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Assessment of early treatment response by rapid cardiothoracic ultrasound in acute heart failure: Cardiac filling pressures, pulmonary congestion and mortality

Jonas Öhman[1], Veli-Pekka Harjola[2], Pasi Karjalainen[3] and Johan Lassus[4,5]

Abstract

Background: It is unclear how to optimally monitor acute heart failure (AHF) patients. We evaluated the timely interplay of cardiac filling pressures, brain natriuretic peptides (BNPs), lung ultrasound (LUS) and symptoms during AHF treatment.

Methods: We enrolled 60 patients who had been hospitalised for AHF. Patients were examined with a rapid cardiothoracic ultrasound (CaTUS) protocol, combining LUS and focused echocardiographic evaluation of cardiac filling pressures (i.e. medial E/e' and inferior vena cava index [IVCi]). CaTUS was done at 0, 12, 24 and 48 hours (±3 hours) and on the day of discharge, alongside clinical evaluation and laboratory samples. Patients free of congestion (B lines or pleural fluid) on LUS at discharge were categorised as responders, whereas the rest were categorised as non-responders. Improvement in congestion parameters was evaluated separately in these groups. The effect of congestion parameters on prognosis was also analysed.

Results: Responders experienced a significantly larger decline in E/e' (2.58 vs. 0.38, $p = 0.037$) and dyspnoea visual analogue scale (1–10) score (7.68 vs. 3.57, $p = 0.007$) during the first 12 hours of treatment, while IVCi and BNPs declined later without no such rapid initial decline. Among patients experiencing a >3 U decline in E/e' during the first 12 hours of treatment, 18/21 were to become responders ($p < 0.001$). LUS response was the only congestion parameter independently predicting both 6-month survival regarding all-cause mortality and the composite endpoint of all-cause mortality or rehospitalisation for AHF.

Conclusion: E/e' seemed like the most useful congestion parameter for monitoring early treatment response, predicting prognostically beneficial resolution of pulmonary congestion.

Keywords

Echocardiography, lung ultrasound, haemodynamics, acute heart failure, pulmonary congestion, prognosis

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Introduction

Acute heart failure (AHF) is a syndrome that is characterised mainly by elevated cardiac filling pressures causing symptoms via congestion.[1–3] Dyspnoea is the leading symptom causing emergency department (ED) visits and hospitalisation in these patients, and is mainly due to pulmonary congestion.[3,4] There is to date virtually no prognostically beneficial, guideline-determined medical therapy existing for AHF,[5,6] and hospitalisations are lengthy and expensive.[7] Residual congestion at discharge is also

[1]Division of Internal Medicine and Cardiology, Turku University Hospital, Turku, Finland
[2]Emergency Medicine, University of Helsinki, Department of Emergency Medicine and Services, Helsinki University Hospital, Helsinki, Finland
[3]Heart Center. Department of Cardiology. Pori Central Hospital, Pori, Finland
[4]Cardiology, University of Helsinki, Helsinki, Finland
[5]Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland

Corresponding author:
Jonas Öhman, Division of Internal Medicine and Cardiology, Turku University Hospital, Turku, Finland.
Email: jonas.ohman@tyks.fi

common after hospitalisation for AHF and is associated with poor prognosis.[8–10]

Although rapid treatment initiation in AHF has been associated with improved prognosis,[11,12] it has not gained as much attention in AHF as in other cardiovascular emergencies. Studies on vasodilators have shown that a rapid decline in left-sided cardiac filling pressures can be achieved with rapid treatment initiation in AHF,[2,13] which may result in rapid dyspnoea relief.[14] In recent years, echocardiographic estimation of cardiac filling pressures and evaluation of pulmonary congestion with lung ultrasound (LUS) have stepped more firmly into clinical practice in AHF.[15,16] There is, however, little information about the timely interplay between cardiac filling pressures, congestion and symptoms during AHF treatment, about how these changes should be monitored and how rapidly a favourable treatment response can be achieved.

Our primary target in this study was to evaluate whether a favourable treatment response by means of cardiac filling pressures, pulmonary congestion, symptoms and brain natriuretic peptides (BNPs) can be achieved already during the first 12 hours of treatment. Our second aim was to show how early these changes might predict treatment response, defined as resolution of pulmonary congestion, and how this might affect prognosis.

Methods

Enrolment

This single-centre study was performed in a tertiary care hospital. Inclusion criteria consisted of dyspnoea at rest, structural heart disease on conventional echocardiography, pulmonary congestion on LUS and a medial E/e' >15. Patients with pulmonary fibrosis, mitral stenosis or previous mitral valve procedure, chronically bed-ridden patients, intubated patients and patients with altered mental status were excluded. Patients were treated as per usual protocol by their treating physicians during hospitalisation, and the protocol in this study was not used to guide treatment.

