

Role of transthoracic echocardiogram in acute heart failure

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Acute Heart Failure (AHF) is an increasingly common condition with a poor prognosis. In contrast to CHF where advances in medical therapy and devices has led to significant improvement in morbidity and mortality, the prognosis for AHF has not changed significantly in the last few decades despite efforts to find effective treatment. There are multiple factors that contribute to the high mortality and morbidity of AHF; it can be a diagnostic challenge, determining whether decongestion has been achieved can be difficult, and persisting congestion is commonly present at discharge contributing to early decompensation and rehospitalisation. Transthoracic echocardiogram (TTE) is a unique imaging modality that is non-invasive, can be done at the bedside, in real time during procedures, is affordable and easy to access both in community and inpatient settings. Small hand held 'point of care' scans are increasingly available and being used as an adjunct to improve clinical examination. Consequently, the use of echocardiography to improve outcomes for patients with cardiac disease continues to evolve. In chronic heart failure TTE has established roles in the quantification of HF phenotype, and determination of treatment initiation, escalation and success. However, the role of echocardiogram in AHF is not as well established with society guidelines relying on expert consensus for their recommendations. Use of TTE at all stages of AHF has potential to reduce morbidity and mortality. This review discusses the evidence for use of TTE to improve the diagnosis, prognosis and management of AHF.

Keywords

Acute heart failure; Transthoracic echocardiogram; Diagnosis; Prognosis; Treatment

1. Introduction

Heart failure (HF) is a global pandemic affecting approximately 38 million people worldwide [1]. In developed nations 1–2% of the population suffer from heart failure, rising to $\geq 10\%$ in people over 70 years of age [2]. By 2030 prevalence is predicted to increase by 50% compared to 2013; less than two decades earlier [3]. In 2019 The Heart Failure Society of America (HFSA), the Heart Failure Association of the European Society of Cardiology (HFA-ESC) and the Japanese Heart Failure Society (JHFS) agreed on a universal definition of HF as “a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or sys-

temic congestion” [4]. Acute HF (AHF) is a “rapid onset or worsening of symptoms and/or signs of HF requiring urgent evaluation and treatment” [2]. AHF is the leading cause of hospital admission in individuals aged 65 years or more in the UK [5, 6]. Despite considerable advances in medical and device therapy improving outcomes in chronic HF (CHF), no equivalently effective treatment for AHF has been found [7, 8]. After an initial hospitalisation with HF 25–30% will be dead in 12 months; a mortality rate worse than most cancers [5, 9]. Re-hospitalisation for HF or complications of HF and its treatment are common, occurring in 20–25% of patients within the first 30 days and up to 50% within 60 days from admission with AHF [10–12]. Even in the favourable conditions of a clinical trial re-admission is common. In the PIO-NEER trial, assessing the safety of sacubitril/valsartan combination (Entresto), the latest pharmacological advancement in HF treatment, 8% of patients receiving Entresto were re-admitted within the 8-week trial period and 57% experienced one of a composite of clinical endpoints (the majority an increase of diuretic dose $> 50\%$) [13].

There are multiple factors that contribute to the high mortality and morbidity of AHF. AHF is a complex clinical syndrome that can be a diagnostic challenge. Studies suggest, that similar to acute coronary syndromes, a delay in diagnosis of AHF leads to higher mortality and morbidity [14, 15]. Determining whether decongestion has been achieved with treatment can be difficult; particularly in patients with other co-morbidities. In many patients persisting congestion, often subclinical, contributes to early decompensation and rehospitalisation [16, 17]. In the months immediately following discharge from an episode of AHF patients are particularly vulnerable to re-admission with both cardiac and non-cardiac conditions; despite some success of intensive monitoring programmes trialled during this period [18].

Transthoracic echocardiogram (TTE) uses ultrasound to obtain a non-invasive, evaluation of the morphological and functional status of the heart. TTE has evolved considerably since M-mode was first developed to assess left ventricular (LV) size in the 1950s. M-mode, 2D and 3D imaging allow quantification of cardiac structure as well as left and right ventricular function. Doppler measurements are an accurate

non-invasive estimate of LV filling pressures (LVFP), pulmonary hypertension (PASP) and valvular function. Strain imaging identifies abnormal myocardium even in the context of a preserved ventricular ejection fraction. All sub-modalities of echocardiography are useful in the assessment of patients with heart failure [19]. Other imaging modalities are also able to evaluate cardiac structure and function but echocardiogram remains the 'work-horse' of everyday cardiac imaging as it can be performed at the bedside and during procedures, is affordable, and easy to access both in community and inpatient settings. Therefore it is an established, integral part of current medical practice that guides the diagnosis and management of cardiac diseases [20].

In heart failure, TTE has established roles in the quantification of HF phenotype and determination of treatment initiation, escalation and success [2, 6, 8, 21, 22]. However, the role of echocardiogram in AHF is less well established. This review aims to examine the potential of TTE in the diagnosis, prognosis and management of AHF.

2. Role of transthoracic echocardiography in diagnosis

Current guidelines limit their recommendation for immediate TTE to patients with haemodynamic instability or those suspected to have an acute life threatening structural or functional cardiac abnormality [2, 6, 23]. Consideration of TTE within 48hrs is recommended in all patients with de-novo HF or in patients with HF where cardiac function is unknown. The majority of admissions with AHF are in patients with known heart failure who experience an acute decompensation; often within a year of their last TTE. In this situation TTE is not universally recommended if there is a clear precipitant for decompensation [2, 6, 24]. Repeated TTE during an admission is not recommended unless there is a relevant deterioration in clinical status [2]. These guidelines are expert opinion (Level of Evidence 1c) as no studies had been published addressing these questions when they were written.

