The prevalence and clinical associations of ultrasound measures of congestion in patients at risk of developing heart failure.

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Abstract

Aims: Congestion is a cardinal feature of untreated heart failure (HF) and might be detected by ultrasound (US) before overt clinical signs appear.

Methods and Results: We investigated the prevalence and clinical associations of subclinical congestion in 238 patients with at least one clinical risk factor for HF (diabetes, ischaemic heart disease or hypertension) using three US variables: 1) inferior vena cava (IVC) diameter; 2) jugular vein distensibility (JVD) ratio (the ratio of the jugular vein diameter during Valsalva to that at rest); 3) the number of B-lines from a 28-point lung US. US congestion was defined as IVC diameter >2.0 cm, JVD ratio <4.0 or B-lines count >14. The prevalence of subclinical congestion (defined as at least one positive US marker of congestion) was 30% (13% by IVC diameter, 9% by JVD ratio and 13% by B-line quantification). Compared to patients with no congestion on US, those with at least one marker had larger left atria and higher plasma concentrations of natriuretic peptide (NP). Patients with raised plasma NT-proBNP/BNP had a lower JVD ratio (7.69 vs. 8.80; P=0.05) and more often had at least one lung B-line (74% vs. 63%; P=0.05). However, plasma NP concentrations were more closely related to left atrial volume than other US measures of congestion.

Conclusions: Subclinical evidence of congestion by ultrasound is common in patients with clinical risk factors for heart failure. Whether these measurements provide additional value for predicting the development of HF and its prevention deserves consideration.

Key words: IVC, jugular vein, lung ultrasound, heart failure risk, congestion, b-lines.

Introduction

Signs of venous congestion, such as peripheral oedema, are common in patients with heart failure,[1] but are late manifestations of disease.[2] Raised venous pressure may be detected by ultrasound, either by measuring surrogates of intravascular pressure (inferior vena cava (IVC) or jugular vein (JV) diameter) or pulmonary interstitial oedema (as assessed by B-lines)).[3] A substantial proportion of patients without symptoms or signs of congestion may still have evidence of congestion on ultrasound (subclinical congestion).[4]

The CHAMPION study found that increasing the dose of diuretics in patients with heart failure in response to increasing pulmonary artery pressure reduces the risk of hospitalisation for heart failure,[5] which is usually caused by congestion.[6] Subclinical congestion will usually precede the onset of clinically overt heart failure; this prodromal phase of heart failure might exist for many years before the gradual onset of symptoms and signs becomes sufficiently severe to cause a diagnosis. Alternatively, an event, such as an arrhythmia, myocardial ischaemia or infection, may trigger the abrupt onset of heart failure in patients who have long-standing subclinical congestion. It is a sad indictment of current healthcare that the diagnosis of heart failure is often made only after the symptoms and signs are so severe that the patient needs to be admitted to hospital. The opportunity for prevention in the potentially long prodromal phase of subclinical congestion is substantial.

Approximately 30% of patients with established, or at high risk of, cardiovascular (CV) disease have raised plasma concentrations of natriuretic peptide, [7,8] which are associated with an increased risk of incident heart failure.[9] However, the prevalence of ultrasound features of subclinical congestion in this population is unknown, which we now describe.

Methods

Patient population

We invited patients who consented to screening at two centres participating in the Heart OMics in AGEing (HOMAGE) randomised trial between September 2016 and June 2018 to participate in an additional observational study. HOMAGE was an open label, randomised, multi-centre clinical trial studying the effects of spironolactone versus standard care on biomarkers of fibrosis in patients at risk of developing heart failure (NCT02556450),[10] which included one or more of: diabetes, hypertension, a previous myocardial infarction or coronary artery revascularization. Patients with a clinical suspicion of heart failure (including peripheral oedema) or atrial fibrillation, those treated with loop diuretics or with grossly elevated plasma NP (BNP>280 ng/L or NTproBNP >1000 ng/L) or left ventricular ejection fraction (LVEF) ≤45 % were excluded.

The study conforms to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. Patients signed written consent prior to any investigations. Data on medical history, blood results (full blood count, biochemistry and NTproBNP (in Hull) or BNP (in Glasgow)), electrocardiograms (ECG), and echocardiograms were collected on the same day and stored on secure National Health Service servers.