We used a specially designed rapid cardiothoracic ultrasound (CaTUS) protocol consisting of LUS combined with echocardiographically derived bilateral filling pressures (medial E/e' and inferior vena caca index [IVCi]) for follow-up of these patients. In this study, we wanted to evaluate the timely association of declining cardiac filling pressures and other congestion parameters with resolution of pulmonary congestion among treatment-responsive patients. Hence, patients were categorised into one out of two categories depending on whether they were to achieve resolution of pulmonary congestion on LUS, and the evolvement of cardiac filling pressures, alongside other congestion parameters, were evaluated in each group. Patients who achieved resolution of pulmonary congestion were classified as responders, whereas patients discharged with residual pulmonary congestion were classified as non-responders. This study complies with the Declaration of Helsinki. The study was approved by the locally appointed ethics committee, and written consent was obtained from all participating patients.

All patients had the CaTUS study done in the ED upon arrival with clinical parameters, a symptom questionnaire and laboratory samples obtained directly after CaTUS. The CaTUS examination, clinical parameters, symptom questionnaire and laboratory samples where then obtained at the following four pre-fixed time points during follow-up: 12, 24 and 48 hours (±3 hours) and on the day of discharge. CaTUS was always conducted before obtaining clinical or laboratory parameters and before the symptom questionnaire. All enrolled patients also had a conventional echocardiography performed in the ED. The symptom questionnaire consisted of dyspnoea assessment by visual analogue scale (VAS) score on a scale of 0 to 10. Laboratory studies included BNP (Siemens ADVIA Centaur® assay), creatinine and electrolytes, and were analysed in the local routine laboratory. Estimated glomerular filtration rate (eGFR) was derived from creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation. All ultrasound examinations were performed with the Philips CX 50® device using the cardiac (S5-1) probe only. Patients were also followed up 6 months after hospital discharge in order to determine vital status (all-cause mortality).

Cardiothoracic rapid ultrasound protocol

Figure 1A shows the components of the CaTUS protocol. CaTUS included LUS and a focused echocardiography examination. All CaTUS measurements were conducted with the patient in a supine position with the upper body elevated at an angle of approximately 30° for maximum patient comfort. Slight leftward rotation of the patient was allowed only if necessary for sufficient visualisation, in order to avoid postural alteration of cardiac filling pressures.

AHF: acute heart failure; E/e': ratio of mitral inflow early diastolic E wave to medially derived early diastolic tissue Doppler e' wave; IVC: inferior vena cava.LUS included evaluation of B lines in two regions bilaterally: the apical and mammillary regions in a mid-clavicular line. Additionally, pleural fluid (PF) was searched for in the lower basal region bilaterally. B lines were positive for one region if three or more B lines were visualised within one intercostal space.[16] PF was defined as 5 mm or more of free fluid seen in the pleural space basally in the mid-axillary line. LUS was considered congestive if presenting bilateral B lines in at least one region or bilateral PF, and