2.1 TTE in the emergency setting to improve diagnostic accuracy

The clinical presentation of AHF is non-specific. The majority of patients with AHF present with dyspnoea and congestion, however "traditional" features of AHF (e.g., pulmonary congestion on chest radiograph) are frequently absent and over-reliance on these factors contributes to delayed or missed diagnosis in up to 20% of patients [25]. Patients with known CHF are commonly co-morbid with conditions that present a similar clinical picture when decompensated [25, 26]. Despite diagnosing AHF based on clinical presentation, ECG and CXR, clinicians remain "uncertain" about their diagnosis in 44% of cases and a different final diagnosis is concluded in nearly one in 4 patients [26]. When natriuretic peptide testing is available this improves diagnostic accuracy, though misclassification remains as high as 14–29% [26]. Utilisation of TTE as part of an initial diagnostic strategy in patients with symptoms suggestive of AHF can

improve the timely diagnosis of AHF [2, 25, 27, 28]. However TTE in the acutely unwell patients can be technically challenging. A full TTE study can take 30mins in a well compliant patient in an outpatient setting. Patients in AHF often have severe dyspnoea which presents multiple challenges to acquiring good images and a full study is often not tolerable. With the increasing availability of portable echocardiograms and hand held 'point-of-care' ultrasounds, focussed studies that answer dichotomous questions done by emergency physicians have emerged as a practical answer to improve diagnostic yield [25, 29]. "FoCUS" scans are 2D qualitative imaging undertaken to specifically assess biventricular size and function, identify the presence of pericardial effusion or tamponade and recognise gross valvular dysfunction or intra-cardiac mass [29, 30]. In a study of 2683 patients presenting with acute dyspnoea, 20% had AHF as their final diagnosis. A protocol using combined focused TTE and lung ultrasound was more sensitive (88 vs 77%) and equally specific (96 vs 98%) as clinical examination but reduced time to diagnosis by several hours (24 ± 10 min vs 186 ± 72 min; $P = 0.025$) [30].

2.2 Importance of comprehensive echocardiographic study in patients with AHF

As well as assisting with the clinical diagnosis of AHF, TTE is able to help quantify severity of LV dysfunction, elevation of LVFP, presence of valvular dysfunction, right ventricular (RV) dysfunction and raised PASP; — all of which impact on treatment choice and success and cannot be adequately assessed in a FoCUS scan. The diagnostic utility of individual TTE indices that comprise a comprehensive TTE is summarised in Table 1.

2.2.1 Establishing LV function

Currently quantification of left ventricular size with volume assessment (LV end-diastolic and end-systolic volumes, LVEDV and LVESV respectively), and LV ejection fraction (LVEF) by 2D imaging determines the categorisation of patients HF ejection fraction phenotype which guides initiation of evidence-based treatment (including pharmacological and device-based therapies) [2, 6, 20, 23]. The modified biplane Simpson's method is recommended to establish LVEF which has the advantage of requiring only two apical views to be calculated [2, 23, 27]. If the TTE is technically challenging intravenous echocardiographic contrast can be given to improve diagnostic accuracy [27] or failing this a visual estimate of LVEF can be utilised, which in experienced hands has a good correlation with LVEF established by the Simpsons biplane method ($R = 0.898$) [31]. However, in clinical practice it is recognised that interpretation of 2D images is limited by significant intra and inter-observer variability [19].

3D evaluation of the LV has been shown to be more accurate than 2D at determining volumes and is increasingly being measured in patients with CHF [8, 32–34]. Strain imaging is another increasingly available modality with equivalent or better diagnostic accuracy of LV function and greater con-

Table 1. Diagnostic Utility of individual TTE indices.

	Diagnostic cut off for abnormal function	Strengths	Limitations
LV function			
2D	Volume assessment	2D imaging is well established modality, accessible, can be done quickly in acute situations	Foreshortened views are common and don't allow 'true' measure of LV volume and EF LVEDVi preload dependent, LVESVi afterload dependent
	LVEDVi Female: >61 mL/m ² Male: >74 mL/m ² LVESVi Female: >24 mL/m ² Male: >31 mL/m ²		
	LVEF HFrEF <40% HFmrEF 40–49% HFpEF ≥50% (in combination with other TTE findings of increased LVFP)	LVEF can be qualified by visual estimate, able to be assessed in nearly all patient (with the use of contrast as required)	EF influenced by volume, loading, heart rate, LBBB, inotropic status, contrast may be required
3D	Volume assessment	Easier to reproduce volumes and more accurate in repeated measures than 2D, doesn't rely on geometric assumptions	Not in common clinical use, very dependent on image quality
	LVEDVi Female: >72 mL/m ² Male: >80 mL/m ² LVESVi Female: >29 mL/m ² Male: >33 mL/m ²		
	LVEF Reduced : Female: 57%, Male <54%		
GLS	16% to 18% borderline <16% mild impairment <10 severe impairment	Good inter- and intra-observer reproducibility, all myocardial function included in measurement, not affected by LBBB and dysynchrony	Dependent on frame rate 40–120ms, results from different vendor not compatible, grey zone for normal function
LV Filling pressures			
Doppler measurements (major)			
E:A ratio	>2 >0.8–<2 need to evaluate with other doppler indices >50% change with Valsalva	Better estimate of LVFP than above measures of LV function, change with Valsalva highly specific for elevated LVFP, reproducible	Less accurate with arrhythmia including sinus tachycardia, Mitral annular velocities are needed to differentiate normal from pseudo-normal pattern, age dependent
TRV	>2.8 m/s	Validated measure of RVFP and LVFP	Not measurable in up to 40% of patients Not accurate measure of LVFP when significant primary pulmonary disease is present

Table 1. Continued.

