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Beyond clinical examination and natriuretic peptides: comprehensive quantification of congestion with ultrasound in ambulatory heart failure patients

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Clinical congestion plays a central role in the development of heart failure (HF)-related symptoms and is the cause of the majority of hospitalizations for HF (HHF).^{1,2} Relieving congestion is consequently an important goal of HF management.³ Physical examination in patients with HF has limited accuracy for the detection of congestion,⁴ which supports using additional tools in the evaluation of HF patients to improve risk stratification and possibly guide patient management. In the latest European Society of Cardiology HF guidelines, using ultrasound measurement of inferior vena cava (IVC) diameter for assessment of volume status has a IIbC recommendation, whereas the use of thoracic ultrasound is cited in the text but does not have a formal recommendation.³

The toolbox of sonographic methods that are relevant to congestion evaluation includes pulmonary congestion on lung ultrasound (LUS) (B-lines, pleural effusions), haemodynamic congestion on echocardiography (e.g. E/e' and systolic pulmonary artery pressure) and vascular ultrasound [IVC and jugular vein diameter (JVD) measurement]. LUS is a semi-quantitative, simple, and rapid method to assess pulmonary congestion⁵; this technique produces vertical lines defined as 'B-lines' by scanning along the intercostal spaces using either a phased array or curvilinear transducer. Pulmonary congestion identified by LUS has been shown to be a strong predictor of outcomes following a HHF^{6–8} and in ambulatory patients with HF.^{8,9} E/e' and elevated pulmonary artery pressures measured using echocardiography have been shown to be associated with increased risk for HHF in patients with HF.^{10,11} In addition, both IVC and JVD measurements have been employed in the assessment of haemodynamic congestion in ambulatory patients with HF with heterogeneous results with respect to their prognostic utility.^{12–15} Sonographic JVD evaluation can be either based on the evaluation of JVD at rest or the ratio of JVD during the

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Valsalva manoeuvre and at rest. This sonographic measurement has been shown to be associated with adverse clinical outcomes by one research group so far.¹³ Whether each of these sonographic markers individually or combined are associated with important adverse events in ambulatory patients with HF had not been previously evaluated in a large cohort.

In this issue of the Journal, Pellicori and colleagues report the association of most available sonographic markers of congestion with the composite outcome of death or HHF in ambulatory patients with HF, as well as the prevalence of these measures in patients without congestion on physical examination.¹⁶ The key findings of this study are that: (i) nearly 50% of ambulatory patients with HF thought not to be congested based on the traditional evaluation of signs and symptoms actually had sonographic evidence of congestion (either based on B-lines quantification, JVD ratio or IVC diameter), (ii) these three sonographic features of congestion were associated with the aforementioned composite outcome in univariable analysis and improved risk prediction [based on net reclassification improvement (NRI) and integrated discrimination improvement (IDI)] beyond prognostically important clinical variables [namely age, sex, New York Heart Association (NYHA) class, creatinine, haemoglobin and left ventricular ejection fraction], and (iii) adding JVD ratio to similarly prognostically important clinical variables, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), further improved re-classification (by IDI only).

The most striking clinical message of this study is that ultrasound of the lungs, jugular vein and IVC identified 'congestion' in almost half of those ambulatory HF patients who did not have any physical exam findings of congestion. This would suggest that congestion-focused ultrasound could detect and quantify subclinical congestion in patients with HF using simple techniques and widely available technology.

When comparing these results with previous studies, the most surprising finding of Pellicori's study is the weak association of LUS findings with long-term outcomes in multivariable models. This result stands in contrast to three prior observational studies in ambulatory patients with HF. Scali *et al.*¹⁷ demonstrated that > 8 B-lines on 28-zone LUS at rest is prognostically important for the composite of death or HHF at 12 month as demonstrated by an area under the curve of 0.98 [95% confidence interval (CI) 0.93–1.0]. Similarly, in a cohort of 195 NYHA class II–IV HF patients, three or more B-lines (using an 8-zone technique) was independently associated with a higher rate of 6-month death or HHF (adjusted hazard ratio 4.08, 95% CI 1.95–8.54; $P < 0.001$).⁹ Dwyer *et al.*¹⁸ reported similar results in low-risk patients with HF. The discrepancy between these former and the current study may be related to a higher degree of pulmonary congestion in the HF cohort in the current study, differences in LUS technique (e.g. number of zones examined and variable LUS clip duration), longer follow-up period, a lower event rate compared to previous reports (26% over a 6-month period in the report of Platz *et al.*⁹ vs. 18% during a median follow-up of 234 days in the current report of Pellicori *et al.*) or due to adjustment for NT-proBNP.

