[Original article]

Subclinical volume overload in stable outpatients with chronic heart failure

Levinia BOONEN[1,2]*, BS; Frederik Hendrik VERBRUGGE[1,3]*, MD, PhD; Petra NIJST[1,3], MD; Patrick NOYENS[1], MD; Philip DE VUSSER[1], MD, David VERHAERT[1], MD; Johan VAN LIERDE[1], MD; Mathias VROLIX[1], MD; Matthias DUPONT[1], MD; Wilfried MULLENS[1,4], MD, PhD

[1]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [2]Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; [3]Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; [4]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium.

*Both authors contributed equally to the manuscript

Objective The objective of this study was to characterize stable outpatients with subclinical volume overload in chronic heart failure (CHF) by using bioelectrical impedance analysis (BIA) measurements.

Methods and results Venous blood sampling and BIA were performed in consecutive CHF patients (n = 58) free from clinical signs of volume overload and treated with oral loop diuretics. Subclinical volume overload was defined as excess extracellular water on BIA. Patients with (n = 34) versus without (n = 24) subclinical volume overload were significantly older (72 ± 10 versus 65 ± 9 years; *P*-value = 0.016), had higher systolic blood pressure (126 ± 20 versus 114 ± 17 mmHg; *P*-value = 0.012), and took angiotensin-converting enzyme inhibitors more often (65% versus 33%; *P*-value = 0.032). Dyspnoea symptoms were similar among both groups. Subclinical volume overload was associated with low serum albumin (*P*-value = 0.014) and protein levels (*P*-value = 0.041). In contrast, serum sodium levels (141 ± 3 versus 139 ± 2 mEq/L; *P*-value = 0.033) but not chloride levels (99 ± 14 versus 101 ± 3 mEq/L; *P*-value = 0.980) were significantly higher in patients with versus without subclinical volume overload, respectively. The former versus latter group also demonstrated lower plasma aldosterone levels [276 (195-475) versus 400 (306-717) ng/L, respectively; *P*-value = 0.032].

Conclusions Subclinical volume overload assessed by BIA in stable CHF is associated with low serum protein levels, increased serum sodium but not serum chloride, as well as decreased neurohumoral activation.

Keywords *Dyspnoea – electric impedance – renin-angiotensin system – serum albumin.*

INTRODUCTION

Signs and symptoms of congestion are the leading cause of hospitalizations in patients with chronic heart failure (CHF)[1]. Current treatments aim to treat volume overload in such cases with diuretics and subsequently prevent or even reverse disease progression in the long-term with initiation and uptitration of neurohumoral antagonists as well as device therapy for selected patients[2,3]. Importantly, persistent congestion after a hospital admission for heart failure is associated with worse clinical outcomes, i.e., early readmissions and all-cause mortality[4]. However, volume overload in the setting of CHF is often subtle and clinical signs and symptoms may lack sensitivity to detect congestion[5]. Therefore, in a stable outpatient setting, CHF patients may develop subclinical volume overload that is not readily uncovered[6]. This subclinical volume overload may accrue over time and eventually culminate in decompensated heart failure. Indeed, around half of the patients who are hospitalized with decompensated heart failure gain > 1 kg of weight on a slow and steady pace during the weeks before, while almost all demonstrate a pattern of increased right-sided cardiac filling pressures[7,8].

Address for correspondence:

Frederik H. Verbrugge, MD, PhD,
Department of Cardiology, Ziekenhuis Oost-Limburg,
Schiepse Bos 6, 3600 Genk, Belgium.
E-mail: frederik.verbrugge@zol.be

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Bioelectrical impedance analysis (BIA) has emerged as a non-invasive technique to determine body composition and hydration status. BIA measurements are based on the electrical resistance that is encountered by an alternating current flow sent through the body, in which the extracellular path is modelled as a resistor and the intracellular path as a resistor and capacitor in series. BIA estimations of total body water can be used to aid the diagnosis of heart failure in an emergency care setting and have been shown to correlate with clinical outcome[9-11]. Moreover, BIA might be promising to detect dynamic changes in total body water during decongestive treatment[12-14].

