higher the magnitude of peripheral oedema.[5,30] Serum electrolytes were not correlated with peripheral congestion, which suggests that serum osmolarity, mainly related to serum sodium and chloride, did not play an important role in the pathophysiology of peripheral congestion. These findings confirm the RELAX-AHF data,[5] although other reports found a weak ($P = 0.04$) association between low sodium level and more extensive peripheral oedema.[7]

Our third major finding is the association between the reduction in haemoglobin levels and peripheral congestion. Similar results were observed by Melenovsky et al.[29] In their study, low hemoglobin levels emerged as a strong predictor of increased lung congestion independently from BNP, albumin, and estimated glomerular filtration rate.[29] It is suggested that anemia in subjects with peripheral oedema but without heart failure has a generalised vasodilation action and neurohormonal activation, with sodium and water retention (up to 748 mmol of sodium retention and nearly 4 L of fluid excess, respectively).[14] Therefore, anemia per se can promote peripheral oedema. Anemia is common in AHF (ranging in prevalence from 30% to 70%), and it is generally considered secondary to

Table 4
Stepwise multiple regression for Hydration Index (%)

Hydration Index (%) Model 1	Final model		Sequential models
	Coefficient ± SE	*P*-value	R^2
COP (mmHg)	−0.52 ± 0.07	<0.001	0.12
BUN (mg/dL) × 10	0.24 ± 0.07	<0.001	0.18
Relative PVS (%)	−0.18 ± 0.03	<0.001	0.22
Haemoglobin (g/dL)	−1.26 ± 0.19	=0.002	0.24
LnBNP (pg/mL)	1.40 ± 0.64	=0.015	0.25
eCrCl (mL/min per 1.73 m^2) × 10	−0.24 ± 0.13	=0.070	
Model 2			
COP (mmHg)	−0.51 ± 0.07	<0.001	0.12
Relative PVS (%)	−0.20 ± 0.03	<0.001	0.16
eCrCl (mL/min per 1.73 m^2) × 10	−0.46 ± 0.11	<0.001	0.20
Haemoglobin (g/dL)	−1.38 ± 0.19	<0.001	0.23
LnBNP (pg/mL)	1.55 ± 0.65	=0.009	0.24

Coefficient ± standard error.
BNP: brain natriuretic peptide; **BUN:** blood urea nitrogen; **COP:** serum colloid osmotic pressure**; eCrCl:** estimate creatinine clearance; **LVEF:** left ventricular ejection fraction; **PVS:** plasma volume status.
Model 1: The multivariate model included COP, BUN, relative PVS, haemoglobin, Ln BNP, eCrCl.
Model 2: Variables in model 1 without BUN.

hemodilution. However, the impact on peripheral congestion was independent of plasma volume.

The absence of correlation between congestion and LVEF in our study also confirms the findings from previous studies.[5,8,31] In agreement with our previous data,[12] we found higher levels of BNP in BIVA "wet" as compared with "dry" AHF patients. Nevertheless, BNP levels in the present study resulted in a weak, independent predictor of BIVA "wet" at multivariate analysis; thus, its role seems marginal.

Conclusions

The current data demonstrated that biomarkers of renal function, COP (i.e., serum albumin), relative PVS, haemoglobin, and BNP are fundamental determinants of the presence and entity of peripheral congestion. As a consequence, this frequent clinical sign, rapidly and objectively evaluated by BIVA, is related to several biomarkers that have a negative prognostic impact on AHF patients. Targeting peripheral oedema formation after a prompt recognition by means of BIVA could represent an important strategy to reverse or prevent AHF congestion and, therefore, the prognosis of these patients.

Declarations of interest

None

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.hrtlng.2019.04.009.

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