	Diagnostic cut off for abnormal function	Strengths	Limitations
E:e' ratio	>14	Average (E/e' septal and lateral) has high specificity as a single marker of elevated LVFP, repeated measures reflects 'real – time' change in LVFP, measure obtainable in most patients	Less accurate when LBBB, pacing or severe MAC, MS or MR is present, septal e' abnormal in pulmonary hypertension with RV dysfunction
LAVI	>34 mL/m ²	Is a marker of chronicity of HF	In AF, significant MV disease, high cardiac output state and post cardiac transplant may be elevated with normal LVFP
Septal e'	<7 cm/s	Significant marker of LV relaxation independent of LVFP	Less accurate when LBBB, pacing or severe MAC, MS or MR is present
Lateral e'	<10 cm/s	Lateral can differentiate cardiac cause for high LVFP in presence of pulmonary HTN	
Doppler measurements (minor)			
EDT	<150 ms	Accurate in AF and sinus tachycardia	Not accurate in normal LVEF, or when fusion of E to A waves is present
Pulmonary vein S:D ratio	<1	Measure of LA compliance and contraction	Less accurate with atrial arrhythmia, HCM or when severe MS or MR is present
LA reservoir strain	Cut off value not definitively established	Measure of both LA compliance and contraction in normal and reduced LVEF	Difficult to measure in large LA, novel marker with reference range not well established
Right heart function			
TAPSE	<17 mm	Simple, can be done with sub-optimal image quality, reproducible	Measurement of single segment of RV which may not reflect true RV function
Tricuspid annular s'	<9.5 cm/s	Simple, reproducible, has been validated in population based study to discriminate normal from abnormal RV function	Measurement of single segment of RV which may not reflect true RV function, angle dependent
IVC size	>2.1 cm	Measure obtainable from subcostal window in most patients, correlates well with RA pressure	Less accurate with high PASP secondary to respiratory pathology or high IAP
collapsibility	<50%		

Table 1. Continued.

	Diagnostic cut off for abnormal function		Strengths	Limitations
PASP	>35–40 mmHg		Validated measure of RVFP and LVFP	Requires TR jet to calculate (not obtainable in up to 40% of patients)
FAC	<35%		Shown to correlate with RVEF measured on cMRI	Off axis imaging is common
RIMP	PD-RIMP >0.4 TD-RIMP >0.55		Accurate in both bradycardias and tachycardias, doesn't require TR jet to measure	Unreliable when RA pressure is elevated and in AF
3D				
	RVEDVi	Male: 89 mL/m ² , Female: 10% less than male	More accurate measure of RV volume than other indices, reproducible	Normal values not definitively established, used predominantly in research studies not clinical care currently
	RVESVi	Male: 45 mL/m ² , Female: 10% less than male		
RV strain imaging	Free wall GLS <23%		Measure of contractility and less load dependent than other parameters of RV function	Normal values and reproducibility not definitively established, angle dependent
Valvular function				
MR	Severe: EROA ≥ 0.4 cm ² , Regurgitant volume ≥ 60 mls, Regurgitant fraction $\geq 50\%$		Can change rapidly with treatment to reflect diuresis of volume overload	Uniform consensus on severity criteria not established, can be technically challenging to measure

2D, 2 dimensional; 3D, 3 dimensional; AF, Atrial fibrillation; cMRI, cardiac magnetic resonance imaging; EDT, E wave deceleration time; EROA, Effective regurgitant orifice area; FAC, Fractional area change; GLS, Global longitudinal strain; HCM, Hypertrophic cardiomyopathy; HFrEF, Heart failure with reduced ejection fraction; HFmrEF, Heart failure with mid-range ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HTN, Hypertension; IAP, Intra-abdominal pressure; IVC, Inferior vena cava; LA, Left atrial; LAVI, Left atrial volume index; LVEDVi, Left ventricular end-diastolic volume index; LVESVi, Left ventricular end-systolic volume index; LVEF, Left ventricular ejection fraction; LVFP, Left ventricular filling pressure; LBBB, Left bundle branch block; MAC, Mitral annular calcification; MV, mitral valve; MS, Mitral stenosis; MR, Mitral regurgitation; PASP, Pulmonary artery systolic pressure; PD, Pulse doppler; RA, Right atrial; RVEF, Right ventricular ejection fraction; RVFP, Right ventricular filling pressure; RVEDVi, Right ventricular end-diastolic volume index; RVESVi, Right ventricular end-systolic volume index; RIMP, RV index of myocardial performance; S:D, Systolic to diastolic ratio; TAPSE, Tricuspid annular plane systolic excursion; TD, Tissue doppler; TRV, tricuspid regurgitation velocity.

cordance between observers than 2D images [35]. In strain imaging, speckle tracking of gray-scale images measures the deformation of the myocardium. Strain has the advantage over 2D volume measurements in that it detects dysfunction of myocardial shortening and twisting not just radial displacement. As such in measuring overall LV function, speckle tracking derived global longitudinal strain (GLS) accounts for regional abnormalities which is not accounted for in 2D calculation of LVEF by Simpson's biplane method [27, 36]. This is particularly important in HF caused by coronary artery disease where overall LV systolic function may be normal and heart failure with preserved ejection fraction (HFpEF) [36–39]. Several studies have suggested that GLS is more sensitive than LVEF at detecting minor changes in LV systolic function which is particularly useful in a dynamic situation such as AHF [35, 40, 41].

As well as determining global LV function, 2D, 3D and strain imaging can qualify the presence of regional wall motion abnormalities (RWMA), which may be present even when LVEF is normal. The underlying cardiac abnormality responsible for a patient's episode of AHF, for example acute coronary artery disease, is often identifiable by characteristic patterns of RWMA.

2.2.2 LV filling pressure (LVFP)

More than 90% of hospitalisations due to HF result from elevations of LVFP and fluid overload [18]. Importantly, severity of impairment of LVEF is not correlated with severity of LVFP [42]. While many patients with an LVEF <50% have elevated LVFP, up to 40% have normal pressures [43]. Elevated LVFP from diastolic dysfunction is a key contributor to HFpEF which accounts for ~50% of HF and 30–50% of presentations with AHF [22]. Although absolute LVFP cannot be measured using TTE, TTE-derived indices have been shown to be an accurate reflection of LV filling pressure in multiple studies [18, 19, 27, 44].