In this study, BIA was used to assess total body water and compartmentalization in stable outpatients with CHF. The first objective was to evaluate whether such patients, without any clear signs of volume overload and without recent hospital admission or therapy change, may have subclinical volume overload. The second objective was to search for characteristics associated with subclinical volume overload.

METHODS

Study design

This prospective observational cohort study was performed at the outpatient cardiology clinic of a single tertiary centre (Ziekenhuis Oost-Limburg, Genk, Belgium) between December 2014 and April 2015. The second and last author designed the study protocol, while the first author collected the data. The first and second author wrote the first draft of the manuscript together, which was subsequently revised and approved by all authors. *The study complies with the Declaration of Helsinki and the study protocol was approved by the institutional committee on human research. Written informed consent was obtained from every patient before any study-specific procedure was performed.*

Study population

All patients, scheduled for routine clinical follow-up at the outpatient cardiology clinic, were screened for study participation if they were aged ≥ 18 years and received daily maintenance therapy with an oral loop diuretic at any dose. Other inclusion criteria were: (1) a left ventricular ejection fraction < 40%; or (2) a previous hospitalization with a primary diagnosis of heart failure. Exclusion criteria were: (1) hospital admission for heart failure < 3 months before study inclusion; (2) change in the maintenance dose of loop diuretics, renin-angiotensin-aldosterone system blockers or beta blockers < 3 months before study inclusion; (3) initiation of cardiac resynchronization therapy < 3 months before study inclusion; and (4) either one of the following clinical signs of volume overload: more than trace oedema, ascites, hepatomegaly or lung congestion.

Bioelectrical impedance analysis

The BioScan 920-II-S device (Maltron International Limited®, Essex, United Kingdom) was used to perform BIA in every patient. In brief, patients were placed in supine position and their weight, height, age, gender, and race were entered as covariates into the device. The general principle behind BIA is that total body water is inversely correlated with resistance to a current sent through the body. In addition, the BioScan 920-II-S device determines the relative proportion of intra- versus extracellular water by transmitting an alternating current through the body at different frequencies. At low frequencies (5 kHz), this current is conducted only through extracellular fluid, whereas at high frequencies (> 50 kHz) it penetrates cell membranes as well, passing through both the intra- and extracellular compartment. BIA measurements in this study were obtained using the whole body electrode configuration specified by the manufacturer. In this configuration, two sets of electrodes – each consisting of a signalling (distal) and detecting (proximal) electrode – were applied to the skin. The first set was applied between the talus and 3rd digit of the right foot, whereas the second set was applied to the same side between the wrist and 3rd knuckle of the hand. Patients in whom excess extracellular body water was detected by the BioScan 920-II-S were considered to have subclinical volume overload. The intra-class correlation coefficient for two separate measurements performed in the same body position with a time interval of 30 minutes without replacing the electrodes was 0.97 (95% confidence interval = 0.95-0.99), indicating very high reproducibility.

Laboratory measurements

A venous blood sample was obtained after BIA measurements. Serum albumin levels were assessed by the Roche bromocresol green assay (Roche, Rotkreuz, Switzerland). Plasma N-terminal of the prohormone of B-type natriuretic peptide (NT-proBNP) levels were measured by the Roche Diagnostics assay (Roche, Rotkreuz, Switzerland). Plasma renin activity was determined using the GammaCoat® radioimmunoassay (DiaSorin, Sallugia, Italy). Plasma aldosterone levels were assessed by the Aldosterone Maia radioimmunoassay (Adaltis, Rome, Italy).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation when normally distributed and as median

(interquartile range) in case of a non-normal distribution. Normality was assessed by the Shapiro-Wilk statistic. The independent-samples Student's *t*-test and Mann-Whitney *U* test were used as indicated to compare between groups. Categorical variables are expressed as percentages and compared using Fisher's exact test or Pearson's χ^2-test in case of a non-binary response. Statistical significance was always set at a two-tailed probability level of < 0.05. All statistics were performed using IBM SPSS® (Chicago, Illinois, USA) (version 22.0 for Mac).

