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## **Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure**

Short title:- Congestion by ultrasound in Heart Failure

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\*~Pierpaolo Pellicori MD, FESC, \*Parin Shah, \*Joe Cuthbert, \*Alessia Urbinati MD,

\*@Jufen Zhang, PhD, \*Anna Kallvikbacka-Bennett BA, \*Andrew L Clark MA, MD,

FRCP, ~#John GF Cleland MD, FRCP, FESC, FACC.

\*Department of Cardiology, Castle Hill Hospital, Hull York Medical School (at University of Hull), Kingston upon Hull, HU16 5JQ, UK

#National Heart & Lung Institute and National Institute of Health Research Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals, Imperial College, London

~Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow, G12 8QQ.

@Faculty of Medical Science, Anglia Ruskin University, Chelmsford, UK

Corresponding author: Dr Pierpaolo Pellicori

Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow, G12 8QQ, UK.

Tel: +44 0 141 330 4744; Fax: +44 0 141 330 5094

Email: [pierpaolo.pellicori@glasgow.ac.uk](mailto:pierpaolo.pellicori@glasgow.ac.uk)

## **Abstract**

**Aims and methods:** Even if treatment controls symptoms, patients with heart failure may still be congested. We recorded clinical and ultrasound (lung B-lines; inferior vena cava (IVC) diameter; internal jugular vein diameter before and after Valsalva (JVD ratio)) features of congestion in patients with heart failure during a routine check-up to assess their prevalence, relationships and prognostic significance.

**Results:** Of 342 patients, predominantly in NYHA I or II (257; 75%), who attended, 242 (71%) had at least one feature of congestion, either clinical (139; 41%) or by ultrasound (199; 58%). Amongst patients (n=203, 59%) clinically free of congestion, 31 (15%) had  $\geq 14$  B-lines, 57 (29%) had a dilated IVC ( $> 2.0$  cm), 38 (20%) had an abnormal JVD ratio ( $< 4$ ), 87 (43%) had at least one of these and 27 (13%) had two or more.

During a median follow-up of 234 (IQR: 136-351) days, 60 patients (18%) died or were hospitalized for heart failure. In univariable analysis, each clinical and ultrasound measure of congestion was associated with increased risk but, in multivariable models, only higher NT-proBNP and IVC, and lower JVD ratio, were associated with the composite outcome.

**Conclusions:** Many patients with chronic heart failure with few symptoms have objective evidence of congestion and this is associated with an adverse prognosis. Whether using these measures of congestion to guide management improves outcomes requires investigation.

**Key words:** lung ultrasound, congestion, B-lines, IVC, jugular vein ultrasound.

## **Introduction**

Congestion is a common cause of hospitalization for patients with heart failure (1). Poorly controlled congestion may also lead to unfavourable atrial and ventricular remodelling, clinical progression of disease, recurrent admissions, and an increase in mortality (2-5).

Accurately quantifying congestion is difficult (6), and may commonly be missed unless it is obvious (7-9). Also, some clinical features of congestion are not specific for cardiac dysfunction and may occur with many other conditions, including nephrotic syndrome, liver or thyroid disease, or venous insufficiency, or as a side-effect of commonly prescribed drugs to treat hypertension, such as calcium channel blockers, or diabetes, such as glitazones.

Congestion can only be managed appropriately if it is recognised (10). Detection of congestion before it becomes clinically overt in patients with heart failure should lead to better management, particularly with respect to diuretic dose (11, 12). However, many apparently stable out-patients with heart failure without clinical evidence of congestion might have sub-clinical congestion detected by biomarkers, ultrasound or other non-invasive techniques.

We therefore investigated the prevalence and clinical relevance of congestion in out-patients with chronic heart failure (CHF) attending a routine follow-up clinic using ultrasound to detect, contemporaneously, pulmonary interstitial oedema (lung B-lines) and intra-vascular fluid overload (inferior vena cava (IVC) diameter, and the internal jugular vein diameter before and after a Valsalva manoeuvre (JVD ratio) (13-18).

## **Methods**

### *Study Population*

Between April 2016 and March 2017, we enrolled consecutive patients with a prior clinical diagnosis of heart failure attending a routine follow-up visit to a heart failure clinic serving a local population of about 550,000 people. In our clinic, stable out-patients on optimal treatment are reviewed by heart failure specialist nurses and doctors at regular intervals, usually every 12 months, unless an appointment is requested sooner by the patient, physician or specialist nurse. All subjects gave their written informed consent. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies.