Doppler imaging is a routine part of a standard echocardiogram that uses pulsed and continuous waves to measure blood flow and myocardial velocities which are indirect measures of intra-cardiac pressures [27, 43, 45, 46]. Doppler indices include: LV pulsed wave transmitral filling velocities (E:A ratio, E wave deceleration time [EDT], and isovolumetric relaxation time), tissue doppler imaging (TDI) (e' wave), ratio of mitral inflow velocity to early diastolic velocity of the mitral annulus (E:e' ratio), M-mode colour Doppler propagation velocities and pulmonary venous flow. Estimation of LVFP and diastolic dysfunction is not as simple as evaluation of LVEF with multiple rather than single Doppler indices, often in combination with 2D derived left atrial volume index (LAVi), required to accurately quantify these measures. To increase practical utility the 2016 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) simplified their guidelines to focus on four key variables (mitral E/A ratio, TRV, average E/e' ratio, and LAVi) incorporated into two diag-

nostic algorithms (see Fig. 1) [45, 46]. These simplified algorithms had superior discriminatory accuracy in predicting LVFP than the more complicated guidance in the earlier 2009 guidelines [47, 48]. In 450 patients referred for cardiac catheterisation the 2016 algorithm detected elevated pulmonary capillary wedge pressure (PCWP) in 91% of patients with EF <50% and 84% in patients with EF ≥50% and when added to clinical criteria for HF improved the accuracy of diagnosis by 10% [43].

Patients with AHF frequently have tachycardia, either sinus tachycardia or tachycardia due to arrhythmias such as atrial fibrillation, and may have significant functional mitral regurgitation; all situations where accurate Doppler imaging has limitations. One possible index that may be singularly useful and less effected by heart rate and valvular regurgitation is the E:e' ratio. Regardless of age, an E:e' is very rarely >14 in normal individuals [45]. A level >14 has been shown to accurately correlate with LV pressures measured invasively during cardiac catheterisation and serial monitoring reliably detected raised LAP when compared to an internal LAP detection device in ambulatory patients with CHF [49, 50]. However this may not be true across the spectrum of HF with two recent meta-analyses concluding there was insufficient evidence to support the assertion that E:e' can reliably estimate LVFP in patients with HFpEF and further prospective clinical trials were required [51, 52]. In the aforementioned validation study the averaged E:e' ratio correctly identified elevated LVFP in 82% of patients [43]. Importantly, the validation study did not specify the proportion of patients with AHF therefore diagnostic accuracy of E:e' has not been definitively established in these patients.

2.2.3 Mitral regurgitation

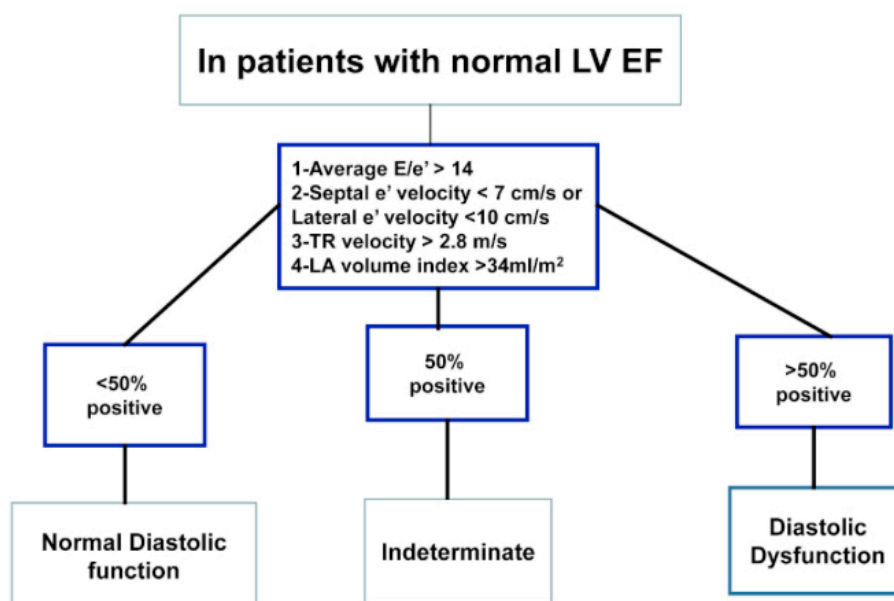
As with other valvular dysfunction, mitral regurgitation (MR) can be a cause of AHF. However mitral regurgitation can also occur secondary to LV dysfunction, i.e., 'functional MR'. When present it is an important marker of HF severity. Functional MR can be distinguished from structural causes of MR by a characteristic tethering of the valve leaflets, and a central or posteriorly directed jet on colour Doppler in the absence of anterior leaflet prolapse [19].

2.2.4 Right heart function

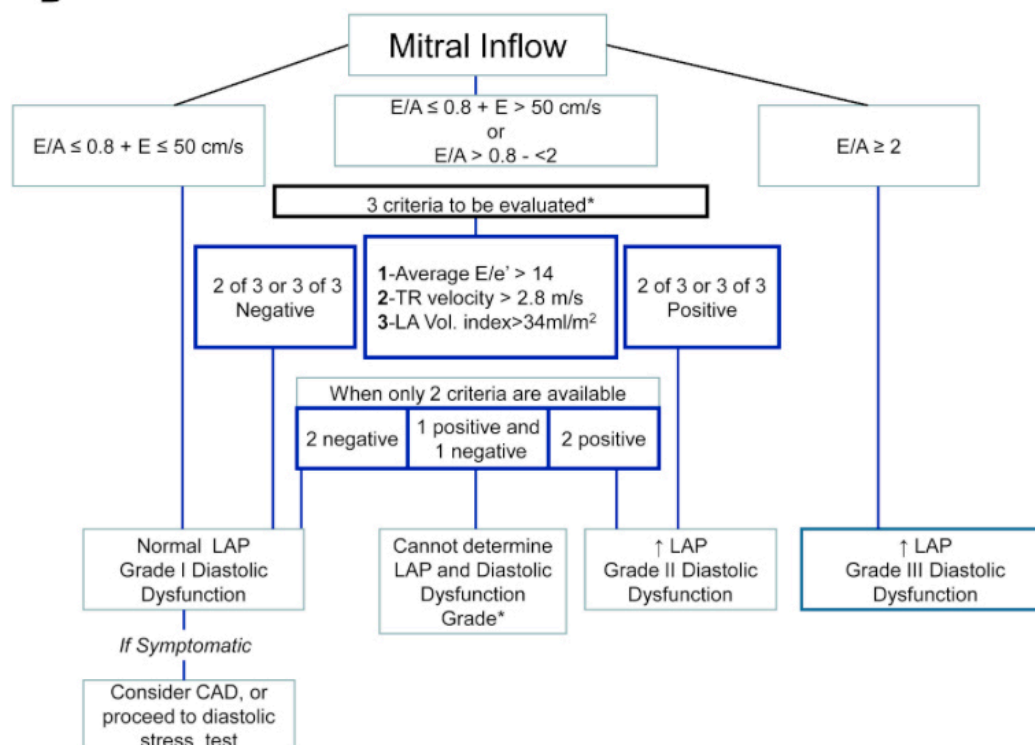
Right heart dysfunction and raised pulmonary artery pressure (PAP) are often important factors in a patients' clinical presentation with HF. In AHF increased PAP has been demonstrated to correlate with dyspnoea at rest [53].

