Ultrasound indices of congestion in patients with acute heart failure according to body mass index

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Abstract

Background The inverse relationship between body mass index (BMI) and natriuretic peptide levels complicates the diagnosis of heart failure (HF) in obese patients. Assessment of congestion with ultrasound could facilitate HF diagnosis but it is unclear if any relationship exists amongst BMI, inferior vena cava (IVC) diameter and the number of B-lines.

Methods We performed a comprehensive echocardiographic evaluation within 24 h from hospital admission in patients with HF, including lung B-lines and IVC diameter, and studied their relationship with BMI and outcome.

Results 216 patients (median age 81 (77–86) years) were enrolled. Median number of B-lines was 31 (IQR 26–38), median IVC diameter was 23 (22–25) mm and median BNP 991 (727–1601) pg/mL. BMI was inversely correlated with B-lines ($r = -0.50$, $p < 0.001$), but not with IVC diameter ($r = -0.04$, $p = 0.58$). Compared to overweight patients (BMI 25–29.9 kg/ m^2; n = 100) or with a normal BMI (BMI < 25 kg/m^2; n = 59), obese patients (BMI ≥ 30 kg/m^2; n = 57) had lower B-lines [28 (24–33) vs 30 (26–35), and vs 38 (32–42), respectively; $p < 0.001$] but similar IVC diameter. During the first 60 days of follow-up, there were 53 primary events: 29 patients died and 24 had a HF-related hospitalisation. B-lines and IVC diameter were independently associated with an increased risk. However, B-lines were less likely to predict outcome in the subgroup of patients with a BMI ≥ 30 kg/m^2.

Conclusions Assessment of IVC diameter or B-lines in patients admitted with AHF identifies those at greater risk of death or HF readmission. However, assessment of B-lines might be influenced by BMI.

Introduction

Heart failure (HF) is a common and deadly disease, but its accurate diagnosis is a complex task. [1, 2] Current European Society of Cardiology-HF guidelines [3] highlight the diagnostic importance of clinical history and physical examination, electrocardiography, echocardiography and natriuretic peptides levels. Signs and symptoms, such as peripheral oedema or dyspnoea, are not specific for heart failure, and might be absent, or of mild intensity, even in patients who require a hospitalisation. [4-6] Echocardiography identifies left ventricular (LV) systolic dysfunction, impaired LV filling patterns, or valve disease, but many patients admitted with symptoms of heart failure have a high mortality risk and only mild echocardiographic abnormalities. [7] Nevertheless, the frequent lack of cardiologists and specialised sonographers in the emergency services often delays the diagnosis of HF. To overcome these limitations, guidelines recommend to measure natriuretic peptides plasma levels as initial diagnostic test to exclude HF. However, interpretation of natriuretic peptides levels requires significant experience because they might be influenced by several factors, including age, renal function or atrial fibrillation.

Lung ultrasound (LUS) has been proposed as an inexpensive and safe diagnostic tool that could assist physicians in the emergency department to distinguish between cardiogenic from non-cardiogenic dyspnoea [8]. Because air cannot be visualized by ultrasound, in a normal lung all structures below the pleura should look “dark” at LUS. However, when extra-vascular water replaces air in the lungs, ultrasound beams are not fully reflected backwards and might produce echogenic signals perpendicular to the pleura, which are called B-lines, or lung ‘comets’. [9] LUS could offer rapid and complementary information to physical examination and chest radiography during a fast track echocardiography. [7-9]

Although assessment of B-lines might improve diagnostic accuracy, its clinical relevance in obese or overweight patients has rarely been studied. Indeed, an elevated BMI represent a risk factor for development of HF. Obese individuals are more likely to develop symptoms or signs mimicking HF, due to decreased mobility, deconditioning, inefficient venous return, and sodium retention, but conducting an appropriate clinical examination or detailed echocardiography in patients with elevated BMIs might be difficult. Moreover, obesity is another factor associated with low levels of natriuretic peptides, which complicates the diagnostic process in these individuals. [10-12] Therefore, in this study, we aimed to clarify a potentially important clinical issue: the relationships amongst ultrasound signs of congestion (inferior vena cava (IVC) diameter and B-lines) with BMI in patients admitted with a diagnosis of acute heart failure (AHF).

Methods

Study Population

This is a post-hoc analysis of a prospective, single centre observational study conducted at S. Maria alle Scotte Hospital, Siena, in Italy. Between January 2014 and September 2018, we recruited 309 patients admitted who had a clinical diagnosis of new-onset or worsening heart failure, elevated B-type natriuretic peptide (BNP) levels (≥100 pg/mL), and required intravenous treatment with a loop diuretic. All patients gave their written informed consent to clinical and research procedures, and a local ethical committee (C.E.A.V.S.E.) approved the study. Within 24 hours from admission, all patients underwent comprehensive echocardiography, including IVC diameter and LUS. Height and body weight were also measured at admission, and BMI was calculated as weight (in Kg) divided by height^2 (in meters).

