INTRODUCTION

Signs and symptoms of congestion are the leading cause of hospitalizations in patients with chronic heart failure (CHF). 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. Importantly, persistent congestion after a hospital admission for heart failure is associated with worse clinical outcomes, i.e., early readmissions and all-cause mortality. Therefore, in a stable outpatient setting, CHF patients may develop subclinical volume overload that is clinically-unapparent. This subclinical volume overload may predict future readmissions and contribute to decompen- sated heart failure. Indeed, around half of the patients who are hospitalized with decompen- sated 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.

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 versus without 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). 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 is common in stable CHF patients and is associated with lower serum albumin but not chloride, as well as decreased neurohumoral activation.

Keywords

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 tertiary centre (Ziekenhuis Oost-Limburg, Genk, Belgium) between December 2014 and April 2015. 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 met the following inclusion criteria: (1) hospital admission with a primary diagnosis of heart failure < 3 months before study inclusion; (2) initiation of renin-angiotensin system blockers or beta blockers, and the maintenance dose of loop diuretics, renin-angiotensin system blockers or beta blockers, or (3) 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, 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 genotype was modelled as a resistor and capacitor in series. BIA estimations in this configuration, consisting of a signalling (distal) and detecting (proximal) electrode configuration specified by the manufacturer for this configuration, assessed the extracellular and intracellular fluid volumes by determining the relative proportion of intra- versus extracellular fluid determined by transmitting an alternating current through the body at different frequencies. At high frequencies (>50 kHz), this current is conducted only through interstitial fluid, whereas at low frequencies (<1 kHz), it penetrates cell membranes as well, passing through both the interstitial and intracellular compartments. BIA measurements of total body water are obtained using the whole body electrode configuration specified by the manufacturer for this configuration, and are used to derive a formula containing total body water volume detected by the BioScan 920-II-S was considered to have subclinical volume overload, which was subsequently revised and approved by all authors. The study complied with the Declaration of Helsinki and the appropriate institutional ethics committees. Written informed consent was obtained from every patient before any study-specific procedure was performed.

Laboratory measurements

A venous blood sample was obtained after BIA measurements. Serum albumin levels were assessed by the 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 Elecsys® immunoassay (Roche, Rotkreuz, Switzerland). Plasma aldosterone levels were measured by the Aldosterone Maia radioimmunoassay (Adaltis, Rome, Italy). Plasma renin activity was determined using the GammaCoat® radioimmunoassay (DiaSorin, Saluggia, Italy). Plasma renin activity was determined using the GammaCoat® radioimmunoassay (DiaSorin, Saluggia, Italy). Plasma aldosterone levels were measured by the Aldosterone Maia radioimmunoassay (Adaltis, Rome, Italy).

Statistical analysis

Continuous variables are expressed as mean ± standard deviation when normally distributed and as median and interquartile range when not normally distributed and as median
Subclinical congestion in chronic heart failure

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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, 10 patients had no excess extracellular water, while 8 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) 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).

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, 10 patients had no excess extracellular water, while 8 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) 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).

Table 1. Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Euvolemic Patients</th>
<th>Subclinical Volume Overload</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 9</td>
<td>72 ± 10</td>
<td>0.016</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>114 ± 17</td>
<td>126 ± 20</td>
<td>0.012</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors (%)</td>
<td>33%</td>
<td>65%</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Statistical comparison in chronic heart failure

Fig 1. Study flowchart.

Screensed population

December 2014 – April 2015

(n=287)

Eligible population

(100)

Study population

(58)

Recognized volume overload (<3 months; n=42)

Medication change (<3 months; n=23)

Clinical signs of volume overload (n=8)

Bioelectrical impedance analysis not possible (n=3)

Daily diuretic dosing measurements (n=67)

Other (n=1)

Refused participation (n=182)
Table 1  Baseline characteristics of the study population (n = 58)