RV function can be quantified by visual estimate or calculated by one or a combination of tricuspid annular plane systolic excursion (TAPSE), tissue Doppler-derived tricuspid lateral annular systolic velocity (s'), fractional area change (FAC) and either pulse doppler (PD) or tissue doppler (TD) derived RV index of myocardial performance (RIMP). RV systolic dysfunction is suggested by TAPSE <17 mm, s' velocity <9.5 cm/s, FAC <35%, PD-RIMP >0.4 TD-RIMP >0.55

A



B



(* : LAP indeterminate if only 1 of 3 parameters available. Pulmonary vein S/D ratio <1 applicable to conclude elevated LAP in patients with depressed LV EF)

Fig. 1. Algorithm for diagnosis of LV pressures and diastolic dysfunction in: (A) patients with normal LVEF (B) patients with depressed LVEF and, patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data [45] (reprinted with permission from © Elsevier).

[2, 27]. As with assessment of LV systolic function, 3D and strain imaging improves quantification of RV systolic function but these modalities are not well studied in AHF and cur-

rently are only recommended to be performed by specialized cardiac sonographers or clinicians [2].

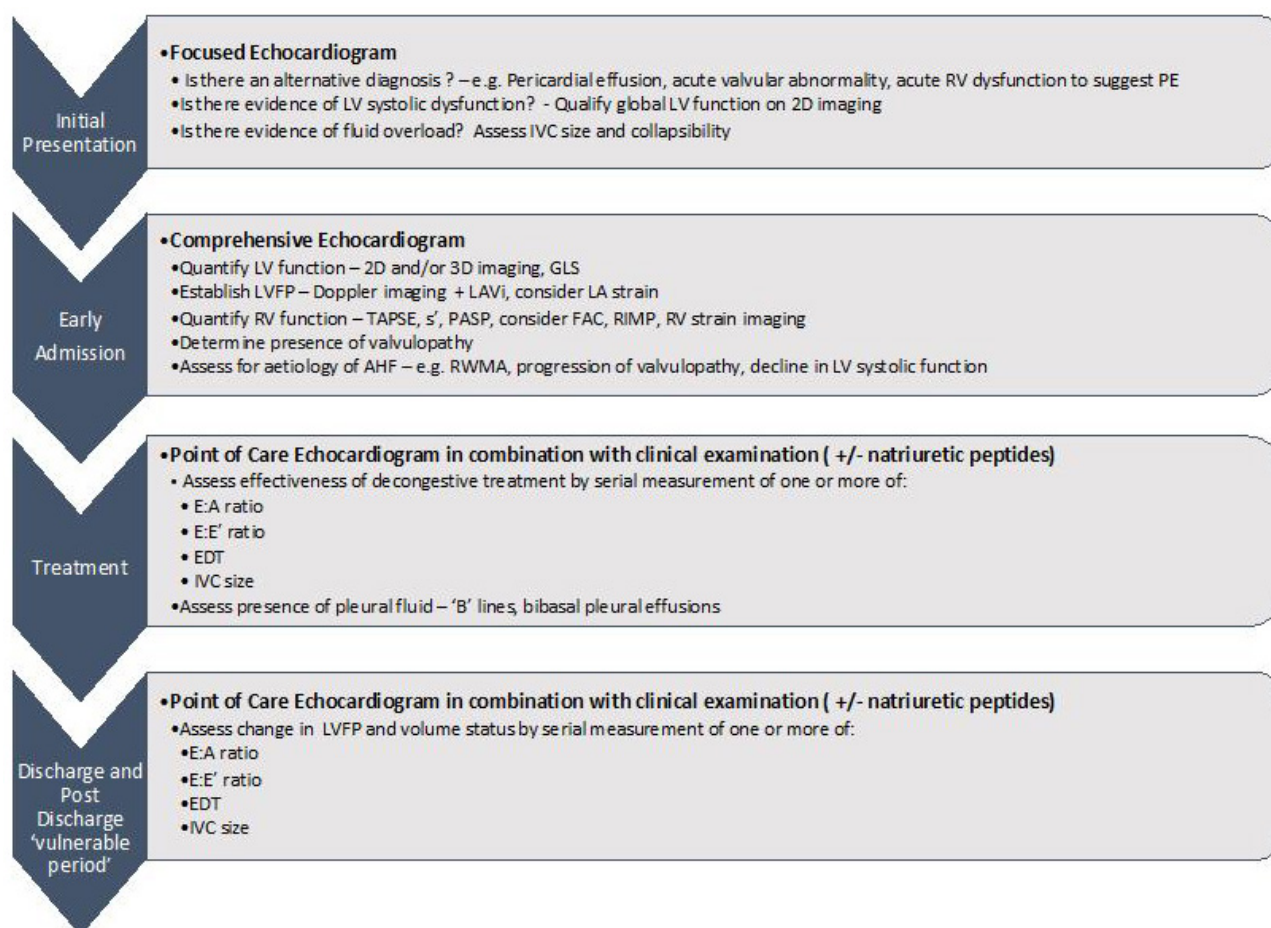


Fig. 2. Flowchart suggesting how echocardiogram could be utilised in each stage of AHF to improve patient outcomes.