In the current analysis, we excluded 37 patients who had incomplete echocardiographic and clinical data, 44 who had a poor acoustic window, 11 patients lost to follow-up and 1 patient who died in hospital soon after signing the consent. [Figure 1 supplementary] Patients with advanced (II and III degree) atrio-ventricular block, those presenting with cardiogenic shock or those who had a recent myocardial infarction (within 30 days before hospital admission), pneumonia or pneumothorax at chest x-ray, cancer, dementia or immune diseases with systemic involvement were not recruited.

Laboratory Test

BNP assay (Biosite Inc., San Diego, CA, USA) was performed at admission to confirm a diagnosis of AHF. A blood sample was taken into sterile tubes containing ethylenediaminetetraacetic acid (EDTA). Patients with BNP values <100pg/mL were excluded**.**

Clinical assessment

Two physicians assessed patients for the presence of clinical signs of congestion (pulmonary rales, third heart sound, jugular venous distention, peripheral oedema and hepatomegaly) at admission, regardless of their severity.

Echocardiography and lung ultrasound

An echocardiogram was performed by two experienced cardiologists following the recommendations of the American Society of Echocardiography [13] within 24 hours of admission with a Vivid E95 (GE Health care). LUS was performed by the same operators just after echocardiography. With patients in a semi-recumbent position (45°), and using the same probe used for echocardiography, we scanned eight chest zones [14], and counted the number of B-lines in each zone to obtain the total B-lines count. For B-lines count, intra- and inter-observer variability were 5% and 7%, respectively. All echocardiograms and LUS were reviewed offline using an EchoPAC station (GE Health care).

Follow-up

The primary outcome was a composite of hospitalisations primarily due to, or complicated by, heart failure or all-cause mortality within 60 days after discharge. All patients received regular clinical appointments for six months after discharge, and were reviewed by different clinicians who provide the local HF service. Clinical information was obtained through information from patients or their relatives, face by face or by telephone calls, and review of hospital discharge letters. Hospital discharge letters were reviewed for emergency heart failure related hospitalisations lasting >24 hours, which included a primary diagnosis of heart failure or pump failure, acute coronary syndromes complicated by heart failure, ventricular arrhythmias associated with left ventricular dysfunction, or heart failure associated with worsening renal function.

Statistical analysis

Categorical data are presented as number and percentages; normally and non-normally distributed continuous variables as median and interquartile range (IQR). Patients with heart failure were divided according to BMI in those with normal BMI (<25 Kg/m^2), overweight (25≤BMI<30 Kg/m^2) and obese (BMI≥30 Kg/m^2).

Continuous variables were compared using Mann Whitney or Kruskal Wallis tests, and chi-squared test was used for categorical variables. Spearman rho's correlation coefficient was calculated to assess relations among variables. Two different multivariable Cox proportional hazard regression models were used to investigate the relationship between ultrasound signs of congestion and prognosis using a limited number of variables to prevent statistical overfitting. In Model A (Clinical Model) five candidate variables of interest (age, atrial fibrillation, respiratory rate, peripheral oedema, logBNP) were chosen prospectively in addition to ultrasound measurement of congestion, singly or in combination. For model B we selected the echocardiographic variables that were most strongly associated with prognosis in univariable analysis (highest χ^2) in addition to ultrasound measurements of congestion, age and logBNP.

We considered statistically significant results associated with a $p \leq 0.05$. We used the SPSS software (version 20.0) for all analysis.

Results

Patient characteristics (table 1)

216 patients (median age 81 [77-86] years) were included in this study; 133 had a reduced left ventricular ejection fraction (LVEF) < 50% (HFrEF) and 83 had a preserved (≥50%) LVEF (HFpEF). Median B-lines was 31 [26-38], median IVC diameter was 23 [22-25] mm, and median BNP 991 [727-1601] pg/mL. Compared to patients with normal BMI (<25 kg/m^2) those with higher BMIs had lower respiratory rate and a smaller left atrial area, but similar age and LVEF. Compared to patients with normal BMI (<25 kg/m^2) those with higher BMIs had lower BNP and B-lines, but similar clinical signs of congestion and IVC diameter [Table 1].

Compared to those with HFpEF, patients with HFrEF were more likely to have clinical signs of congestion; they also had higher BNP, lower BMI, but similar IVC diameter [23 (22-24) vs 22 (21-25), respectively, p=0.95) and number of B-lines [32 (27-38) vs 30 (25-36), respectively, p=0.07). (Supplementary table 1).