The work of Pellicori *et al.*¹⁶ should be applauded as it represents an important step forward in our understanding of how ultrasound can aid in the detection of congestion in ambulatory patients with HF. Important strengths of this study are its size (342 ambulatory patients with HF) and the comprehensive sonographic evaluation of congestion, including LUS,

echocardiography, IVC and JVD assessment. However, a few limitations should be considered. First, although an experienced reader analysed ultrasound videos off-line, it is not clear if this reader was blinded to clinical characteristics and subsequent outcomes. Second, the duration of the LUS recordings were based on heart beats (at least five); as shorter clip duration is associated with lower B-line counts, this recording strategy could have resulted in a lower B-line count in sicker patients with higher heart rates. Finally, treating physicians were not blinded to the echocardiogram and the ultrasound of the lungs, jugular vein and IVC. Physicians could have altered therapy based on these findings, which may have impacted the study findings. The reproducibility of these results using appropriate blinding of readers and treating clinicians should be assessed in future investigations.

This study greatly adds to our knowledge regarding the value of sonographic congestion measures in ambulatory patients with HF. It paves the way for a more comprehensive evaluation of congestion in patients with HF by including both sonographic pulmonary and haemodynamic congestion assessment. Congestion-focused ultrasound examinations could complement the clinical examination in ambulatory patients with chronic HF and allow for early detection of subclinical congestion. In Figure 1, we provide a brief overview of the current literature for the three steps of congestion assessment (i.e. clinical, laboratory, and imaging evaluation of congestion); we also detail current gaps in evidence and propose future research directions in the field.^{7,8,10–14,16–25}

Important gaps in knowledge remain. To our knowledge, a comprehensive sonographic congestion assessment including the aforementioned tools has not been evaluated in a randomized trial. In addition, there is a lack of evidence regarding how improved congestion assessment could better inform HF treatment (e.g. based on which sonographic cut-off values specific therapies should be altered). Ultrasound-based congestion parameters could potentially become important diagnostic risk stratification measures. Yet, the degree to which these sonographic congestion parameters can be modified by therapies and whether outcomes can be improved as a result needs to be examined in well-designed clinical trials.

Despite the established use of echocardiography in the assessment of patients with HF and availability of ultrasound equipment, comprehensive sonographic congestion assessment beyond echocardiography is not routinely performed. Demonstrating that acting on subclinical sonographic congestion in the setting of chronic HF does improve patient outcome could prompt its wide spread use and support its formal inclusion in HF guidelines.

Conflict of interest:

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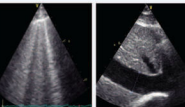
	CONGESTION ASSESSMENT		
	Clinical markers	Laboratory markers	Imaging markers
Parameters	 <p>Dyspnea / Orthopnea JVD Rales Peripheral edema</p>	 <p>Natriuretic peptides Estimated plasma volume (evaluated from hemoglobin and hematocrit) <i>Most conveniently used as point of care measurements</i></p>	 <p>Lung ultrasound JVD and IVC measurements Echocardiographic markers (E/e', pulmonary artery pressures...)</p>
Observational data regarding risk stratification	<p>A clinical congestion score to be performed at hospital discharge was validated in the EVEREST trial data: it was strongly associated with all-cause mortality and the risk for HF hospitalization¹⁹</p> <p>In the outpatient setting, the Rohde score, based on the quantification of orthopnea, JVD, rales and edema has been shown to be associated with mortality²⁰</p>	<p>Reported association with HF hospitalization and/or mortality: Natriuretic peptides^{21,22} Estimated plasma volume²³</p> <p>Significantly improved prediction: Natriuretic peptides²¹ Estimated plasma volume²³</p>	<p>Reported association with HF hospitalization and/or mortality: LUS^{8, 12, 17, 18} JVD measurements¹³ IVC measurements¹⁴ Echocardiographic markers^{10, 11}</p> <p>Improved risk prediction for HF hospitalization or mortality: LUS⁷ JVD measurements¹⁶ Echocardiographic markers¹¹</p>
Randomized trial-based evidence	<p>Trials unlikely to be performed as clinical markers are part of routine clinical care</p>	<p>A meta-analysis of individual patient data reported that natriuretic peptide-guided compared with symptom-guided therapy resulted in significantly lower mortality and fewer HF admissions in HFrEF patients²⁴.</p> <p>However, the most recent trial, GUIDE-IT²⁵, was neutral; in this trial, NT-ProBNP was mostly use to trigger changes in background treatment rather than treatment targeting congestion.</p>	<p>Trials to be performed</p>

Figure 1.

The three steps of congestion assessment in ambulatory heart failure (HF) patients. HFrEF, heart failure with reduced ejection fraction; JVD, jugular vein diameter; IVC, inferior vena cava; LUS, lung ultrasound; NT-ProBNP, N-terminal pro-B-type natriuretic peptide.