Patients provided a detailed clinical history and had blood tests (including haematology, biochemistry profile and NT-proBNP), ECGs and echocardiograms done on the same day. The information was systematically recorded in a dedicated electronic health record stored on a secure NHS server. Treating clinicians had access to the entire echocardiographic exam performed prior to the visit, including B-lines, IVC and JVD examination; however, they were blinded to blood results, including NT-proBNP.

The minimum follow-up period was three months. The primary outcome of interest was a composite of all-cause mortality or HF hospitalization. Our hospital is the only one in the region offering acute medical services. With consent obtained from patients, we have access to both primary and secondary care records. Data regarding deaths and hospitalisations were collected from the hospital's electronic systems, supplemented by information from discharge letters, patients, and their family doctors. For the purpose of this study, a hospitalisation was

considered due to heart failure only if HF was mentioned as primary diagnosis on the discharge letter by the discharging physician from our hospital.

### *Clinical assessment*

Clinical examinations were performed before echocardiography. A clinical congestion score was applied, based on lung auscultation (normal, presence of basal, mid zone or diffuse crackles), JVP (not visible, raised 1-4 cm, raised to earlobe), and peripheral oedema (none, ankles, below or above knees) with one point attributed for each degree of severity. When the total score was 0, patients were considered clinically uncongested; those scoring  $\geq 3$  were defined as severely congested (4).

### *Echocardiographic measurements*

Echocardiography was performed by an experienced operator (AB) using a Vivid Seven (GE Health care, UK) system operating at 1.7-3.4MHz. Doppler tracings and two-dimensional images were obtained from parasternal long- and short-axis, apical and subcostal views. Echocardiograms were stored and reviewed by an experienced operator (PP) using an EchoPAC station (GE Health care, UK). LVEF was measured using Simpson's biplane method. LA volume was measured in the four chamber view and indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was used to assess right ventricular (RV) systolic function. The maximum trans-tricuspid systolic gradient was also measured (based on the modified Bernoulli equation,  $\Delta P = \text{Max TR velocity}^2 \times 4$ ). With the patient in the supine position, the maximum inferior vena cava (IVC) diameter during the respiratory cycle was measured between one and three centimeters before merger with the right atrium. The IVC collapse following deep inspiration (a brief sniff) was visually

estimated as  $\geq 50$  or  $< 50$  %. Intrahepatic veins were recorded as visible, and their maximum diameter during the cardiac cycle was measured, or not visible.

### *Jugular Vein ultrasound*

With the patient semi-recumbent at  $45^\circ$ , jugular venous (JV) ultrasound was performed as previously described (19). Briefly, with the patient reclining and head and neck elevated at  $45^\circ$ , a linear high frequency probe (10 MHz) was placed on the left side of the neck below the angle of the jaw and moved inferiorly toward the angle of Louis until the left internal JV was identified. Internal JV diameter and its changes were then measured continuously by M-mode or in the 2-dimensional frame at rest (expiratory phase), during a Valsalva manoeuvre (performed by forceful expiration against a closed glottis) and, finally, during deep inspiration. The ratio between maximum JV diameter during Valsalva and diameter at rest was calculated (JVD ratio).

### *B-lines*

B-lines, or lung comets, are echogenic, perpendicular signals arising from the pleura during lung ultrasound, often indicating the presence of extravascular lung water (20, 21). Although different methods to assess them have been proposed, we scanned a total of 28 chest sites (from the second to the fifth intercostal space on the right hemithorax, and from the second to the fourth intercostal space on the left hemithorax along the parasternal, mid-clavicular, anterior axillary and mid-axillary lines (22)) and counted the number of B-lines found at each site. All patients were analysed in a near-supine position with the same probe used for echocardiography. B-lines were recorded for at least 5 beats for each chest site, and images were subsequently stored and reviewed off-line by an experienced operator (PP).

We defined congestion by ultrasound as an abnormal JVD ratio ( $<4$ ), a distended IVC ( $>20$  mm) or B-lines above or equal to the lower boundary of the highest tercile ( $\geq 14$ ).

## Statistical methods

Categorical data are presented as number and percentages; normally distributed continuous data as mean  $\pm$  SD and non-normally distributed continuous variables as median and interquartile range (IQR). We present the ultrasound variables as median and IQR to demonstrate the distribution of each variable within the studied population.