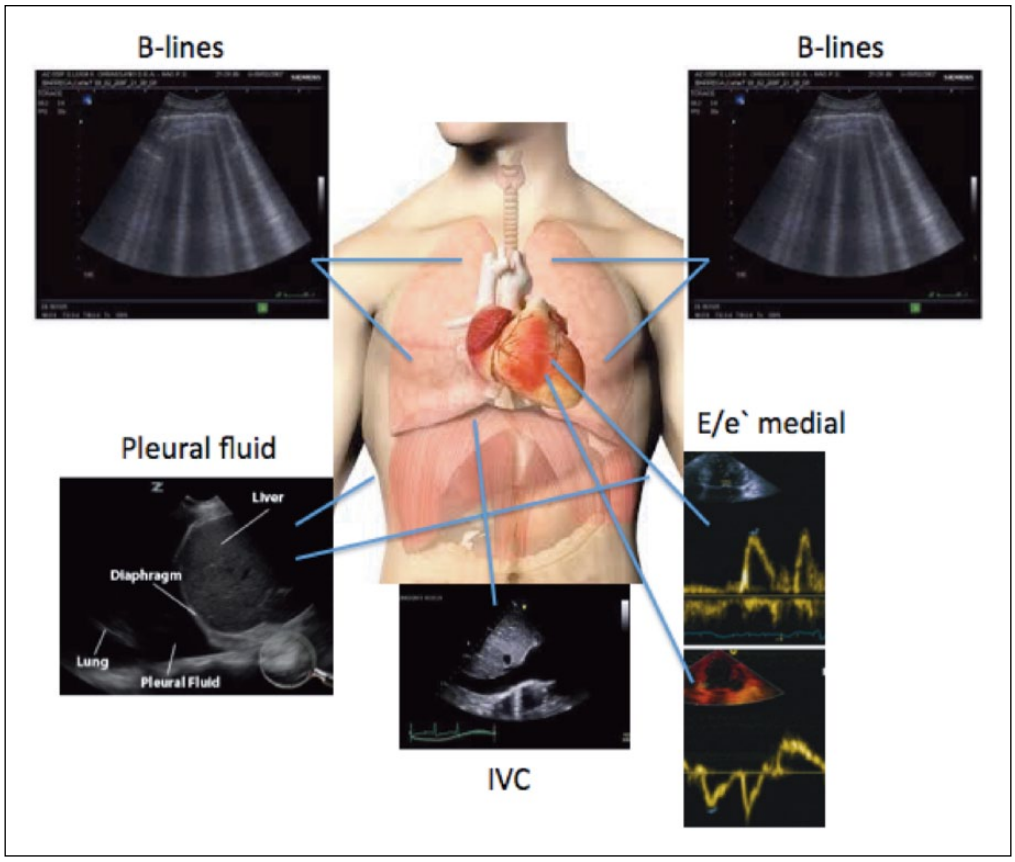

Figure 1. (A) Components of the cardiothoracic rapid ultrasound protocol. (B) Cursor placements for obtaining the medial E/e' ratio in the apical four-chamber view with echocardiography.

decongestive when absent of these. The focused echo examination in the CaTUS protocol evaluating cardiac filling pressures included medial E/e' ratio and a three class-scaled IVCi derived from IVC calibre and respiratory variation. Medial E/e' ratio was chosen in the planning phase due to the high number of bundle branch block, causing lateral dyssynchrony, possibly disturbing lateral e' measurements, while the average E/e' ratio was considered too time-consuming for this rapid protocol.

Correct cursor placement for obtaining the medial E/e' ratio can be seen in Figure 1B. The E wave was recorded using pulse wave Doppler (PW) at the tips of the opened mitral valve. If the patient was in sinus rhythm or any other regular rhythm, three consecutive cycles at end-expiration were recorded, and the average of these three E waves was registered. If the patient was presenting with an irregular rhythm, such as atrial fibrillation or extrasystolia, five consecutive cycles and the average of these five E waves were registered. Sweep speed was adjusted to fit a proper number of cardiac cycles into one picture frame. The e' wave was measured using tissue PW with the sample volume placed at the medial mitral annulus. Both the E waves and the e' waves were recorded from an apical four-chamber window using minimal angulation. Gain settings were optimised in order to obtain a crisp, clear signal without signal aberration.

IVC was recorded from the subcostal window. The recommended point of measurement was immediately caudal to the first hepatic vein, but if this point was poorly visualised, an optional point as close as possible could be used. Use of M mode was not mandatory, but encouraged if a clear perpendicular view was to be obtained. If no visualisation was recorded from the subcostal view, a lateral trans-hepatic view was used if feasible. IVC findings were graded into one of three categories: (1) maximum diameter ≤21 mm *and* >50% respiratory variation; (2) maximum diameter >21 mm *or* respiratory variation ≤50%; and (3) maximum diameter >21 mm *and* respiratory variation ≤50%.[17]

Since this was a single-centre, single-operator study, LUS classifications, as well as echocardiographic filling pressure measurements (E/e' and IVC grading), were both validated separately using experienced blinded validators. Regarding qualitative assessment of congestion on LUS, inter-observer agreement was 100%, and thus the κ coefficient was 1.0. For IVCi, the mean inter-observer coefficient

of variation was 4.37%, and for E/e' this was 9.99%. Thirty dyspnoeic patients, of which 15 were classified as having AHF by CaTUS and who were to be enrolled in this study, were randomly assigned to a senior cardiologist review of patient data for validating AHF diagnoses, and all of these 15 patients were also classified as having AHF by the senior cardiologist review. The conventional echocardiography is described in the Appendix.

Statistical analysis

Statistical analysis was done using the SPSS version 23 software. Continuous variables were presented as mean values including SD or median values including interquartile range (IQR), as was appropriate. Categorical variables were presented as counts and percentages. Differences between two groups were determined by unpaired t-test or Mann–Whitney U test for continuous variables and Pearson χ^2 test for grouped variables. Differences in survival between groups were analysed with the log-rank test and graphically displayed with Kaplan–Meier survival curves. Univariable analysis by Cox proportional hazards model was performed in order to assess the association between each variable and outcome. Gender, age and all variables with $p < 0.10$ by univariable analysis were taken as candidate variables for the multivariate analysis. Multivariable analysis was performed using a backward-conditional stepwise selection technique using Cox regression with the proportional hazards assumption fulfilled for all variables.