<table>
<thead>
<tr>
<th></th>
<th>Total study population (n = 58)</th>
<th>No excess extracellular volume (n = 24)</th>
<th>Subclinical volume overload (n = 34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 ± 10</td>
<td>65 ± 9</td>
<td>72 ± 10</td>
<td>0.016</td>
</tr>
<tr>
<td>Male gender</td>
<td>76%</td>
<td>79%</td>
<td>74%</td>
<td>0.759</td>
</tr>
<tr>
<td>White race</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>1.000</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 10</td>
<td>171 ± 8</td>
<td>167 ± 11</td>
<td>0.088</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 ± 15</td>
<td>86 ± 15</td>
<td>85 ± 16</td>
<td>0.889</td>
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<td>Body mass index (kg/m²)</td>
<td>30 ± 4</td>
<td>29 ± 4</td>
<td>31 ± 5</td>
<td>0.196</td>
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<tr>
<td><strong>Heart failure characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aetiology</td>
<td></td>
<td></td>
<td></td>
<td>0.099</td>
</tr>
<tr>
<td>Ischaemic</td>
<td>59%</td>
<td>50%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Dilated</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>7%</td>
<td>17%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Preserved ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since heart failure diagnosis (years)</td>
<td>3 (2-6)</td>
<td>3 (1-6)</td>
<td>4 (2-6)</td>
<td>0.430</td>
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<tr>
<td><strong>NYHA functional class</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.350</td>
</tr>
<tr>
<td>I</td>
<td>43%</td>
<td>38%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>48%</td>
<td>58%</td>
<td>41%</td>
<td></td>
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<tr>
<td>III</td>
<td>9%</td>
<td>4%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.726</td>
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<tr>
<td><strong>History and comorbid conditions</strong></td>
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<tr>
<td>Ischaemic heart disease</td>
<td>62%</td>
<td>58%</td>
<td>65%</td>
<td>0.784</td>
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<tr>
<td>Atrial fibrillation</td>
<td>52%</td>
<td>42%</td>
<td>59%</td>
<td>0.286</td>
</tr>
<tr>
<td>Aortic valve surgery</td>
<td>3%</td>
<td>8%</td>
<td>-</td>
<td>0.167</td>
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<tr>
<td>Mitral valve surgery</td>
<td>16%</td>
<td>17%</td>
<td>15%</td>
<td>1.000</td>
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<tr>
<td>Tricuspid valve surgery</td>
<td>10%</td>
<td>17%</td>
<td>6%</td>
<td>0.220</td>
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<tr>
<td>Diabetes</td>
<td>22%</td>
<td>21%</td>
<td>24%</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic kidney disease*</td>
<td>53%</td>
<td>63%</td>
<td>47%</td>
<td>0.420</td>
</tr>
<tr>
<td><strong>Vital parameters and clinical symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70 ± 10</td>
<td>67 ± 9</td>
<td>72 ± 10</td>
<td>0.055</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121 ± 19</td>
<td>114 ± 17</td>
<td>126 ± 20</td>
<td>0.012</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 ± 12</td>
<td>70 ± 12</td>
<td>76 ± 13</td>
<td>0.070</td>
</tr>
<tr>
<td>Visual analogue score for dyspnoea (/100)</td>
<td>34 ± 24</td>
<td>32 ± 28</td>
<td>36 ± 21</td>
<td>0.588</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>19%</td>
<td>17%</td>
<td>21%</td>
<td>1.000</td>
</tr>
<tr>
<td>Bendopnoea</td>
<td>41%</td>
<td>29%</td>
<td>50%</td>
<td>0.176</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnoea</td>
<td>9%</td>
<td>13%</td>
<td>6%</td>
<td>0.640</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance dose of loop diuretics (mg furosemide equivalents)</td>
<td>40 (20-40)</td>
<td>20 (20-40)</td>
<td>40 (20-40)</td>
<td>0.195</td>
</tr>
<tr>
<td>Renin-angiotensin system blocker</td>
<td>76%</td>
<td>67%</td>
<td>82%</td>
<td>0.218</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>52%</td>
<td>33%</td>
<td>65%</td>
<td>0.032</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>26%</td>
<td>33%</td>
<td>21%</td>
<td>0.364</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>88%</td>
<td>96%</td>
<td>82%</td>
<td>0.221</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>64%</td>
<td>71%</td>
<td>59%</td>
<td>0.366</td>
</tr>
<tr>
<td>Non-loop diuretic</td>
<td>17%</td>
<td>17%</td>
<td>18%</td>
<td>1.000</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12%</td>
<td>17%</td>
<td>9%</td>
<td>0.432</td>
</tr>
</tbody>
</table>

*Estimated glomerular filtration rate < 60 mL/min/1.73 m² according to the Chronic Kidney Disease Epidemiology Collaboration formula.
Subclinical congestion in chronic heart failure

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

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 group.

Bioelectrical impedance analysis

For a similar body weight (85 ± 16 versus 86 ± 15 kg, respectively; P-value = 0.204) and total body water (42.7 ± 8.3 versus 42.1 ± 8.4 L, respectively; P-value = 0.004), patients with versus without subclinical volume overload had more extracellular and less intracellular water. Figure 2 shows that bendopnoea, which was defined as dyspnea when bending forward (i.e., tie shoelaces) was the only characteristic that might have had some discriminative value although the result was not significant (P-value = 0.176).
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 neurohumoral activation was more pronounced in patients who had no excess extracellular water compared to patients with subclinical volume overload (Table 2).