Patients with HF were grouped by phenotypes (heart failure with reduced (HF<sub>r</sub>EF, LVEF $<40\%$ ), mid-range (HF<sub>mr</sub>EF, LVEF 40-49%), or preserved (HF<sub>p</sub>EF, LVEF $\geq 50\%$ ) LVEF) or by terciles of B-lines, IVC and JVD ratio or NT-proBNP. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

*Analysis 1.* Two different multivariable Cox proportional hazard regression models were used to investigate the relationship between JVD ratio, IVC and B-lines, and prognosis using a limited number of variables to prevent statistical overfitting. In Model A (Clinical Model) five candidate variables of interest (age, NYHA class III vs I/II, urea, haemoglobin and log [NT-proBNP]) were chosen prospectively in addition to each ultrasound measurement of congestion. For model B (Echocardiographic Model), the three echocardiographic variables that were most strongly associated with prognosis in univariable analysis (highest  $\chi^2$ ) were included in addition to each ultrasound measurement of congestion, age and Log [NT-proBNP].

Forward and backward procedures were used to determine which variables independently predicted the primary composite outcome. Assumptions of the models were tested, such as multicollinearity and proportional hazards.

*Analysis 2 (Discrimination and reclassification improvement analysis).* In order to estimate the predictive value of the different variables of interest, we constructed a basic a priori model, which included variables of clinical interest that are easily available in a heart failure clinic (age, sex, NYHA (III vs II/I), creatinine, haemoglobin and LVEF) and then tested the added value of each measure (and combinations of measures) of congestion, in turn. The variables of interest added to the basic model were: log[NT-proBNP]; and/or ultrasound measurements of congestion (either IVC diameter, JVD ratio or B-lines). The incremental value of the variables (the model's cumulative discrimination) was measured using Harrell's C statistic: the mean values of IVC diameter, JVD ratio and logNT-proBNP were used to impute missing values. The higher discriminative value associated with the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) for ultrasound measurements of congestion were assessed at 1 year of follow-up.

Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

All analyses were performed using SPSS and Stata software. A 2-sided P value < 0.05 was considered statistically significant.

## **Results**

### **Patient characteristics (n=342, table 1)**



Median age (inter-quartile range [IQR]) was 75 [68-82] years, and median plasma NT-proBNP was 1275 [461-2659] ng/L. Mean LVEF was 45 ( $\pm 14$ ) %. LVEF was <40% in 124 patients, 40-49% in 68 patients (39 previously had LVEF <40%) and 150 had LVEF  $\geq 50\%$  (45 previously had LVEF <40%). Approximately 85% of patients were treated with beta-blockers and ACE-inhibitors and 75% were taking loop diuretics.

Some evidence of clinical congestion was similarly common amongst the three heart failure phenotypes (36-44%), although patients with HF<sub>r</sub>EF were more likely to be treated with a loop diuretic and mineralocorticoid antagonist than those with HF<sub>m</sub>rEF or HF<sub>p</sub>EF. There was no difference in the number of patients amongst the phenotypes who had their diuretics increased or decreased at the clinical visit. There was no difference between the phenotypes in ultrasound measures of congestion (Table 1).

### **Clinical vs ultrasound congestion**

It was possible to measure B-lines in all patients, whilst the IVC was not visualised in 7 (2%). Due to a technical problem (the 10 MHz linear probe needed repair) it was not possible to assess JVD ratio in 23 patients (7%).

Congestion by ultrasound was more common, and more severe, with increasing severity of clinical congestion (Table 1 supplementary). When clinical congestion was severe, B-lines were almost ubiquitous, IVC was dilated in around 90% of cases, and JVD ratio was abnormal in >80% patients. However, of the 187 patients with complete ultrasound data who had no clinical sign of congestion, 87 (47%) had at least 1 sign of congestion on ultrasound, with 10 (5%) having all three ultrasonic signs of congestion (figure 1).

Correlations amongst ultrasound measures of congestion were generally modest. Correlations between ultrasound measures of congestion and age, haemoglobin, left atrial volume,

estimated PA pressure and NT-proBNP were also modest. Ultrasound measures of congestion were poorly correlated with LVEF. There was an inverse correlation between body mass index (BMI) and B-lines, but not with JVD ratio or IVC diameter (table 2 and table 2a-d and 3 supplementary).

Compared to patients in sinus rhythm, those in atrial fibrillation had more severe congestion by ultrasound (table 3 supplementary).

## **Outcome**

There were 60 primary outcome events during a median follow-up of 234 (IQR: 136-351) days. The first qualifying event was hospitalisation due to worsening HF in 35 patients and death in 25 patients.