Results

After screening 118 consecutive dyspnoeic patients from our tertiary care ED, we enrolled a total of 60 hospitalised AHF patients. Baseline characteristics of responders (i.e. patients who achieved resolution of pulmonary congestion on LUS) as compared to non-responders (i.e. patients discharged with residual pulmonary congestion) are shown in Table 1. In the entire population, 27 patients (45%) had an ejection fraction (EF) of less than 40% (heart failure with reduced ejection fraction - HFrEF), 14 patients (23%) had an EF of between 40% and 50% (hf with mildly reduced ef - HFmrEF) and 19 patients (32%) had an EF of over 50% (hf with preserved EF - HFpEF).[5] Of the baseline parameters, baseline BNP was smaller and eGFR larger in responders compared to non-responders. At discharge, 37 patients (61.7%) were classified as responders by LUS, and 23 (38.3%) were classified patients as non-responders (i.e. were discharged with residual congestion on LUS).

Compared to non-responders, responders had a significantly larger absolute decrease in E/e', VAS score and IVCi during treatment and a lower E/e', VAS score and IVCi on the day of discharge, with no significant difference in these parameters on admission (Table 1). Responders also had a significantly lower BNP at discharge and a significantly larger proportional, albeit not absolute, decrease in BNP during the treatment course (Table 1). A total of 81.1% of the responders became asymptomatic (VAS = 0) during the treatment course compared to 47.8% of the non-responders ($p = 0.010$) (Table 1), while seven responders (18.9%) remained symptomatic at discharge despite the absence of pulmonary congestion on LUS. Among responders, the first LUS examination without B lines, indicating resolution of pulmonary parenchymal congestion, occurred at a median time point of 24 hours (IQR 12–48 hours).

The timely interplay of cardiac filling pressures, symptoms and BNP with resolution of pulmonary congestion during the first 48 hours of treatment can be seen in Figure 2. Responders displayed a rapid mean decrease in E/e' and dyspnoea VAS scores during the first 12 hours of treatment, predicting pulmonary decongestion, and these decreases were significantly larger in responders compared to non-responders. IVCi in turn decreased rather linearly among responders, with no such significantly faster initial decrease. No significant correlation was found between initial decline in E/e' or symptoms and length of hospitalisation in either of the groups, nor was the mean length of stay shorter among responders compared to non-responders, as can be seen in Table 1. Among non-responders, cardiac filling pressures decreased very little at all during the whole treatment course, while symptoms decreased linearly throughout hospitalisation.

When more closely investigating the rapid decrease in E/e' among responders during the first 12 hours, we found out that this decrease was a combination of a non-significantly larger decrease in the mean E wave (19.4 vs. 4.61 cm/second) and a non-significantly larger mean *increase* in e' (0.92 vs. –0.48 cm/second) as compared to non-responders. Thus, both of these two parameters seemed to contribute to the rapid decrease in E/e'.

Among 21 patients displaying an absolute decrease in E/e' of >3 U during the first 12 hours, only three patients remained as non-responders ($p < 0.001$), and none of these three non-responders presented any further decrease in E/e' during the rest of their hospitalisation.

Among responders, there was a significant negative correlation between the absolute decline in E/e' during the first 12 hours and the rest of the stay ($R^2 = 0.276$, $p = 0.001$), indicating that 'late bloomers' who displayed a lesser decline in E/e', but whose pulmonary congestion disappeared, were more likely to experience a substantial decline in E/e' later on. Median BNP did not decrease, but instead *increased* in both groups during the first 12 hours, and significantly more so among non-responders. Later on, BNP decreased slowly in both groups, but median values at 48 hours were still close to baseline (304 vs. 433 ng/L in responders and 1001 vs. 1225 ng/L in non-responders), (p = NS for both).

Table 1. Baseline and treatment-related characteristics in lung ultrasound responders compared to non-responders.