Natriuretic Peptides

Blood samples were taken and sent to the local NHS laboratory according to routine clinical practice. NT-proBNP was measured using the Roche and BNP using the Abbott assay. Patients were classified by NTproBNP and BNP cut-offs derived from the most recent ESC heart failure guidelines (BNP Group 1 (“normal”) – NTproBNP <125 ng/L or BNP <35 ng/L

and BNP Group 2 ("raised") – NTproBNP 125 - 1000 ng/L or BNP 35-280 ng/L). Correlations between NP and clinical and echocardiographic variables were done separately for NT-proBNP (n = 195) and BNP (n = 43) and for the overall population (n = 238) by multiplying BNP by 3.5 (as used by heart failure guidelines)[1] – "normalised BNP".

Echocardiographic measurements

Echocardiography was performed using a Vivid 7 (GE Health care, UK) system operating at 1.7-3.4MHz in Hull, and an ACUSON SC2000 system operating at 1.5-3.5 MHz (Siemens, UK) in Glasgow. Echocardiograms were performed by JJC and AKB (Hull) and by PP (Glasgow), and JVD assessment and lung ultrasound was performed by JJC (Hull) and PP (Glasgow). All images were stored and reviewed off-line by the same operator in Hull (JJC) and Glasgow (PP) both of whom had substantial experience in echocardiography, and in the comprehensive assessment of congestion by ultrasound.[4] PP is accredited by the British Society of Echocardiography and had oversight of echocardiographic, JVD assessment, and lung ultrasound data collection at both sites.

Assessment of left ventricular systolic and diastolic function

LVEF was measured by modified Simpson's biplane method. Diastolic function and cardiac filling pressures were assessed by five different variables recommended by current European Society of Cardiology (ESC) heart failure guidelines to diagnose left ventricular diastolic dysfunction: 1) left atrial volume index (LAVI) >34 ml/m^2; 2) left ventricular mass index (LVMI) >115 g/m^2 for men and >95 g/$m^2$for women; 3) E:A <1; 4) E' mean <0.09 m/s measured with tissue Doppler imaging and 5) E/e' >13.[1]

Assessment of congestion by ultrasound

Inferior vena cava measurements

Inferior vena cava (IVC) diameter increases with right atrial pressure (RAP).[11] Maximum IVC diameter was measured ~2 cm before it merged with the right atrium in the supine position from the subcostal view.

Jugular vein measurements

We measured the jugular vein diameter as described previously.[12] With the patient semi-recumbent at 45°, we placed a linear high frequency probe (10 MHz) below the angle of the jaw on the left side of the neck and moved downwards toward the angle of Louis until the left internal jugular vein was identified. Jugular vein diameter at rest and during Valsalva (forced expiration against a closed glottis) were measured using 2-D or M-mode echocardiography. The ratio between the diameter during Valsalva and that at rest was calculated as the jugular vein distensibility (JVD) ratio.

Lung ultrasound

B-lines are vertical artefacts seen on ultrasound originating from the visceral pleura due to an impedance mismatch caused by increased density in the lung parenchyma – such as fluid within aerated lung.[3,13]. We scanned 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 to give a total of

28 sites. We counted the number of B-lines in each window. All patients were assessed whilst lying at 45 degrees and each window was recorded for 3-5 seconds.

Definition of subclinical congestion

A patient was considered to have subclinical congestion by ultrasound if they met one or more of the following criteria: IVC diameter >2.0 cm, JVD ratio <4, or lung B-line count >14.[4]

Statistical analysis

Categorical data are presented as number and percentages and continuous data are presented as median and quartiles.

Chi-squared or Fisher's exact tests were used to compare categorical variables, unpaired t test were used to compared normally distributed variables, and Mann-Whitney U tests were used to compare continuous variables that were not normally distributed. The relation between ultrasound markers of congestion (IVC diameter, JVD ratio and number of B-lines) as continuous variables and other variables was assessed using Pearson correlation coefficients , and uni- and multivariable binary logistic regressions. Log transformed NTproBNP, log transformed BNP, and log transformed normalised BNP were used.

Results

Patient characteristics by BNP Group

Of 253 patients screened; 15 had clinical evidence of heart failure and were excluded from the analysis (figure 1). Amongst the remaining 238, the median age was 72 years, 77% were men, 94% had ischaemic heart disease and 51% had a history of myocardial infarction (MI) (table 1). Overall, 73% of patients had elevated NP levels (NTproBNP 125 - 1000 ng/L or BNP 35-280 ng/L) and were older, more likely to be prescribed a beta-blocker and had a lower haemoglobin than patients with an NP in the normal range (Group 1) (table 1). Differences between the Glasgow and Hull cohort are presented in supplementary table 1.