RESULTS

Study population

During the study period, 287 consecutive patients who were scheduled for a visit at the outpatient cardiology clinic and took a daily maintenance dose of loop diuretics were screened for eligibility. A total of 95 patients were eligible for study enrolment, of whom 58 provided informed consent. A detailed study flowchart is provided in figure 1. In one patient, no blood sample was available because of difficult venous access. There were no other missing data. Table 1 presents the baseline characteristics of the study population. According to BIA measurements, 24 patients had no excess extracellular water, while 34 had some degree of subclinical volume overload. The daily maintenance dose of loop diuretics (mg furosemide equivalents) was not significantly different at 20 mg (20-40 mg) furosemide equivalent dose in euvolemic patients compared to 40 mg (20-40 mg) in patients with subclinical volume overload (*P*-value = 0.195). Patients with versus without subclinical volume overload were significantly older (72 ± 10 versus 65 ± 9 years, respectively; *P*-value = 0.016), had higher systolic blood pressure (126 ± 20 versus 114 ± 17, respectively; *P*-value = 0.012), and took angiotensin-converting enzyme inhibitors more often (65% versus 33%, respectively; *P*-value = 0.032). Somewhat more patients with versus without subclinical volume overload had ischaemic rather than valvular aetiology for heart failure, but the difference was not statistically significant (*P*-value = 0.099).

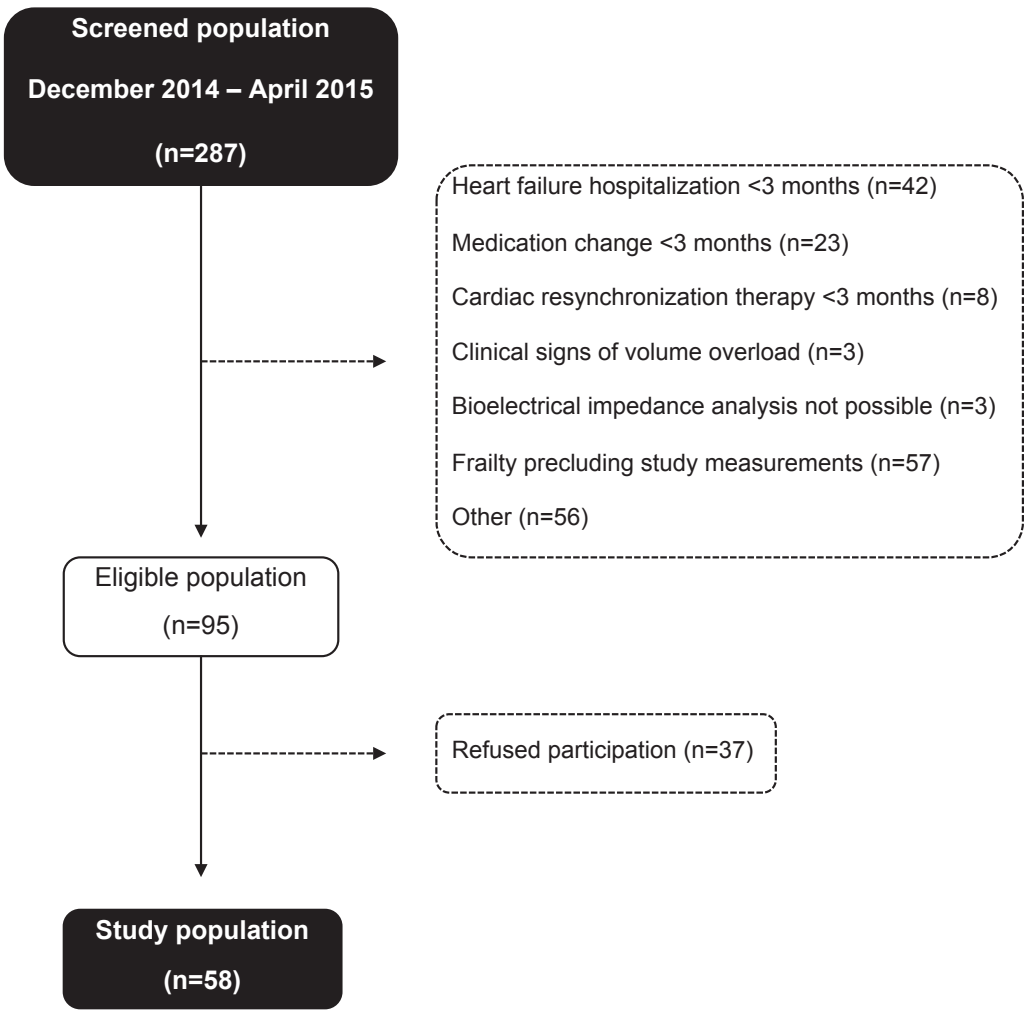

Fig. 1 Study flowchart.