An accurate non-invasive measure of PASP is calculated from Doppler imaging of the flow across the tricuspid valve and an estimate of RA pressure based on the IVC size and collapsibility [2, 27]. One difficulty with PASP is it is not universally obtainable with a wide variation in achievable measurement in both chronic and acute HF published. In a cohort of 1210 patients with AHF, PASP was measurable in only 41.5% of patients [54].

2.3 TTE in patients with known cause for AHF

Currently TTE is not routinely recommended in patients with known HF where a known cause for decompensation is identified. However even in these patients' new important pathology is often identified. A study of 559 patients admitted with AHF where the acute decompensation was secondary to dietary or medication non-compliance found at least one significant change, the most common being an increase in LA diameter, worsening of PSAP or LVEF, on 80% of TTEs; even those repeated less than a year since the last study [55]. In a review of US NHI registry data only 7% of patients with a diagnosis of CHF on admission to hospital underwent TTE but those who did had a significantly lower rate of all-cause mortality (OR 0.82 (0.72–0.94, $P = 0.005$) [24]. While caution must be excised in extrapolating the findings of these ob-

servational studies, they do suggest most, if not all, patients with AHF would benefit from TTE during their admission. Prospective, ideally randomised controlled trials should be undertaken to address this question.

2.4 Pragmatic approach to echocardiography in context of diagnosis of HF

To maximise diagnostic yield a practical approach would be for all patient with suspected AHF to undergo a focussed TTE on presentation with a full study repeated once the initial decompensation has been stabilised. One potential approach to the use of TTE in AHF is described in Fig. 2.

3. Role of transthoracic echocardiography in guiding treatment

There are several stages in the treatment of AHF: the initial management of the acute decompensation, decongestion and stabilisation during hospitalisation and ongoing optimisation or maintenance of function in the 'vulnerable period' during the first 3 months post-discharge [56]. The use of TTE to guide therapeutic decision making in each of these stages, either alone or in combination with lung USS and natriuretic peptides has shown promise in improving patient outcomes. However so far most studies have been single centre studies,

often evaluating change in a single TTE indice in response to titration of one medication, e.g., beta blocker. Therefore, which echocardiographic indices are useful across the spectrum of AHF or whether, akin to diagnosis, separate algorithms would be useful for different phenotypes of HF needs further evaluation.

3.1 Treatment of acute decompensation

Doppler indices on TTE are affected by preload and afterload; both of which are changing rapidly in the early phase of treatment for AHF. This has been utilised in studies of critically unwell patients to monitor change in fluid status [29]. E:e' has also been demonstrated to change in concert with PCWP in patients with AHF. In a study of 79 patients with AHF who underwent left and right catheterisation and TTE simultaneously, E:e' >15 had a sensitivity of 89% and specificity of 91% for PCWP >15 mmHg [57]. Correlation was significantly better in patients without a wide left bundle branch block or cardiac resynchronisation therapy in-situ. Repeated measurements were taken in 11 patients and E:e' accurately identified the change in PCWP between measurements. This result was a direct contradiction of an earlier study of 106 patients with AHF where E:e' >15 demonstrated poor sensitivity and specificity (66% and 50%, respectively) for a PCWP >18 mmHg [58]. However this study was criticized on several grounds, including taking the catheter and echocardiogram measurements in different positions. This criticism highlights the importance position has on Doppler measurements due to the effective change in pre- and afterload with change in position. Use of TTE indices in a rapidly changing situation is also limited as they cannot be measured continuously. No study has established specific levels of echocardiographic indices that improve patient outcomes by guiding patient management in the acute phase.

3.2 Decongestion and stabilisation

Determining whether decongestion has been achieved with treatment for AHF can be difficult using clinical assessment alone. In many patients persisting congestion, often subclinical, contributes to early decompensation and rehospitalisation [16, 17]. In a post-hoc analysis of 496 patients with AHF enrolled in two RCTs (DOSE-AHF and CARRESS-HF), 50% of patients had at least one symptom of congestion on discharge [59]. On the contrary, patients are also at risk of over-diuresis and its secondary complications, including acute kidney injury. Clinical assessment relies on concordance between the right and left ventricle. When there is a mismatch between right and left sided pressures (e.g., high JVP secondary to pulmonary HTN but low or normal LVEDP) overdiuresis is common, occurring in up to 37% of patients admitted with AHF [60].

Current HF guidelines do not provide a standardized or optimal method for in-hospital assessment of congestion. With the increasing availability of portable echocardiograms and hand held scans it is now practical to do repeated studies during a patients stay. Change in JVP, hepatic flow, and

IVC size and collapsibility imaged by point-of care testing reflect whether diuresis is effective, and persistence of abnormal imaging correlates with higher risk of early re-admission [61]. Several algorithms using Doppler TTE indices have been proposed but have yet to be formally tested in a prospective RCT [60, 62]. One protocol tested in a pilot study of 20 patients offers promise that non-invasive haemodynamic measures could realistically and effectively guide treatment decision making. In this study a daily 5 min limited cardiothoracic ultrasound (CaTUS) that assessed 3 parameters — E:e' ratio, IVC size and the presence of pleural fluid ('B' lines or bibasal pulmonary effusions), in addition to standard clinical examination, was used to determine change in treatment [17]. Compared to a cohort of 100 patients with AHF where treatment was titrated based on usual clinical examination findings, treatment guided by CaTUS resulted in a greater improvement in all decongestion parameters (clinical, natriuretic peptides and echocardiogram) at discharge, less inpatient adverse events, a reduction in hospital stay by an average of 4 days and a reduction in the combined outcome of all-cause mortality and re-hospitalisation within 6months driven by a reduction in re-hospitalisation. Of note, half of patients in the standard care control group had residual congestion on cardiothoracic ultrasound at discharge which re-enforces how difficult it is to assess congestion on clinical parameters alone.