Baseline characteristics	All	Responders	Non-responders	*p*-value
Age (years)	76.1 (SD 11.6)	74.5 (SD 12.9)	78.6 (SD 8.71)	0.192
Diabetes	26 (43%)	17 (45%)	9 (39%)	0.789
Gender male	27 (45%)	18 (49%)	9 (39%)	0.595
Renal failure	22 (37%)	10 (27%)	12 (52%)	0.060
Hypertension	48 (80%)	28 (76%)	20 (87%)	0.340
Coronary artery disease	31 (51.7%)	20 (54%)	11 (48%)	0.791
Previously diagnosed heart failure	35 (58%)	18 (49%)	17 (74%)	0.065
Pulmonary disease	16 (27%)	13 (35%)	3 (13%)	0.076
Clinical parameters				
Systolic blood pressure	140 (SD 30.5)	144 (SD 32.8)	134 (SD 26.0)	0.243
Heart rate	82.5 (SD 20.1)	81.1 (SD 19.4)	84.6 (SD 21.4)	0.525
Sinus rhythm	26 (43%)	15 (41%)	11 (48%)	0.603
Atrial fibrillation/flutter	27 (45%)	17 (46%)	10 (44%)	1.000
QRS complex >120 ms	25 (42%)	18 (49%)	7 (30%)	0.189
Rales on auscultation	20 (33%)	11 (30%)	9 (39%)	0.575
Obstruction on auscultation	10 (17%)	8 (22%)	2 (9%)	0.291
Dyspnoea VAS score	6.68 (SD 2.46)	6.59 (SD 2.61)	6.83 (SD 2.25)	0.726
Respiratory rate	23.4 (SD 6.49)	23.4 (SD 6.19)	23.4 (SD 7.10)	0.962
CaTUS parameters				
Pleural fluid	38 (63%)	20 (54%)	18 (78%)	0.097
B lines	56 (93%)	35 (95%)	21 (91%)	0.634
E/e'	20.5 (SD 3.84)	20.5 (SD 3.57)	20.7 (SD 4.33)	0.830
IVC grade (1/2/3)	10%/57%/33%	8/60/32%	13/52/35%	0.778
Laboratory samples				
Median BNP (ng/L) on admission	706 (355–1680)	505 (322–945)	1026 (715–1874)	**0.006**
Mean eGFR (mL/minute/m^2) on admission	53.6 (SD 22.7)	58.3 (SD 23.0)	45.9 (SD 20.3)	**0.038**
Comprehensive echo parameters				
Ejection fraction (%)	44.3 (SD 16.7)	45.2 (SD 18.0)	42.8 (SD 15.5)	0.600
e'	5.75 (SD 1.72)	5.69 (SD 1.85)	5.84 (SD 1.51)	0.735
Right ventricular dysfunction	16 (27%)	11 (30%)	5 (22%)	0.561
Significant valve disease	36 (60%)	20 (54%)	16 (70%)	0.285
Treatment-related parameters				
Length of stay (days)	6.57 (SD 3.78)	6.16 (SD 3.00)	7.22 (SD 4.81)	0.299
Decline in eGFR (mL/minute/m^2)	2.83 (SD 13.4)	5.08 (SD 13.3)	–0.78 (SD 13.0)	0.100
Decline in HR (per minute)	11.3 (SD 22.1)	11.0 (SD 21.8)	11.8 (SD 23.1)	0.886
Decline in SBP (mmHg)	16.2 (SD 32.6)	19.7 (SD 35.5)	10.7 (SD 27.0)	0.303
Decline in E/e'	3.21 (SD 4.58)	4.49 (SD 4.04)	1.14 (SD 4.72)	**0.005**
Final E/e'	17.3 (SD 5.72)	15.9 (SD 5.78)	19.5 (SD 3.91)	**0.017**
Final VAS score	1.30 (SD 2.49)	0.51 (SD 1.28)	2.57 (SD 3.36)	**0.001**
Final IVC grade (1/2/3)	47%/38%/15%	62%/27%/11%	21/57/22%	**0.009**
Median decline in BNP (ng/L)	218 (–5.0 to 536)	218 (16.5–429)	174 (76.0–998)	0.939
Proportional decline in BNP (%)	48.9 (2.2–76.2)	66.2 (48.9–84.8)	1.7 (–19.0 to 41.9)	**<0.001**
Median final BNP (ng/L)	143 (119–876)	128 (114–144)	940 (769–1793)	**<0.001**

Values are expressed as mean ± SD, except for BNP, which is expressed as median (25th–75th interquartile percentile). Categorical variables are expressed as number of cases (%).
VAS: visual analog scale; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; HR: heart rate; SBP: systolic blood pressure; IVC: inferior vena cava; CaTUS: cardiothoracic ultrasound; E/e': ratio of mitral inflow early diastolic E wave to medially derived early diastolic tissue Doppler e' wave.

The impact of baseline and congestion parameters on 6-month mortality and on the composite endpoint of 6-month mortality or hospitalisation for AHF can be seen in Tables 2 and 3. LUS response (i.e. resolution of pulmonary congestion on LUS) was the only independently significant prognostic parameter regarding both endpoints, displaying a hazard ratio of 0.19 (95% confidence interval [CI]: 0.06–0.67, $p=0.010$) regarding all-cause mortality and 0.38 (95% CI: 0.17–0.85, $p=0.017$) regarding the composite endpoint. The survival