Table 1 Baseline characteristics of the study population (n = 58)

	Total study population (n = 58)	No excess extracellular volume (n = 24)	Subclinical volume overload (n = 34)	*P*-value
Demographics				
Age (years)	69 ± 10	65 ± 9	72 ± 10	0.016
Male gender	76%	79%	74%	0.759
White race	100%	100%	100%	1.000
Height (cm)	168 ± 10	171 ± 8	167 ± 11	0.088
Weight (kg)	86 ± 15	86 ± 15	85 ± 16	0.889
Body mass index (kg/m^2)	30 ± 4	29 ± 4	31 ± 5	0.196
Heart failure characteristics				
Aetiology				0.099
Ischaemic	59%	50%	65%	
Dilated	29%	29%	29%	
Valvular	7%	17%	0%	
Preserved ejection fraction	5%	4%	6%	
Time since heart failure diagnosis (years)	3 (2-6)	3 (1-6)	4 (2-6)	0.430
NYHA functional class				0.350
I	43%	38%	47%	
II	48%	58%	41%	
III	9%	4%	12%	
Left ventricular ejection fraction (%)	41 ± 12	40 ± 13	42 ± 11	0.726
History and comorbid conditions				
Ischaemic heart disease	62%	58%	65%	0.784
Atrial fibrillation	52%	42%	59%	0.286
Aortic valve surgery	3%	8%	-	0.167
Mitral valve surgery	16%	17%	15%	1.000
Tricuspid valve surgery	10%	17%	6%	0.220
Diabetes	22%	21%	24%	1.000
Chronic kidney disease*	53%	63%	47%	0.420
Cardiac device				
Implantable cardioverter/defibrillator	48%	58%	42%	0.286
cardiac resynchronization therapy	62%	71%	56%	0.284
Vital parameters and clinical symptoms				
Heart rate (bpm)	70 ± 10	67 ± 9	72 ± 10	0.055
Systolic blood pressure (mmHg)	121 ± 19	114 ± 17	126 ± 20	0.012
Diastolic blood pressure (mmHg)	74 ± 12	70 ± 12	76 ± 13	0.070
Visual analogue score for dyspnoea (/100)	34 ± 24	32 ± 28	36 ± 21	0.588
Orthopnoea	19%	17%	21%	1.000
Bendopnoea	41%	29%	50%	0.176
Paroxysmal nocturnal dyspnoea	9%	13%	6%	0.640
Medication use				
Maintenance dose of loop diuretics (mg furosemide equivalents)	40 (20-40)	20 (20-40)	40 (20-40)	0.195
Renin-angiotensin system blocker	76%	67%	82%	0.218
Angiotensin-converting enzyme inhibitor	52%	33%	65%	0.032
Angiotensin receptor blocker	26%	33%	21%	0.364
Beta blocker	88%	96%	82%	0.221
Mineralocorticoid receptor antagonist	64%	71%	59%	0.413
Non-loop diuretic	17%	17%	18%	1.000
Digoxin	12%	17%	9%	0.432

*Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration formula.
NYHA: New York Heart Association.

Dyspnoea symptoms to detect subclinical volume overload

The severity and qualitative characteristics of dyspnoea were not significantly different between patients with versus without subclinical volume overload (table 1). Figure 2 shows that bendopnoea, which was defined as dyspnoea when bending forward (i.e., typically when tying shoelaces) was the only characteristic that might have had some discriminative value, although the result was not significant (*P*-value = 0.176).