Table 2: Bioelectrical impedance analysis results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total study population (n = 58)</th>
<th>No excess extracellular volume (n = 24)</th>
<th>Subclinical volume overload (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat (%)</td>
<td>34.3 ± 7.4</td>
<td>34.2 ± 5.9</td>
<td>34.5 ± 8.4</td>
<td>0.876</td>
</tr>
<tr>
<td>Lean mass (%)</td>
<td>65.7 ± 7.4</td>
<td>65.9 ± 5.9</td>
<td>65.6 ± 8.4</td>
<td>0.877</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>28 ± 7</td>
<td>29 ± 7</td>
<td>27 ± 7</td>
<td>0.324</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>42.5 ± 8.3</td>
<td>42.1 ± 8.4</td>
<td>42.7 ± 8.3</td>
<td>0.790</td>
</tr>
<tr>
<td>Intracellular water (%)</td>
<td>53.8 ± 1.8</td>
<td>55.0 ± 1.0</td>
<td>52.9 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extracellular water (%)</td>
<td>46.2 ± 2.5</td>
<td>45.0 ± 3.0</td>
<td>47.1 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interstitial fluid (L)</td>
<td>14.9 ± 3.1</td>
<td>14.3 ± 2.7</td>
<td>15.4 ± 3.2</td>
<td>0.161</td>
</tr>
<tr>
<td>Plasma (L)</td>
<td>3.5 ± 0.7</td>
<td>3.4 ± 0.6</td>
<td>3.5 ± 0.8</td>
<td>0.301</td>
</tr>
<tr>
<td>Excess extracellular water (L)</td>
<td>-1.43 (0.68-2.78)</td>
<td>N/A</td>
<td>N/A</td>
<td>0.478</td>
</tr>
</tbody>
</table>

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

**DISCUSSION**

This prospective cohort study of consecutive stable outpatients with CHF and no clinical signs of volume overload sheds 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 neurohumoral activation was more pronounced in patients who had no excess extracellular water compared to patients with subclinical volume overload (Table 2).
event-free survival in such patients can be unmasked by intensifying diuretic treatment.

In contrast, not many studies have used BIA to study subjects with CHF. Castillo-Martinez et al. have reported on BIA measurements from 168 CHF patients in New York Heart Association (NYHA) functional class I-II and 75 in class III-IV. Patients with more advanced NYHA functional class had significantly lower impedances, confirming the results of this study. Alternatively, the combination of weight increase and decreased body fat percentage on BIA indicates fluid accumulation and subclinical volume overload20,21. An additional advantage of using BIA measurements to monitor decongestion in severe patients presenting with decompensated heart failure is that it may be more difficult to assess volume status in elderly patients. Moreover, subclinical volume overload was more difficult to assess volume status in elderly patients. Moreover, subclinical volume overload was not consistently replicated these results and it remains unclear whether BIA measurements represent a suitable tool to monitor fluid balance in patients with subclinical volume overload, which hypothetically might suggest a subclinical volume overload.

In conclusion, our study population indicates that subclinical volume overload is an easily accessible, non-invasive, safe and inexpensive technology that is able to estimate total body fluid volume. BIA is an promising tool to facilitate the diagnosis of subclinical volume overload and subclinical heart failure. 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. Interestingly, our results indicate that excess extracellular water in case of subclinical volume overload predominantly resides in the extracellular compartment, while the plasma volume remains virtually unchanged. This has important implications on 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 cardiovascular compartment. BIA may therefore complement findings of the clinical exam or haemodynamic assessment. It remains unclear what the precise underlying mechanism of accumulation of subclinical volume overload may be in our population. It is certainly a non-invasive tool that is able to estimate total body fluid volume with high accuracy in minutes and therefore may be a suitable tool for monitoring subclinical volume overload.

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

<table>
<thead>
<tr>
<th>Neurohumoral Activation</th>
<th>Subclinical Volume Overload</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (µg/L/h)</td>
<td>11.55 (4.25-24.30)</td>
<td>18.5 (8.70-23.40)</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/L)</td>
<td>337 (219-509)</td>
<td>400 (306-717)</td>
</tr>
</tbody>
</table>

Subclinical congestion in chronic heart failure
In the early nutritional status has been linked to adverse clinical outcomes. Indeed, it is well known that mean 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 cell volume, and an increased risk of adverse outcomes. On the other hand, subclinical congestion may compensate depressor function and for the cause of proteinuria (indeed, important alterations in abdominal organ function are observed with congestion in CHF). Finally, severe albuminuria is an acute-phase reactant, which increases with inflammation and stress. Several studies have already suggested that low plasma albumin levels might explain the link between low serum albumin levels and subclinical volume overload.

STUDY LIMITATIONS

Some limitations should be considered when interpreting the results of this study. First, this was a non-randomized study with limited sample size, rendering its findings hypothesis-generating with the need of confirmation by larger studies. In particular, the sample size permitted limited power to compare differences between the two groups. Indeed, the difference in subclinical volume overload was not statistically significant. Another limitation is the inability to assess whether intensifying decongestive treatment in patients with 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.

CONCLUSION

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.

FUNDING

FV is supported by a PhD fellowship of the Research Foundation – Flanders (FWO, 11L8214N). The study was supported by funding from the Department of Internal Medicine, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital. None of the funding sources was involved in the study design, data collection, and interpretation of the data, reporting of the results to be the manuscript for publication.

CONFLICT OF INTEREST

None.
Subclinical congestion in chronic heart failure

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