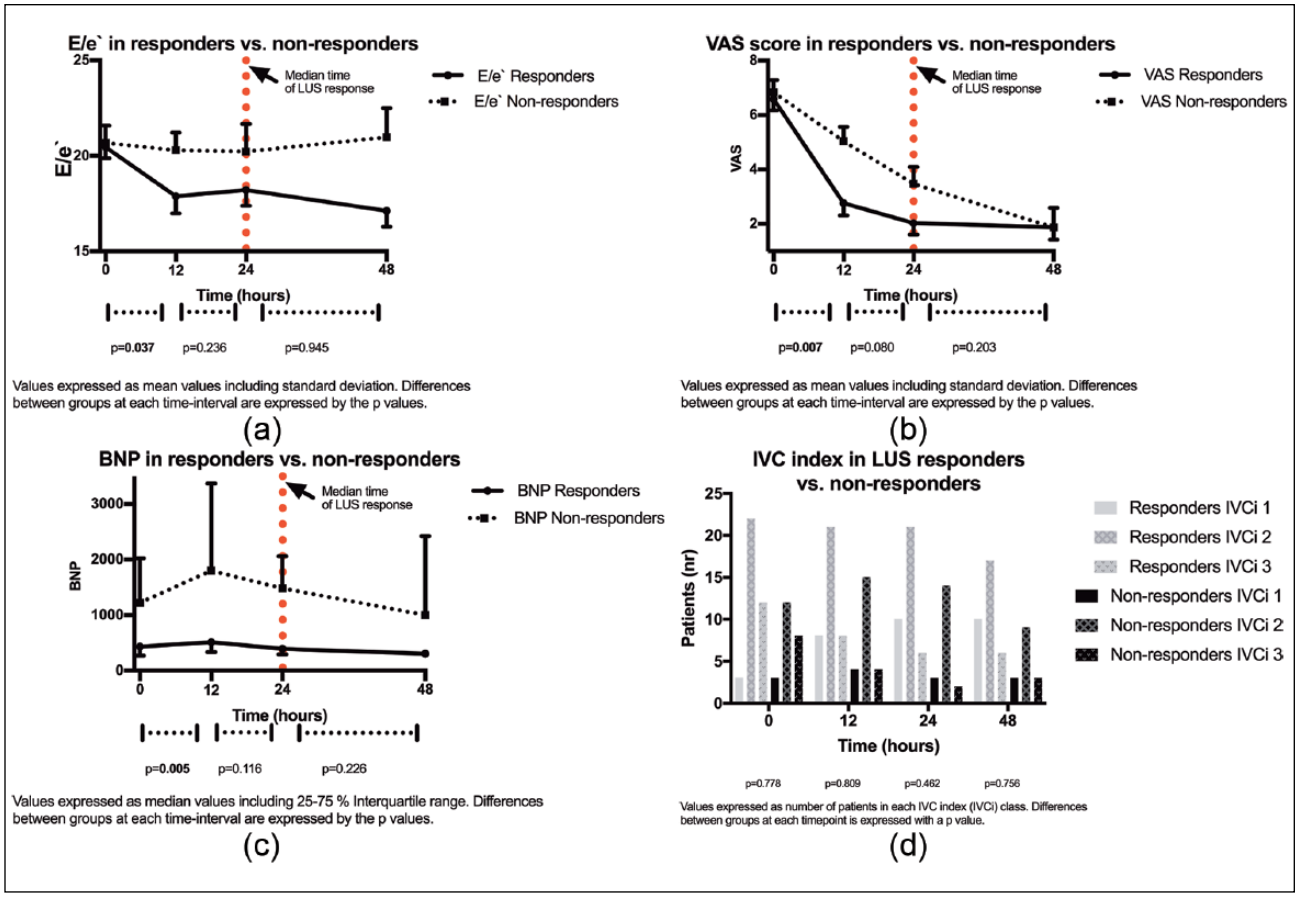

Figure 2. Serial assessment of E/e', VAS score (1–10), BNP and IVCi (1–3) in LUS responders compared to non-responders during the first 48 hours of treatment. Values are expressed as means, including standard error mean, except for BNP, which is expressed as median including 25–75% interquartile range. The vertical red dashed line represents the median time until resolution of pulmonary congestion by LUS (LUS response); *p*-values are expressed for differences in declines between responders and non-responders regarding the three time intervals.
E/e': ratio of mitral inflow early diastolic E wave to medially derived early diastolic tissue Doppler e' wave; VAS: visual analogue scale; IVCi: inferior vena cava index; BNP: brain natriuretic peptide; LUS: lung ultrasound.

curves displaying the impact of LUS response on both prognostic endpoints can be seen in Figure 3.