Bioelectrical impedance analysis

For a similar body weight (85 ± 16 versus 86 ± 15 kg, respectively; *P*-value = 0.889) and total body water (42.7 ± 8.3 versus 42.1 ± 8.4 L, respectively; *P*-value = 0.790), patients with versus without subclinical volume overload had more extracellular and less intracellular water (table 2). The plasma volume was very similar among both groups (3.5 ± 0.8 versus 3.4 ± 0.6 L, respectively; *P*-value = 0.301). Indeed, in patients with subclinical volume overload, 79% of the excess water resided in the interstitial compartment (table 2).

Biomarkers associated with subclinical volume overload

A significant reduction in total serum protein levels (73.7 ± 3.6 versus 75.9 ± 4.2 g/dL; *P*-value = 0.041) as well as serum albumin levels (42.8 ± 2.5 versus 44.6 ± 2.6 g/L; *P*-value = 0.014) was observed in patients with subclinical volume overload compared to patients without excess extracellular fluid (figure 3). In contrast, serum sodium (141 ± 3 versus 139 ± 2 mEq/L; *P*-value = 0.033) but not chloride levels (99 ± 14 versus 101 ± 3 mEq/L; *P*-value = 0.980) were significantly higher in the former

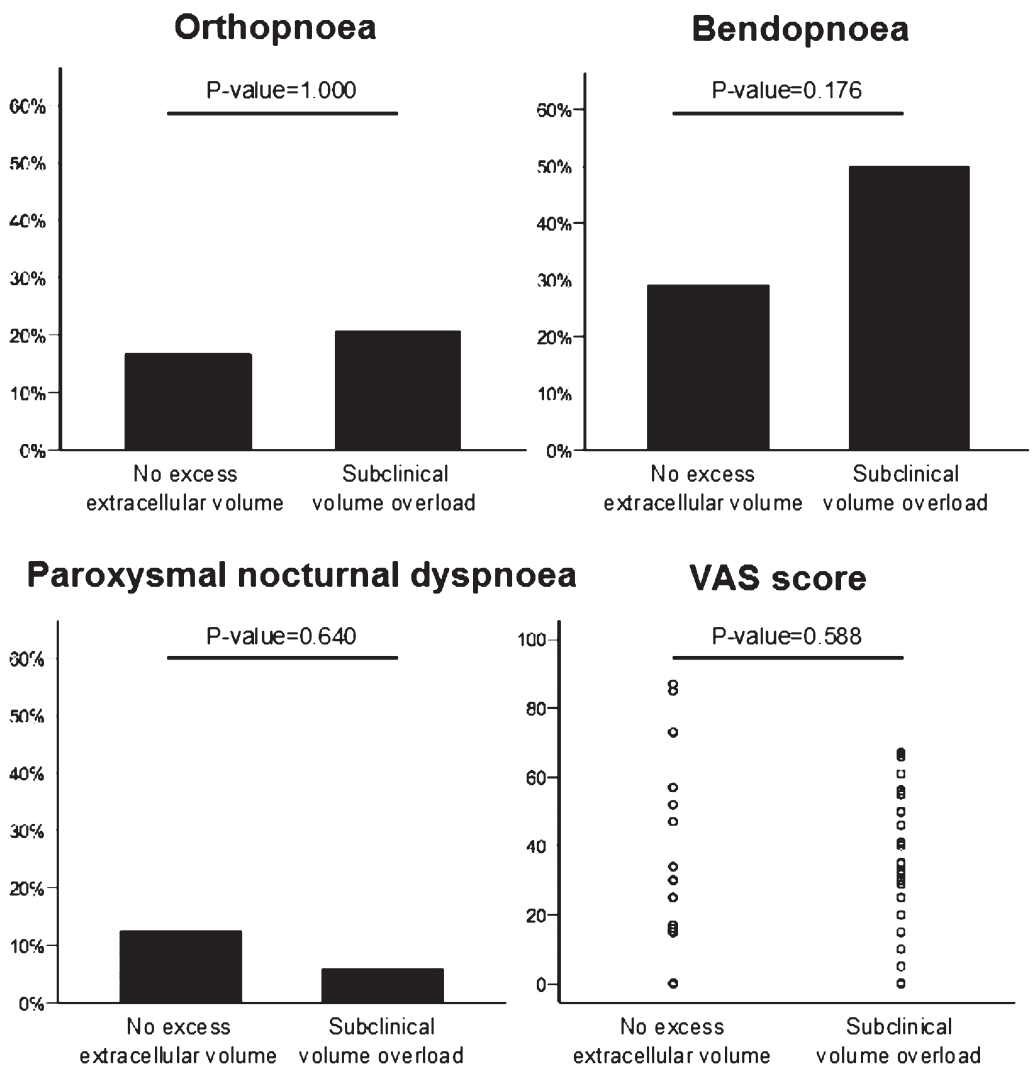

Fig. 2 Severity and qualitative characteristics of dyspnoea in patients with no excess extracellular volume (n = 24) versus subclinical volume overload (n = 34).
VAS: visual analogue scale.

Table 2 Bioelectrical impedance analysis results

	Total study population (n = 58)	No excess extracellular volume (n = 24)	Subclinical volume overload (n = 34)	*P*-value
Fat (%)	34.3 ± 7.4	34.2 ± 5.9	34.5 ± 8.4	0.876
Lean mass (%)	65.7 ± 7.4	65.9 ± 5.9	65.6 ± 8.4	0.877
Muscle mass (kg)	28 ± 7	29 ± 7	27 ± 7	0.324
Total body water (L)	42.5 ± 8.3	42.1 ± 8.4	42.7 ± 8.3	0.790
Intracellular water (%)	53.8 ± 1.8	55.0 ± 1.0	52.9 ± 1.7	< 0.001
Extracellular water (%)	46.2 ± 2.5	45.0 ± 3.0	47.1 ± 1.7	< 0.001
Interstital fluid (L)	14.9 ± 3.1	14.3 ± 2.7	15.4 ± 3.2	0.161
Plasma (L)	3.5 ± 0.7	3.4 ± 0.6	3.5 ± 0.8	0.301
Excess extracellular water (L)		–	1.43 (0.68-2.78)	N/A

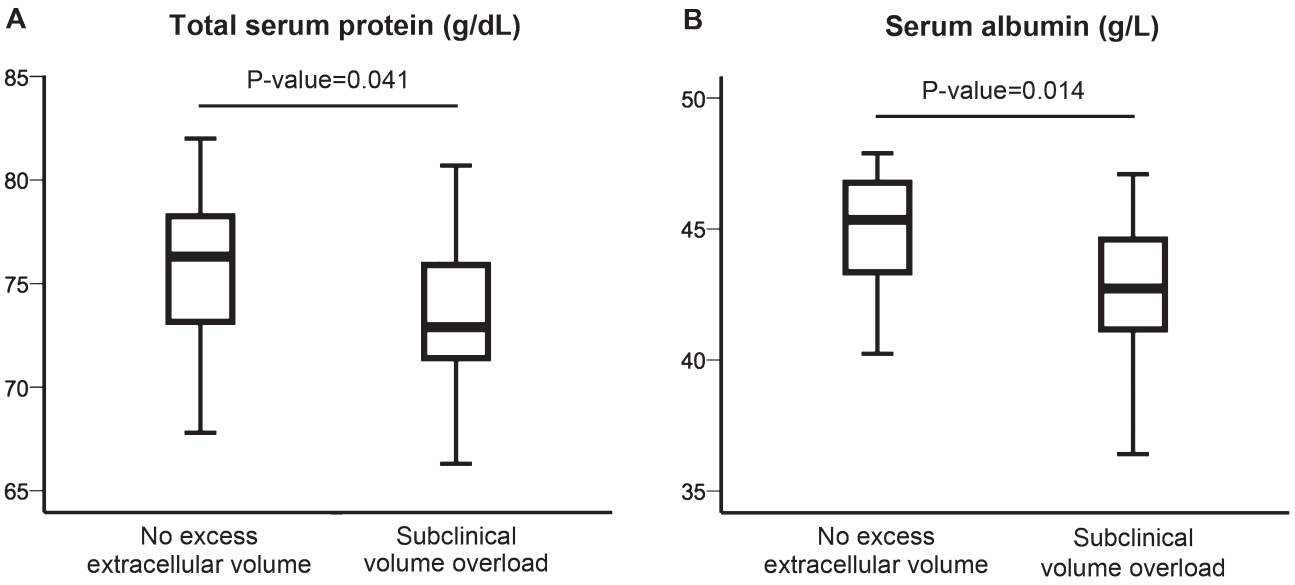

Fig. 3 Total serum protein (A) and serum albumin levels (B) according to the presence of subclinical volume overload.