Patient characteristics by echocardiography

Compared to patients with a normal NP, patients with an elevated NP had substantially larger LA volumes and slightly higher E and E:e' (Table 2). Amongst patients with an elevated NP, there was no difference in IVC diameter or the median number of B-lines, but JVD ratio was lower and the percentage with lung B-lines greater.

Of 214 patients with complete data for all three congestion markers, 70% were free from subclinical congestion by ultrasound, 25% had one marker and 5% had two markers of congestion, but no patient had all 3 markers (figure 2). Left atrial diameter and volume were greater, and plasma NP concentrations higher in patients with one or more marker of congestion compared to those who had none (table 2) (supplementary figure 1). 92% of patients with left atrial dilation and 75% of those with congestion on ultrasound had elevated plasma NP concentrations (figure 2). Conversely, only half of those with an elevated plasma

NP had either left atrial dilation or another ultrasound measure of congestion (supplementary figure 2).

53 patients had mild or moderate mitral regurgitation (MR), and 43 patients had mild tricuspid regurgitation (TR). There was no difference in the prevalence of TR nor the estimated systolic pulmonary artery pressure measured by the Bernoulli equation between patients with raised NP concentrations and normal NP concentrations, nor between patients with one or more markers of congestion and no markers. However, the prevalence of MR was higher amongst patients with raised NP concentrations compared to those with normal NP concentrations, and also amongst patients with one or more markers of congestion compared to those with no markers (table 2).

Correlates of ultrasound markers of congestion or filling pressure.

None of the three ultrasound markers of congestion correlated with another but IVC diameter and the number of B-lines were weakly correlated with left atrial volume (figure 3). The number of B-lines was also inversely correlated with body mass index (BMI) in patients with a BMI <30 kg/m^2 (but not in those with a BMI ≥30 kg/m^2) and body surface area (BSA), and positively correlated with TR gradient (supplementary table 2). Natriuretic peptides were most strongly correlated with LAVI, with weaker correlation to IVCD, JVD, E/e', LVMI, age and systolic blood pressure (supplementary figure 3).

Greater left atrial volume index was associated with higher NP concentrations (hazard ratio (HR) = 1.12 (95% confidence interval (CI) 1.06 – 1.17); $\chi 2 = 19$; P<0.001), the presence of one or more markers of ultrasound congestion (HR = 1.04 (1.01 – 1.08); $\chi 2 = 6$; P=0.02), and

the presence of congestion by IVC diameter (HR = 1.09 (1.04 – 1.14), $\chi 2 = 12$; P=0.001) (supplementary table 3).

Outcomes

During a median follow up of 1282 days (IQR 1156 – 1539) 5 patients were commenced on loop diuretics; 110 patients had a first admission to hospital (87 (80%) of which were unplanned admissions, 36 (41%) of which were cardiovascular admissions); 12 patients were diagnosed with AF; 1 patient was diagnosed with HF; 17 patients were diagnosed with cancer; and 13 patients died.

Numerically, a greater proportion patients with raised, compared to normal, plasma concentrations of NP reached the composite endpoint of unplanned cardiovascular admission, prescription of a loop diuretic, diagnosis of AF, diagnosis of HF, or death (HR = 1.88 (0.98 – 3.62); P=0.06), and amongst those with at least one marker of congestion on ultrasound compared to those with no markers for patients with a complete set of congestion data (N=214) (HR = 1.61 (0.94 – 2.78); P=0.09) (supplementary figure 4).

Those with both raised plasma concentrations of NP and at least one marker of congestion on ultrasound were at three-fold increased risk of the composite endpoint compared to patients with neither of these attributes (HR 3.05 (1.28 – 7.27); P=0.01)) (figure 4).

Discussion

This analysis shows that many patients at increased clinical risk of developing heart failure have one or more ultrasound markers of subclinical congestion. However, various measures of congestion were poorly correlated, the strongest association being between left atrial volume and natriuretic peptides. Paradoxically, the lack of strong correlations may offer some advantages. If measurements are tightly correlated, then measuring just one might suffice. Although NP are one of the best predictors of incident heart failure, their accuracy is low; most patients with an elevated plasma NP will not develop heart failure and may not benefit from additional preventive measures. For instance, in the PEACE trial, amongst 3,761 patients with chronic ischaemic heart disease, more than half of patients had an NT-proBNP >125ng/L. Although an elevated NT-proBNP indicated a 2-3 fold increase in the risk of developing heart failure, fewer than 5% went on to do so in the following 5 years.[14] We found that those with both raised plasma concentrations of NP and one marker of congestion on ultrasound were at greater risk of adverse cardiovascular events or death than those with neither. Ultrasound markers of congestion, including left atrial volume, might improve the specificity of NP and help target treatments to prevent heart failure more precisely at patients who have both an elevated NP and ultrasound evidence of congestion, perhaps especially LA dilation.