Discussion

In this study, we wanted to delineate the timely interplay of sequential favourable changes in cardiac filling pressures, symptoms and natriuretic peptides with the resolution of pulmonary congestion among treatment-responsive patients. Thus, we divided our population into two groups: (1) those who were to achieve resolution of pulmonary congestion during their hospitalisation period (i.e. 'responders'); and (2) those who did not achieve resolution of pulmonary congestion and were discharged with residual congestion on LUS (i.e. 'non-responders'). As LUS response eventually was the only congestion parameter independently predicting survival regarding both endpoints, this delineation also seemed rational from a prognostic viewpoint. When comparing the two groups, we found that a rapid decline in E/e' and symptoms occurred among responders by as early as the first 12 hours of treatment, predicting resolution of pulmonary congestion, while IVCi and BNP declined later. By contrast, non-responders showed very little decline in cardiac filling pressures and BNP at all during their entire hospitalisation period, reflecting inadequate decongestion by all measures. A favourable early treatment response seemed to further predict a favourable treatment trajectory throughout the hospitalisation period, since patients achieving a substantial early decrease in E/e' were unlikely to remain as non-responders. Thus, of the different congestive parameters, E/e' seemed to be the fastest reflector of an early treatment response, predicting resolution of pulmonary congestion. Eventually, responders had a significantly greater reduction in all congestion parameters, reflecting complete systemic decongestion. Interestingly, almost 40% of the patients in this study remained as non-responders (i.e. were discharged with residual congestion on LUS), and post-discharge mortality in this group was high.

Table 2. Cox regression analysis of the effect of baseline and treatment-related parameters on all-cause mortality. Parameters are analysed as absolute changes during the hospitalisation course as well as discharge values.

Univariate				Multivariate		
Baseline	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.045	0.99–1.01	**0.093**			
Sex (male)	1.53	0.57–4.11	0.401			
Left ventricular EF (%)	1.011	0.98–1.04	0.461			
RV dysfunction	1.01	0.37–2.77	0.993			
Significant valve disease	1.12	0.41–3.07	0.832			
Pulmonary disease	1.27	0.44–3.62	0.660			
Atrial fibrillation	0.91	0.34–2.43	0.847			
Heart rate (per minute)	0.95	0.93–0.99	**0.004**	0.93	0.88–0.98	**0.004**
Initial systolic BP (mmHg)	0.98	0.96–1.00	**0.019**			
Initial BNP/100 (ng/L)	1.06	1.03–1.09	**<0.001**	1.04	1.01–1.07	**0.006**
Initial eGFR (mL/minute/m^2)	0.97	0.95–0.99	**0.024**			
Initial E/e'	0.95	0.83–1.08	0.426			
Initial IVCi	1.56	0.67–3.57	0.297			
Dynamic parameters						
Decline in eGFR (mL/minute/m^2)	0.97	0.94–1.01	0.119			
Decline in BNP/100 (ng/L)	1.05	1.02–1.09	**0.004**			
Decline in E/e'	0.92	0.82–1.02	0.122			
Decline in IVCi	0.66	0.37–1.20	0.176			
Asymptomatic at discharge	0.2	0.07–0.54	**0.002**			
Resolution of congestion (LUS)	0.28	0.10–0.77	**0.013**	0.19	0.06–0.67	**0.010**
On discharge						
Final E/e'	1.03	0.95–1.12	0.480			
Final IVCi	2.12	1.13–4.00	**0.019**			
E/e' <15	0.85	0.31–2.35	0.758			
Final BNP/100 (ng/L)	1.04	1.01–1.07	**0.014**			

HR: hazard ratio; CI: confidence interval; EF: ejection fraction; RV: right ventricle; BP: blood pressure; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; IVCi: inferior vena cava index; E/e': ratio of mitral inflow early diastolic E wave to medially derived early diastolic tissue Doppler e' wave; LUS, lung ultrasound response.
Bold *p*-values are statistically significant.

How to optimally monitor AHF treatment is not clearly defined to date. Current guidelines[5,6] recommend daily evaluation of the signs of congestion, symptoms, fluid balance, vital signs, body weight and kidney function in hospitalised AHF patients, and adjustment of decongestive therapy accordingly. There is some observational data suggesting that echocardiographic monitoring of cardiac filling pressures and serial LUS examinations during AHF treatment could be potentially useful for assessing treatment response. Echocardiographically derived cardiac filling pressures have been shown to correlate with BNPs at day 7 compared to baseline in patients treated for AHF.[18] Echocardiographically derived filling pressures have also decreased in association with pulmonary capillary wedge pressures following inodilative drug infusions,[19] and pulmonary congestion on LUS has disappeared after dialysis,[20] successful in-hospital AHF treatment[9,21] and even after pre-hospital positive continuous positive airway pressure.[22] Pre-discharge pulmonary decongestion on LUS after AHF hospitalisation has also been associated with poor prognosis.[9,21] However, there are no data that exist regarding regular, serial monitoring during early treatment using these modalities, and serial monitoring is also not mentioned in the heart failure guidelines.[5,6] Regarding natriuretic peptides, the evidence supporting their use for treatment monitoring is scarce, as is recognised in the guidelines, but there is some evidence supporting the use of pre-discharge values.[5,6] Their slower kinetics, however, especially in the presence of renal failure, make them seemingly less suitable for early treatment monitoring.[23]