versus latter group, respectively. There was no significant difference in serum osmolality between groups (305 ± 10 versus 304 ± 8 mOsm/L, respectively; *P*-value = 0.737). Plasma NT-proBNP levels were not significantly different among both groups [1,063 ng/L (391-2,602 ng/L) versus 744 ng/L (347-1,378 ng/L, respectively); *P*-value = 0.230]. Neurohumoral activation was more pronounced in patients who had no excess extracellular water compared to patients with subclinical volume overload (table 3).

DISCUSSION

This prospective cohort study of consecutive stable outpatients with CHF and no clinical signs of volume overload adds some important insights into the pathophysiology of congestion in heart failure: (1) some degree of subclinical volume overload, assessed by BIA, was present in 59% of the population studied, despite deliberate inclusion of patients who were deemed stable in an outpatient context; (2) subclinical volume overload correlated poorly with dyspnoea characteristics or severity, although bendopnoea (i.e., dyspnoea while bending forward) might possess some discriminative value; (3) subclinical volume overload in CHF is located predominantly in the interstitial compartment, while the plasma volume remains unchanged; (4) older age, higher blood pressure and lower serum protein levels characterized the population with subclinical volume overload in this study. Larger studies are needed to confirm or refute these findings and assess whether quality of life and

Table 3 Neurohumoral activation according to the presence of subclinical volume overload

	Total study population (n = 58)	No excess extracellular volume (n = 24)	Subclinical volume overload (n = 34)	*P*-value
Plasma aldosteron (ng/L)	337 (219-509)	400 (306-717)	276 (195-475)	0.032
Plasma renin activity (μg/L/h)	11.55 (4.25-24.30)	18.5 (8.70-23.40)	9.9 (2.95-24.90)	0.133

event-free survival in such patients can be ameliorated by intensifying decongestive treatment.

BIA is an easily accessible, non-invasive, safe and inexpensive technology that is able to estimate total body composition and hydration status. It has been used in sports medicine to assess muscle and fat mass, as well as in patients with chronic kidney disease undergoing renal replacement therapy to quantify volume overload and optimal *dry weight*[15,16]. In patients with unexplained dyspnoea, BIA is a promising tool to facilitate the diagnosis of volume overload and decompensated heart failure[9,11]. It has been suggested that combined natriuretic peptide and BIA assessment offers incremental information on volume status in comparison to either measurement alone, something which is further confirmed by the results of this study[13,17]. Alternatively, the combination of weight increase and decreased body fat percentage on BIA indicates fluid accumulation and suggests worsening heart failure[18,19]. Coodley et al. first used BIA measurements to monitor decongestion in tweve patients presenting with decompensated heart failure and demonstrated a strong correlation with changes in body weight[12]. However, subsequent studies have not consistently replicated these results and it remains unsure whether BIA measurements represent a suitable tool to monitor fluid balance in patients with acute decompensated heart failure undergoing diuretic treatment[20,21].

In contrast, not many studies have used BIA in *stable outpatients* with CHF. Castillo-Martinez et al. have reported raw BIA measurements from 168 CHF patients in New York Heart Association (NYHA) functional class I-II and 75 in class III-IV [22]. Patients with more advanced NYHA class had significantly lower impedance values, suggesting excess volume accumulation. Indeed, NYHA III-IV compared to I-II patients also had significantly more clinically overt oedema. Our results add to this observation and suggest that dyspnoea severity, even when assessed with a more detailed visual analogue scale, correlates poorly with presence of *subclinical* volume overload. In contrast, CHF patients with subclinical volume overload were characterized by a significantly older age compared to their peers without excess extracellular water. As the maintenance dose of loop diuretics was not significantly higher in the group with subclinical volume overload and the use of angiotensin-converting enzyme inhibitors also more frequent, a more lenient pharmacological management in such patients was not evident. Rather, our results suggest that it may be more difficult to assess volume status in elderly patients. Alternatively, subclinical volume overload may indicate more severe underlying CHF. However, left ventricular ejection fraction was very similar, blood pressure higher, and major comorbid conditions (notably including chronic kidney disease) comparably prevalent among patients with versus without subclinical volume overload.