3.3 Post discharge in the 'vulnerable' period

No study has evaluated singular TTE guided management of HF in the immediate period post-discharge or in CHF. However, there are data available when echocardiography is used in combination with NTproBNP in CHF. In a retrospective study of 1137 stable patients with CHF, propensity matching was used to compare a combined echo-BNP-guided protocol vs standard clinical care. The combined end-point of death and/or worsening renal function was observed in 54 (18%) patients in the echo-BNP-guided group compared to 115 (39%) patients in the clinically-guided group (HR 0.49 [95% CI: 0.36–0.67], $P < 0.0001$) [63]. One of the key findings was the diuretic doses were more often down-titrated and disease modifying therapy (B blocker) up-titrated in the echo-BNP-guided cohort, whereas diuretics were increased and ACE-I decreased in the standard care cohort. This demonstrates once more how difficult it can be to accurately determine LVFP by clinical examination alone. The findings from this study suggest that the addition of echo-BNP-guided protocol to standard clinical care might improve clinical outcomes for patients with CHF. This needs to be assessed further in prospective, randomised, controlled trials, particularly in the immediate period post discharge following an admission with AHF.

3.4 Summary of role of echocardiography in treatment of patients with HF

Point-of care testing has allowed TTE to become a practical extension of clinical examination. Multiple indices have

demonstrated potential as a clinical aid to diagnosis LVFP. International agreement is now needed on which indices should be taken forward to large multi-centre RCTs. This would enable protocols on measurement of intra-cardiac pressures, in particular LVFP, with point-of-care testing to be developed that reduce intra and inter-observer error. Whether one algorithm can be accurately applied in all phases of treatment for all patients; or if a phenotype-specific response is required, as it is for diagnosis, for the heterogeneous population who develop AHF could also be established.

4. Role of transthoracic echocardiography in prognosis

All of the TTE modalities have demonstrated prognostic significance in CHF, albeit not consistently. Whether one modality has superior prognostic utility in AHF or if a combination of modalities has a synergistic effect is yet to be definitively established. Consequently, there is no guideline on how best to use TTE to determine prognosis

4.1 Measures of LV function

As GLS imaging increasingly becomes part of a standard TTE, studies assessing its prognostic value compared to 2D-LVEF suggest it has greater prognostic utility in patients with AHF [35, 41, 64, 65]. A study of 4172 patients across the spectrum of EF (2195 HFrEF, 642 HFmrEF, 1335 HFpEF) determined that GLS was strongly predictive of 5 year all-cause mortality whereas 2D LVEF was not [41]. In multivariable analysis, each 1% increase in GLS was associated with a 5% lower risk for mortality ($P < 0.001$). In 468 Australian patients GLS was an independent predictor of 30 day re-admission (HR 1.13 [95% CI 1.07–1.19]) whereas LVEF was not [65]. Likewise in an African American population of 291 patients, progressive worsening of GLS but not LVEF was associated with an increased risk of re-admission [64]. Importantly in the aforementioned Australian study GLS significantly improved re-classification of risk, particularly in patients with HFpEF (categorical net reclassification improvement, 0.34; $P = 0.04$). There has been one dissenting study of 618 patients with AHF where neither 2D LVEF or GLS were predictive of the composite endpoint of death or re-hospitalisation with heart failure [66]. The superior performance of GLS is likely due to its ability to detect abnormal myocardial function in HFpEF who now account for up to 50% of patient with AHF. Of note the one dissenting study was when TTE was done in stable patients prior to discharge, compared to within 48 hours of admission for all the positive studies. This raises the question of what impact timing of TTE has on prognosis.

4.2 Measures of LV filling pressures

In a study of 156 patients with AHF, the E/e' ratio was found to be the strongest predictor of cardiovascular death and superior to all other echocardiographic and clinical variables [67]. In 289 patients who underwent right heart catheterization and a TTE within 30 days, an $E:e' > 15$ was

an independent predictor of future HF events [44]. However this has not been universally found across the spectrum of HF with contrary results demonstrated in patients with HFpEF and advanced decompensated HF [47, 58, 68]. The simplified diagnosis of diastolic dysfunction in the 2016 joint guidelines from the ASE and EACVI has also been shown to accurately classify patients, according to their cardiovascular outcomes, particularly patients with HFpEF [47, 48, 69, 70]. In a study of 481 patients Grade III Diastolic dysfunction was an independent predictor of the composite endpoint of CVS death or unplanned rehospitalisation with HF with a HR of 1.89 (95% CI 1.17–3.07, $P = 0.009$) in all patients and HR 2.55 (95% CI 1.1–5.93, $P = 0.03$) in patients with HFpEF [69]. The individual indices that combine to diagnose diastolic dysfunction in the algorithm were only weakly correlated with outcomes when assessed individually including $E:e'$.

LA strain is a novel indice that has shown potential in small, exploratory studies as an accurate surrogate of LVFP both individually and in addition to the guideline recommended diagnostic algorithm for diastolic dysfunction in patients with HF [71, 72]. Importantly, in patients with HFpEF, it was an independent risk factor for morbidity and mortality [73, 74]. In AHF its utility as a prognostic marker has been assessed retrospectively in a registry of 4312 patients with AHF. Peak atrial longitudinal strain (PALS) was measurable in 88% of patients and was an independent predictor of death or HF hospitalisation (HR 0.984 (95% CI 0.971–0.996)) regardless of LVEF group but lost prognostic power in patients with AF [75]. Given the limitations of E/e' ratio for prediction of prognosis across the spectrum of AHF, the potential role of LA strain either as an individual marker or in combination with Doppler indices deserves further investigation

4.3 Valvular function

The presence of moderate to severe MR is increasingly recognised as an important prognostic factor in patients with AHF with reduced EF [76, 77]. However, this is not true for patients with HFpEF. In the ARIC study of 17931 patients, moderate/severe MR was an independent risk factor for mortality in patients with HFrEF (OR 1.30 (95% CI 1.16–1.45)) but not in patients with HFpEF (OR 0.99 (95% CI 0.88–1.11)) [78].

4.4 Right heart function

The importance of impaired RV systolic function or elevated PASP for prognosis in CHF is well established [79, 80]. In contrast, in patients with AHF, small studies have reported contrary results with no large multi-centre study available from which definitive conclusions can be established.