*Analysis 1.* In univariable Cox regression analysis, worsening clinical congestion and increasing B-lines were associated with an increased risk of events (Table 4 supplementary and Figure 2). In multivariable analysis, increasing log [NT-proBNP] and IVC diameter, or decreasing JVD ratio (with increasing urea) were the only variables independently related to an adverse outcome in both Model A (Table 3a) and Model B (Table 3b).

### *Analysis 2. Discrimination and reclassification improvement analysis*

For the entire cohort of patients, the baseline clinical model yielded a c-index 0.74, which did not increase significantly when logNT-proBNP or ultrasound measures of congestion were added singly or in combination. In contrast, adding any of logNT-proBNP or ultrasound measures of congestion improved prediction of outcome at 1 year and increased IDI and NRI. Adding JVD ratio to a model that included logNTproBNP further improved re-classification

by IDI only. The greatest improvement by IDI was when B-lines and JVD ratio were simultaneously added (Table 4).

Patients who were simultaneously in the top tercile of NT-proBNP ( $\geq 2045$  ng/L) and the highest terciles of B-lines, JVD ratio or IVC diameter had the worst outcomes (Figure 3).

## **Discussion**

This analysis confirms previous reports suggesting that increasing IVC diameter (17, 18) or number of B-lines by ultrasound (13-15) identify patients with CHF who have higher plasma concentrations of NT-proBNP and a greater risk of an adverse outcome, regardless of their LVEF. We also confirm the clinical and prognostic utility of a novel ultrasonic method to assess fluid overload; the JVD ratio (16, 23). However, probably the most important finding was that nearly 50% of ambulatory patients with CHF thought not to be congested had evidence of congestion on ultrasound and that when multiple such measures are present the prognosis is poor.

In the current era, practising evidence-based medicine should be the norm; however management of clinical congestion, and the use of diuretics in patients with heart failure, is still an inexact medical art. For patients hospitalized with cardiac decompensation, some clinical algorithms for the evaluation and assessment of congestion have been proposed, but they are constructed on subjective variables, such as symptoms and signs, and obviously open to bias (24, 25). For patients with CHF, recommendations to detect, monitor and treat congestion during follow-up are rather vague, and will vary according to local organisation and resources (26).

NT-proBNP is a consistently strong prognostic marker for patients with stable CHF, although its prognostic utility in the acute setting is more doubtful (27, 28) and values may be affected by comorbidities, such as atrial fibrillation and renal dysfunction. Several randomized clinical trials have assessed whether serial measurements of plasma natriuretic peptide concentrations might be used to guide treatment for HF; their results are controversial, perhaps because guideline-recommended treatment is effective and perhaps because trials of a natriuretic peptide-guided strategy have not lead to substantial differences in therapy between randomised groups (29-30). Natriuretic peptides are a measure of congestion rather than of cardiac dysfunction or its cause, which is both their strength and weakness; their strength because congestion is strongly related to prognosis; their weakness because congestion may be renal or cardiac in origin to varying degrees and because it is important to know the cause of heart failure in order to decide on treatment. It is also possible that renal dysfunction leads to reduced clearance of NT-proBNP and an increase in plasma concentration unrelated to congestion, although it is likely that reduced renal clearance of NT-proBNP is associated with diuretic resistance and reduced salt and water excretion. However, ultrasound can determine the presence of congestion and quantify similarly in the presence or absence of renal dysfunction. Clearly, a measurement of renal function is important to determine both the reason for an elevated NT-proBNP and the cause of congestion. Whether a strategy starting with measuring NT-proBNP and urea/creatinine first followed by ultrasound evaluation when results indicate congestion; or whether ultrasound could supplant natriuretic peptides is worthy of investigation. In a primary-care setting, blood markers are likely to be the preferred strategy for the evaluation of congestion. However, in a cardiology clinic where echocardiography is readily available, obtaining an instantaneously available measurement of congestion along with the opportunity to gather information on valve and ventricular function, ultrasonic evaluation might be favoured.

Absence of congestion on ultrasound might be a measure of treatment success associated with an excellent outcome and might also help avoid over-treatment especially for patients who have other reasons for their breathlessness such as chronic obstructive pulmonary disease. On the other hand, persistence of sub-clinical congestion might be a measure of inadequate treatment. Quantifying congestion by ultrasound might also provide an objective measure of response to novel treatments, help guide the intensity of diuretic use, facilitate personalised therapy tailored to the individual patient's needs and decide on the frequency of follow-up appointments or determining when it might be appropriate to reassure patients and discharge them back to primary care. The increasing availability of hand-held, low-cost ultrasound devices and the demonstration that skills can be rapidly taught to people with little or no prior experience increases the feasibility of this approach (31).