Interestingly, our results indicate that excess extracellular water in case of subclinical volume overload predominantly resides in the interstitial compartment, while the plasma volume remains virtually unchanged. This has important implications as clinical signs that rely on filling of the vascular compartment, such as jugular venous pressure or even invasively measured cardiac filling pressures, may not always adequately reflect filling of the interstitial compartment. BIA may therefore complement findings of the clinical exam or haemodynamic assessments. It remains unclear what the precise underlying mechanism of accumulation of subclinical volume overload was in our population. If anything, neurohumoral activation was lower in this group, with significantly lower plasma aldosterone levels. Remarkably, serum sodium but not chloride levels were significantly higher in patients with subclinical volume overload, which hypothetically might suggest a diminished buffering of sodium in the interstitial compartment by proteoglycans[23]. Consequently, excess sodium available in the interstitium and circulation may stimulate fluid retention. However, this hypothesis should be the target of further investigation.

Another interesting observation of this study is that serum protein and albumin levels were lower in patients with subclinical volume overload. Previous work has indicated that reduced serum albumin levels are associated with decreased survival in CHF[24]. Moreover, this also applies in acute decompensated heart failure, where hypo-albuminaemia is associated with a two-fold increased mortality risk[25]. Some recent studies have

linked poor nutritional status in heart failure to adverse clinical outcome[26-28]. Indeed, it is well known that serum protein and albumin levels are sensitive biomarkers for impaired nutritional status. Based on the results of this study, one might speculate that poor nutrition, which is exceedingly common in elderly patients, contributes to low plasma protein levels, decreased colloid osmotic pressure, and hence interstitial oedema formation. On the other hand, subclinical congestion in the abdominal compartment may compromise digestive function and be the cause of protein deficiency. Indeed, important alterations in abdominal organ function are observed with congestion in CHF[29]. Finally, serum albumin is an acute phase reactant, which decreases with inflammation. As congestion in CHF has been demonstrated to result in low-grade inflammation, this may also explain the link between low serum albumin levels and subclinical volume overload[30].

STUDY LIMITATIONS

Some limitations should be considered when interpreting the results of this study. First, this was a single-centre study with limited sample size, rendering its findings hypothesis-generating with the need of confirmation by larger studies. In particular, the sample size provided limited power to compare dyspnoea characteristics and severity between patients with versus without subclinical volume overload. Therefore, although the symptom of bendopnoea was found in half of the patients with subclinical volume overload versus only in 29% without, this difference was not statistically significant. Another larger study did suggest that bendopnoea might be a useful marker of elevated cardiac filling pressures[31]. Second, although 287 patients were screened, only 58 were included in this study. However, most of the exclusions reflected efforts to carefully select a population with *stable* CHF. In this respect, the finding that some degree of volume overload was still detected in 59% of patients is remarkable. Third, BIA measurements were not validated against the gold standard method for plasma volumetric assessment, which is a radio-nucleotide assay[32]. However, it has been demonstrated previously that BIA measurements in stable patients with CHF correlate well with assessments by radio-nucleotide assays[33]. Fourth, the finding that subclinical volume overload was more frequently present in elderly patients with hypertension may indicate that it is just a reflection of poor health status. However, due to the small sample size, propensity-matching of subjects according to age and blood pressure was not possible.

CONCLUSION

Even in carefully selected *stable* outpatients with CHF, subclinical volume overload is present in a considerable amount of patients. Dyspnoea characteristics and severity have low sensitivity and specificity to detect this phenomenon. Low serum protein and albumin levels may serve as a warning sign that subclinical volume overload is likely. Further studies should be performed to assess whether intensifying decongestive treatment in patients with subclinical volume overload detected by BIA results in better quality of life and event-free survival.

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CONFLICT OF INTEREST: none.

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