Relationship between clinical and ultrasound findings of congestion

Compared to patients in the lowest tertile of B-lines (≤27), those in the highest tertiles were more likely to have jugular vein distension or a third heart sound, but similar peripheral oedema or pulmonary rales (Table 2A). Patients in the highest B-lines tertile had more elevated levels of BNP and larger IVC diameter.

Patients in the lowest IVC tertile ($\leq$21 mm) had less clinical signs of congestion, lower BNP levels and reduced number of B- lines compared to those with larger IVC (Table 2B).

Overall, the number of B-lines, but not IVC diameter, was correlated with BMI and logBNP.
[Figure 1, Figure 2]

Outcome

During the first 60 days of follow up, there were 53 primary outcome events; 29 patients died and 24 had a heart failure related hospitalisation. In univariable analysis, apart from pulmonary rales, all clinical signs of congestion were associated with adverse outcome, whilst BMI was not, either as continuous or as a categorical variable. (Supplementary Table 2)

In multivariable analysis, adjusted for clinical variables, increasing IVC diameter, B-lines and respiratory rate, and atrial fibrillation, were independently associated with adverse outcomes (Table 3a). Increasing IVC diameter and B-lines, and decreasing TAPSE, were also independently associated with outcome in a model that included echocardiographic variables (Table 3b). However, the strength of association between ultrasound measures of congestion was affected by BMI: an increasing number of B-lines was not associated with poorer outcome in patients whose BMI was$\geq$30 kg/m^2, and only IVC diameter maintained relationship with an adverse outcome regardless of BMI. (Table 4).

Discussion

There are at least three relevant messages in our paper. Firstly, congestion is an important driver of morbidity and mortality in patients with heart failure, regardless of LVEF. Secondly, assessment of B-lines or IVC diameter by ultrasound provides independent prognostic information in patients admitted with AHF. Thirdly, we found an inverse relationship between BMI with both BNP and B-lines, but not IVC diameter, which has important clinical consequences.

Congestion is highly prevalent, but often clinically under-recognized and, therefore, undertreated, in patients with AHF, and is associated with an adverse outcome [15,16]. However, we extend these findings, and suggest that ultrasound patterns of congestion in patients admitted with HF could be different according to BMI profiles: whilst signs of systemic venous congestion are equally distributed amongst patients of different BMIs, patients with obesity have not only lower natriuretic peptides levels, but also a lower number of B-lines at LUS. [10] This is one of the first studies evaluating the relationship between B-lines and BMI in patients with AHF. In line with our finding, a recent paper by Brainin et al, also reported an inverse correlation existing between BMI and the number of B-lines at LUS in patients with acute or chronic HF. [17] Although a possible explanation might be that ultrasound detects pulmonary congestion with difficulty in patients with a large chest and significant fat deposition, other reasons might be possible.

The prevalence and incidence of obesity are both rapidly increasing worldwide. It is common for people with obesity to complain of dyspnea even during a gentle exercise, and obesity is associated with long-standing peripheral edema. Obesity causes sodium retention, an increase in intravascular volume and blood pressure and, a rise in the cardiac afterload, which might produce adverse cardiac remodeling, and contribute to heart failure development. [18] Accordingly, diagnosing heart failure in a dyspneic and/or edematous patient with obesity is very difficult. The identification of a severely depressed LVEF at imaging usually clarifies diagnosis and guides introduction, or adjustment, of life saving treatments. Nevertheless, in the presence of a normal or nearly normal LVEF at imaging, a non-substantial elevation of natriuretic peptides often reassures the clinician, but does not resolve this increasingly common clinical question: are symptoms and signs due to a large amount of fat in the body, heart failure, or possibly both?

Several studies demonstrated that assessment of B-lines might help to diagnose heart failure and identifies patients at greater risk, either in the ambulatory or acute setting. [19-26]. However, our findings suggest that BMI should be taken in consideration not only when interpreting natriuretic peptides, but also the number of B-lines, at least in patients with AHF. There are several reasons why natriuretic peptides, and B-lines, might be lower in patients with an elevated BMI compared to those with a normal BMI. Firstly, a higher than normal BMI is associated with a lower risk of mortality in patients with heart failure, suggesting a less severe disease.[10,27].Secondly, it might be also possible that obese patients with heart failure have different responses to treatments received for heart failure. For instance, in a post-hoc analysis of the DOSE trial, Gupta and colleagues found that patients with a BMI>30 kg/m^2 are more likely to have a greater volume loss with loop diuretics than people who are not obese. [28] Moreover, in patients with HFrEF, the use of mineralocorticoid antagonists might benefit more individuals who have significant abdominal obesity, perhaps because of the associated hyperaldosteronism. [29] Higher BMIs might be associated with greater secretion of neprilysin, an enzyme that degrades BNP and therefore contributes to decrease their circulating levels. [30]