Measuring congestion by ultrasound in patients at risk of heart failure

IVC diameter

Early studies of IVC found a wide range of diameter measured by ultrasound with overlap between healthy people and patients with raised right atrial pressure.[15] Nath and colleagues

found an IVC diameter >2.0cm in about 10% of 3,729 patients with risk factors for heart failure, which is similar to our reported prevalence. Patients with a dilated IVC were at greater risk of incident heart failure, particularly when the IVC collapsed <50% on inspiration (equating to a RAP of ≥10 mmHg). [16,17] Many patients with heart failure have an IVC diameter similar to that of our population with subclinical congestion. Amongst patients with heart failure, a smaller IVC is associated with fewer signs of congestion and less severe symptoms that those with a dilated IVC.[4] However, IVC dilation may not be an early sign of congestion and may only develop after a substantial expansion of plasma volume and rise in right atrial pressure has occurred.

US B-lines

Dwyer and colleagues found that 14% of patients with hypertension had ≥3 B-lines in an 8-zone scan.[18] Similarly, we found that 13% of those with CV risk factors had >14 B-lines in a 28-zone scan and those with raised NP were more likely to have lung B-lines. The presumption is that lung B-lines represent extra vascular lung water that has developed in response to raised pulmonary venous pressure.[19] Consistent with this, we found that the number of lung B-lines positively correlated with LAVI. We also found that most patients with an NT-proBNP <125 ng/L or BNP <35 ng/L had at least one lung B-line. A lung B-line identifies areas of thickened interlobular tissue, which could be due to fluid *or* fibrosis.[13] The clinical significance of lung B-lines in patients with CV disease but without heart failure is uncertain.

JVD ratio

JVD ratio was lower (more congestion) amongst patients who had elevated plasma NP concentrations. The jugular vein (JV) cross sectional area during Valsalva as a percentage of the area at rest is correlated with invasively measured RAP in patients with structural or functional cardiac abnormalities [20,21] and might be a more accurate measure of subclinical congestion than IVC diameter. However, only 9% of patients in the present study had an abnormal JVD ratio and JVD ratio did not correlate with other markers of congestion, including left atrial volume.

The left atrium

Left atrial volume was greater both in patients with raised NPs and those with congestion by ultrasound compared to those without these features. The left atrium is thin walled and dilates in response to small increases in left ventricular filling pressure.[22] A dilated left atrium may be the first sign of subclinical congestion detectable by ultrasound. By comparison, increases in IVC diameter, the presence of lung B-lines and decreases in JVD ratio might only develop as left ventricular filling pressures are transmitted further upstream to the pulmonary vasculature and right atrium. An enlarged left atrium detected on imaging is associated with increased risk of cardiovascular morbidity and mortality, including incident heart failure, in patients with diabetes,[23] or ischaemic heart disease.[24] A dilated left atrium might be the most sensitive ultrasound marker to identify patients with subclinical congestion.

Subclinical congestion and heart failure risk

The ALLHAT, HYVET, SHEP and EMPA-REG OUTCOMES studies show that, in people with risk factors such as hypertension or diabetes, treatment with thiazide diuretic agents or

sodium-glucose co-transporter 2 inhibitor reduced the risk of incident heart failure.[25-28] We found that nearly one third of patients with risk factors for heart failure had congestion by ultrasound. Treatment with agents that alter water and salt balance might treat subclinical congestion and reduce the chance of patients developing clinically overt heart failure.

Study limitations

Not all patients accepted the invitation for screening, therefore we cannot exclude selection bias. Whilst our study benefits from the heterogeneity of two different populations, there were some differences in patient characteristics between sites (supplementary table 1). This may reflect different recruitment strategies: many patients in Hull were invited for screening because they had coronary artery bypass grafting in the previous ten years, whereas patients from Glasgow were recruited from a post-myocardial infarction clinic. Both populations represent patients "at-risk" of heart failure due to shared risk factors (diabetes, hypertension or ischaemic heart disease) and raised plasma concentrations of NP. There are multiple protocols for performing lung ultrasound,[29] our findings may have been different if we had used a different method. Our study lacks directly measured haemodynamic measurements at rest or during exercise and other biomarkers of congestion, such as soluble CD146 and carbohydrate antigen-125, which might have provided further insights into the prevalence and severity of congestion in this population. The study was not intended or powered to assess the relationship of measures of congestion with clinical outcomes, but we included this information at the reviewers request. [30]

Conclusions

Amongst patients at increased risk of heart failure, subclinical evidence of congestion by a variety of ultrasound measures is common, as are increased plasma concentrations of NP. The utility of screening for subclinical congestion, and the optimal combination of NP and ultrasound measures with which to do so, is an active area of research for the prevention of heart failure.