In a study of 326 Israeli patients with AHF, PASP > 50 mmHg was associated with one-year all-cause mortality both independently (HR 1.78, 95% CI 1.11–2.86, $P = 0.016$) and more significantly with RV dysfunction (HR 2.41, 95% CI 1.44–4.03, $P = 0.001$) [53]. RV dysfunction was defined as present when mild or greater systolic dysfunction was diagnosed on visual assessment or the RV fractional area change

<35%. RV dysfunction was not an independent predictor of mortality when PASP <50 mmHg. In 214 Italian patients with AHF and an LVEF <40%, PASP >40 mmHg was an independent predictor in multi-variate modelling of the combined endpoint of all-cause mortality or re-hospitalisation for worsening HF within one year [79]. In an elderly cohort of 401 Belgium patients with AHF pulmonary hypertension defined as a peak tricuspid regurgitation gradient (TRG) \geq 30 mmHg (equivalent to PASP \sim 40 mmHg) predicted all-cause mortality (HR 1.6, 95% CI 1.03–2.4, P < 0.01) at a mean follow up of 405 [81].

In contrast, a study of 1210 Spanish patients with AHF found PASP >60 mmHg was an independent predictor for one-year mortality post discharge but a PASP 45–60 mmHg was not [54]. PASP >50 mmHg was also not predictive of combined endpoint of death, heart transplantation or need for mechanical support in a cohort of 265 Italian patients with advanced HF (HR 1.07, 95% CI 0.65–1.8, P = 0.77) [82]. In this cohort TAPSE \leq 14 mmHg was predictive of outcome when combined with a TR gradient <20 mmHg (HR 2.97, 95% CI 1.19–7.41, P = 0.01) and more significantly again (HR 3.50, 95% CI 2.07–5.88, P < 0.001) when included in the derived variable RVCPI (=TAPSE \times TRG). In the first Italian study TAPSE was predictive of outcome on uni-variate but not multi-variate analysis [79]. In contrast in a further Italian study of 499 patients with AHF neither TAPSE (P = 0.314) nor TAPSE:PASP (P = 0.237) remained independently associated with 1-year mortality on multi-variate analysis though TAPSE:PASP was independently associated with an in-hospital adverse event (P = 0.024) [83].

4.5 Timing of echocardiogram

One of the potential causes for the conflicting prognostic relevance found in the aforementioned studies is the different timing relative to admission the TTEs were performed. Timing may be of particular importance for prognosis. The only published studies that have assessed timing of TTE on prognosis are two Japanese studies [84, 85]. In the OPTIMAL study, of 601 patients prospectively enrolled in a multicentre Japanese registry an admission TTE (within 3 days of admission) occurred in 80% of patients and 36% underwent a pre-discharge TTE (within 3 days of discharge [84]. A pre-discharge TTE was associated with improved survival post-discharge (multi-variate analysis: HR 0.38 (0.2–0.73, P = 0.004) whereas TTE at admission was not (uni-variate analysis: HR 1.26 (0.61–2.6, P = 0.5). Patients, on average, had more than 2 echocardiograms (including point-of care TTEs) during their stay; patients who had undergone a pre-discharge TTE had an average of 2.9 (\pm 1.4) TTEs and 83% of patients with a post-discharge TTE had also undergone an 'admission TTE' so a direct comparison of TTE if performed at only one time point can't be made. A similar result was found in a smaller study of 267 patients at a single Japanese study where multiple parameters on pre-discharge TTE (within 7 days of discharge) but only a single parameter on admission TTE were associated with MACE events

post discharge [85]. Healthcare for patients in Japan differs from most other countries as the average in-patient stay is considerably longer than the global average (median length of stay 19 vs 4 days) for patients with HF, so whether this result will be more widely applicable needs further investigation. These studies contradict the findings in the aforementioned studies assessing the prognostic significance of GLS and LVEF, where studies early during the admission (<48 hours) returned positive results, and the one negative result came from the study assessing pre-discharge TTE measurements.

4.6 Repeated measures within one admission

In a study designed to assess the prognostic relevance of RV dysfunction, repeated measures of PASP demonstrated importance for risk stratification. TTE was performed in 214 patients with AHF and an LVEF <40% both on admission to the coronary care unit and prior to discharge once clinically adjudicated as stabilised. Of the patients with a low TAPSE or high PASP on admission \sim 40% had improved by discharge. Event free survival post discharge was highest in those who had PASP <40 mmHg at admission and discharge, intermediate for those who had PASP >40 mmHg at admission but <40 mmHg at discharge and worst for those who had a sustained PASP >40 mmHg [79]. Change in LV parameters was not assessed. Of note this study also supports the finding in the largest studied cohort of CHF patients that a PASP >40 mmHg is negatively correlated with survival [80].

In a post-hoc analysis of the ESCAPE trial which included 433 patients with AHF who achieved the primary endpoint of death or re-hospitalisation had an increase in their LVEDV during the admission with HF ($+11 \pm 51.4$ mL; P < 0.05) compared to a decrease for those who did not reach the endpoint (-7.7 ± 47.8 mL). Though other TTE indices changed with treatment no other change in TTE indice was associated with the combined endpoint [86].

5. Conclusions

There is clearly a need for more effective tools to help clinicians better diagnose, adequately decongest and stabilise patients with AHF, as well as identify those at high risk of early post-discharge morbidity and mortality. Use of TTE at all stages of AHF has potential to improve outcomes. It is difficult to imagine TTE at a single time point during a patient's admission, where a fluctuating clinical course is common, achieving this potential. Instead repeated TTE where the focus changes from diagnosing cause and identifying LVFP, to achieving adequate de-congestion, to assessing for risk factors for early re-admission and finally monitoring of these in the vulnerable post-discharge period will be required to maximise clinical outcomes for patients with AHF (see Fig. 2). With the increasing availability of point of care TTE, this is now a practical and affordable option. International agreement is now needed on which TTE indices should be used at each stage and subsequent easy to follow algorithms developed and tested in large multi-centre RCTs. This would en-

able assessment of whether one approach can be accurately applied in all phases of treatment for all patients; or if a phenotype-specific response is required, as it is for diagnosis, to improve outcomes in the heterogeneous population who develop AHF.

Author contributions

SF researched and wrote the manuscript. RND critically reviewed and edited the manuscript.

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Conflict of interest

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