It could be also possible that the acute administration of intravenous loop diuretics rapidly resolves pulmonary congestion, but has a lesser effects on IVC diameter. Because the increase BMI has been recently related with better prognosis, our data could explain the different risk of HF recurrence in obese patients that are probably less prone to develop pulmonary congestion compared to the other groups. [10,31] Another plausible explanation is related to the stricter association between obesity and HFpEF, compared to HFrEF. Indeed, pulmonary and systemic congestion appearance could be different in HFrEF and HFpEF. This depends on congestion severity and variety of congested systemic organs. A greater pathophysiological understanding of the different congestion features of the various AHF phenotypes is needed in order to identify targets for therapy and research. *[32]*

Finally, the specificity of B-lines for detection of AHF might be attenuated by pulmonary conditions frequently overlapped with a AHF diagnosis, such as pneumonia, not always clearly identifiable at a chest X-ray. Although we did a chest x ray prior to enrolment, and performed BNP testing, we cannot exclude that some of the patients enrolled had, concurrently, conditions such as pulmonary fibrosis or a chest infection. [33]

Similar to a previous study conducted in outpatients with heart failure, we did not find a correlation between IVC diameter and BMI. [34] Assessing IVC diameter might be a simple method to measure venous congestion, and to identify patients with a poorer short-term outcome, regardless of LVEF and body habitus. Accordingly, a better pathophysiological understanding of the diverse congestion features in relation to different BMI patterns is mandatory in order to identify targets for therapy and research in patients with AHF. [35]

Limitations

This is a single centre study with a relative small sample size but, to the best of our knowledge, this is also the largest study that comprehensively evaluated relationship of clinical, biochemical and ultrasonic signs of congestion with BMI and outcome in patients hospitalised for AHF. Although patients were prospectively recruited, the analysis plan was developed post-hoc, and only patients with complete clinical, echocardiographic and follow-up data were included.

As discussed, patients had received intravenous diuretics prior to enrolment, which might have affected cardiac haemodynamics and therefore our findings. Unfortunately, we did not record the time between the last dose of loop diuretics received by patients and ultrasound.

There is no consensus on how B-lines should be evaluated or quantified. We used a simplified 8-zone protocol, which has been shown to have good diagnostic accuracy and is more practical for clinical use in the emergency department, but findings might have been different if other protocols (ie: 28 chest zones) were used. [36,37]

In addition, physicians conducting clinical examination, echocardiography and LUS were not blinded to chest-x ray and BNP results. This might have introduced further bias. In addition, we did not recruit patients with BNP<100 pg/mL or with dyspnoea of non-cardiac origin, who might have acted as control group.

We only studied patients with AHF; more research is needed to study relationship between BMI, ultrasound signs of congestion and outcome, in different cohorts of patients with acute or chronic HF. Accordingly, we welcome other studies that might support or refute, and expand our findings..

Conclusions

Assessment of IVC diameter or B-lines in patients admitted with acute heart failure identifies those at greater risk of death or HF readmission. However, as for BNP plasma levels, the number of B-lines might be influenced by BMI. Future studies will clarify relationship between BMI and B-lines, and inform whether measuring IVC diameter might be more appropriate to evaluate congestion in patients with AHF.

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Authors' contribution: AP, GR and PP designed the study, interpreted data and drafted the manuscript; AP, GR, BF, IE, BL and RN collected and interpreted the data. GR analysed the data. All authors critically revised and approved the final version of the manuscript.

Ethics approval: The local ethical committee (C.E.A.V.S.E.) approved the study.

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Consent for publication: The local ethical committee and all patients gave their written consent to publish the study.

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Legend to figures

Figure 1. Correlations between B-lines (left) and inferior vena cava (IVC) diameter (right) with body mass index (BMI) amongst patients with heart failure with reduced (HFrEF, in red) or preserved (HFpEF, in blue) left ventricular ejection fraction.

Figure 2. Correlations between B-lines (left) and inferior vena cava (IVC) diameter (right) with logBNP amongst patients heart failure and normal body mass index (BMI≤25 Kg/m^{2,} in red), overweight (25<BMI<30 Kg/m^{2,} in blue) and obese (BMI≥30 Kg/m^{2,} in green).

Figure 1 supplementary: consort diagram showing the number of patients consented, excluded and included in the current analysis.