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Conflict of interest

None.

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Figure legends

Figure 1

Title: CONSORT diagram

Legend: Flow diagram of patients recruited for our study and subdivisions into groups based on plasma concentrations of natriuretic peptides. LVEF – left ventricular ejection fraction; NTproBNP – N-terminal pro-B-type natriuretic peptide; BNP – brain natriuretic peptide; AF – atrial fibrillation.

Figure 2

Title: Venn diagram of patients with different ultrasound markers of congestion

Legend: Only patients with complete data on IVC diameter, JVD ratio and lung B-lines were included in the Venn diagram. Percentages shown are a percentage of total number of patients with complete congestion data. Value in square brackets is median and quartiles of normalised NP. "Normal" natriuretic peptide levels were <125 ng/L for NTproBNP and <35 ng/L for BNP. Abbreviations used: JVD – jugular vein distensibility; IVC – inferior vena cava; NP – natriuretic peptide; LAVI – left atrial volume index.

Figure 3

Title: Univariate correlation matrix for different markers of congestion.

Legend: † P<0.05; ‡ P<0.01; * P<0.001. Value in the shaded boxes is Pearson's correlation co-efficient. Boxes shaded in grey were non-significant (P>0.05). Abbreviations used: NTproBNP – N-terminal pro-B-type natriuretic peptide; BNP – brain natriuretic peptide; normBNP – normalised BNP; LVEF – left ventricular ejection fraction; IVCD – inferior vena cava diameter; JVD – jugular vein distensibility; N – number; LVMI – left ventricular mass

index; LAVI – left atrial volume index; BMI – body mass index; SBP – systolic blood pressure.

Figure 4

Title: Kaplan-Meier curve for the composite outcome by the presence or absence of raised NP concentrations and / or >1 marker of congestion on ultrasound

Legend: Composite outcome of unplanned cardiovascular admission, new prescription of loop diuretic, new diagnosis of AF, new diagnosis of HF, or death. Abbreviations used: NP – natriuretic peptide; HR – hazard ratio; CI – confidence interval; AF – atrial fibrillation; HF – heart failure.

Supplementary Figure 1

Title: Natriuretic peptide concentrations by presence or absence of ultrasound marker of congestion

Legend: White numbers indicated number of patients in each bar. Abbreviations used: BNP – b-type natriuretic peptide; NT-proBNP – N-terminal pro-B-type natriuretic peptide.

Supplementary Figure 2

Title: Venn diagram of patients with different ultrasound markers of congestion

Legend: Only patients with complete data on IVC diameter, JVD ratio and lung B-lines were included in the Venn diagram. Percentages shown are a percentage of total number of patients with complete congestion data. Value in square brackets is median and quartiles of normalised NP. * denotes the number of percentage of patients with a normal NP level and no marker of congestion. "Normal" natriuretic peptide levels were <125 ng/L for NTproBNP and <35 ng/L for BNP. Abbreviations used: JVD – jugular vein distensibility; IVC – inferior vena cava; NP – natriuretic peptide; LAVI – left atrial volume index.

Supplementary Figure 3

Title: Bar chart of median normalised natriuretic peptide concentration by quartiles of different ultrasound measures

Legend: All patients were included. Abbreviations used: Q – quartile; JVD – jugular vein distensibility; IVC – inferior vena cava; BNP – B-type natriuretic peptide; LAVI – left atrial volume index.

Supplementary Figure 4

Title: Kaplan-Meier curves for the composite outcome by the presence of raised NP concentrations and the presence of >1 marker of congestion on ultrasound

Legend: Composite outcome of unplanned cardiovascular admission, new prescription of loop diuretic, new diagnosis of AF, new diagnosis of HF, or death. Abbreviations used: NP – natriuretic peptide; HR – hazard ratio; CI – confidence interval; CV – cardiovascular; AF – atrial fibrillation; HF – heart failure.