## **Limitations**

In our cohort, agreement amongst different methods for assessing congestion by ultrasound was modest when clinical congestion was absent, but increased as clinical congestion became more evident. This might be because the cut-offs used to define “congestion by ultrasound” were not optimal, or it might be because congestion is heterogeneous amongst different organs and compartments. Some patient characteristics, such as a high BMI, might decrease the number of identifiable lung comets, perhaps reflecting less advanced disease (32) or a technical obstruction to their visualisation (14). High BMI or non-uniform body anatomy could affect IVC assessment, or the visualization of intra-hepatic veins.

This was a single centre study of consecutive patients previously diagnosed with HF, regardless of their LVEF. In the absence of a general consensus on how to diagnose HFpEF, it might be possible that our population of patients with HFpEF differs from those from other centres.

There is no recommendation that HF treatment should be guided by signs of congestion on ultrasound, and not all physicians can interpret B-lines, or JVD ratio; however, it is still possible that evidence of congestion on ultrasound might have led to adjustments in treatment in a few patients, and particularly to an increase in diuretic dose. This might have affected our final results. None of our patients had received novel treatments such as sacubitril/valsartan prior to follow-up. Compared to ACE-I, sacubitril/valsartan might decrease NT-proBNP (33).

The number of patients enrolled, and events recorded, are modest: more studies will be needed to clarify whether measuring the upstream consequences of a dysfunctional right ventricle (reduced JVD ratio or dilated IVC diameter) provides more powerful prognostic information than measuring the upstream consequences of a dysfunctional left ventricle (greater number of B-lines). Similarly, more work is needed to see whether these novel ultrasound methods might be used to identify different phenotypes of patients with heart failure, who need different therapies.

However, to the best of our knowledge this is the largest prospective study evaluating B-lines in out-patients with HF (13), also coupled with a detailed and comprehensive clinical, ultrasound and biomarker evaluation of congestion.

B-lines are not specific evidence of lung congestion and may also reflect parenchymal lung disease. We enrolled patients whether or not they had co-morbid lung disease. This might have increased the number of B-lines measured in some patients. We also assessed B-lines in the near-supine position, exploring 28 antero-lateral chest zones, using clips recording 5 heart beats only: the number of B-lines may vary with gravity and postural changes, and might increase with longer evaluations (34). Findings might have been different if other protocols (ie, the 8 antero-lateral chest sites) were used.

We did not study the prevalence of congestion by ultrasound in a control group. It is likely that some people without other evidence of heart or lung disease will have an abnormal number of B-lines, or dilated IVC (35).

## **Conclusions**

Many patients with heart failure free of clinically overt congestion remain sub-clinically congested; these patients have a worse prognosis. Further research to determine whether management guided by ultrasonic measures of congestion improves outcome is warranted.

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## Legend to figures

**Figure 1:** Of the 187 patients with complete ultrasound data who had no clinical sign of congestion, 87 (47%) had at least 1 sign of congestion on ultrasound (a dilated inferior vena cava (IVC), greater than 20 mm, an abnormal JVD ratio (lower than 4), or B-lines greater or equal to the lower boundary of the highest tercile (14)). 10 (5%) patients had all three ultrasonic signs of congestion and the highest levels of NT-proBNP.

**Figure 2.** Multi-panel KM for primary outcome of death from all causes (ACM) and heart failure hospitalizations (HFH) for each echocardiographic marker of congestion by tercile: IVC diameter (top-right; Tercile 1: $\leq 1.7$  cm, Tercile 2: 1.8-2.2 cm, Tercile 3 $> 2.2$  cm), JVD ratio (mid-left: Tercile 1: $\geq 6.6$ , Tercile 2: 4.0-6.5, Tercile 3 $< 4$ ), intrahepatic vein diameter (mid-right; Tercile 1: $\leq 0.5$  cm, Tercile 2: 0.6-0.8 cm, Tercile 3 $> 0.8$  cm) and B-lines (bottom-centre; Tercile 1: $\leq 3$  B-lines, Tercile 2: 4-13 B-lines, Tercile 3 $\geq 14$  B-lines). Also, KM curve for IVC collapsibility (above or below 50%) and outcome are shown (top-left).

**Figure 3.** Multi-panel KM for primary outcome of death from all causes (ACM) and heart failure hospitalizations (HFH) showing additive value of measuring congestion by ultrasound in patients in the highest NT-proBNP tercile ( $\geq 2045$  ng/L).