In this present study, a rapid decline in E/e' among responders was associated with a rapid improvement of symptoms and prognostically beneficial resolution of pulmonary congestion. Although some responders also experienced a decline in E/e' later on, an unfavourable treatment course trajectory was very unlikely in case of an early significant decline in E/e'. Thus, E/e' seems to be the most useful objective congestion parameter for monitoring early treatment. This further supports the rationale of intensive follow-up by as early as the first 12 hours of hospitalisation, since identifying non-responsive patients early theoretically offers the possibility of intensifying treatment

Table 3. Cox regression analysis of the effect of baseline and treatment-related parameters on the composite endpoint of 6-month all-cause mortality or hospitalisation for acute heart failure. Parameters are analysed as absolute changes during the hospitalisation course as well as discharge values.

Univariate				Multivariate		
Baseline	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.03	0.99–1.06	0.127			
Sex (male)	1.54	0.75–3.16	0.239			
Left ventricular EF (%)	1.01	0.98–1.03	0.607			
RV dysfunction	1.32	0.64–2.71	0.450			
Significant valve disease	1.21	0.58–2.54	0.615			
Pulmonary disease	1.27	0.58–2.72	0.545			
Atrial fibrillation	1.11	0.54–2.27	0.780			
Heart rate (per minute)	0.97	0.95–0.99	**0.009**	0.97	0.94–0.99	**0.011**
Initial systolic BP (mmHg)	0.98	0.97–0.99	**0.008**			
Initial BNP/100 (ng/L)	1.04	1.01–1.07	**0.002**	1.03	1.00–1.06	**0.045**
Initial eGFR (mL/minute/m^2)	0.98	0.96–1.00	**0.018**			
Initial E/e'	0.94	0.85–1.04	0.224			
Initial IVCi	1.18	0.66–2.11	0.583			
Dynamic parameters						
Decline in eGFR (mL/minute/m^2)	0.98	0.96–1.01	0.292			
Decline in BNP/100 (ng/L)	1.02	0.99–1.06	0.246			
Decline in E/e'	0.93	0.86–1.00	**0.078**			
Decline in IVCi	0.64	0.41–0.98	**0.040**			
Asymptomatic at discharge	0.77	0.36–1.64	0.493			
Resolution of congestion (LUS)	0.44	0.22–0.90	**0.025**	0.38	0.17–0.85	**0.017**
On discharge						
Final E/e'	1.02	0.96–1.08	0.576			
Final IVCi	1.93	1.21–3.01	**0.005**			
E/e' <15	0.65	0.30–1.39	0.266			
Final BNP/100 (ng/L)	1.04	1.01–1.06	**0.005**			

HR: hazard ratio; CI: confidence interval; EF: ejection fraction; RV: right ventricle; BP: blood pressure; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; IVCi: inferior vena cava index; E/e': ratio of mitral inflow early diastolic E wave to medially derived early diastolic tissue Doppler e' wave; LUS, lung ultrasound response.

early on. Symptoms decreased rapidly alongside E/e' in responders, but they also decreased substantially among non-responders, making them seemingly less useful for distinguishing adequate decongestion. Regarding the other parameters, IVCi and BNPs seemed to clearly be slower markers of treatment response. BNPs actually remained clearly higher among non-responders from the start of the hospitalisation period onwards, probably indicating more severe baseline cardiovascular disease including renal failure, and this hypothesis is further supported by the independent impact of baseline BNPs on both prognostic endpoints and the lower eGFR in non-responders. Thus, standard treatment might not be sufficient to achieve adequate decongestion among patients with high baseline BNPs, thus probably indicating a need for extra therapeutic attention in this patient group. While the proportional decline in BNPs was significantly higher among responders during the entire hospitalisation period, this decline seemed to occur later. During early hospitalisation, BNPs actually increased in both groups, probably reflecting cardiac insult and/or elevation of cardiac filling pressures prior to admission.

The CaTUS protocol used in this study was rapid, taking less than 5 minutes to perform in all patients, despite including both LUS and echocardiography. Thus, the protocol seems useful for the ED and for daily monitoring in a hectic hospital setting. This rapidity was achieved by using a focused echocardiography and LUS protocol, combining only six lung zones in total with only two echocardiographic filling pressure parameters. Although the traditional LUS protocol includes 28 lung zones, excellent results have also been achieved with fewer lung zones,[24] and a protocol with only two lung zones has been successfully validated in critically ill patients in order to assess parenchymal congestion.[25] Since substantial pulmonary congestion normally encompasses the entire lungs bilaterally, faster protocols might be as effective in critically ill patients, and combining haemodynamic assessment by echocardiography with LUS with a protocol such as CaTUS should further improve the diagnostic accuracy for

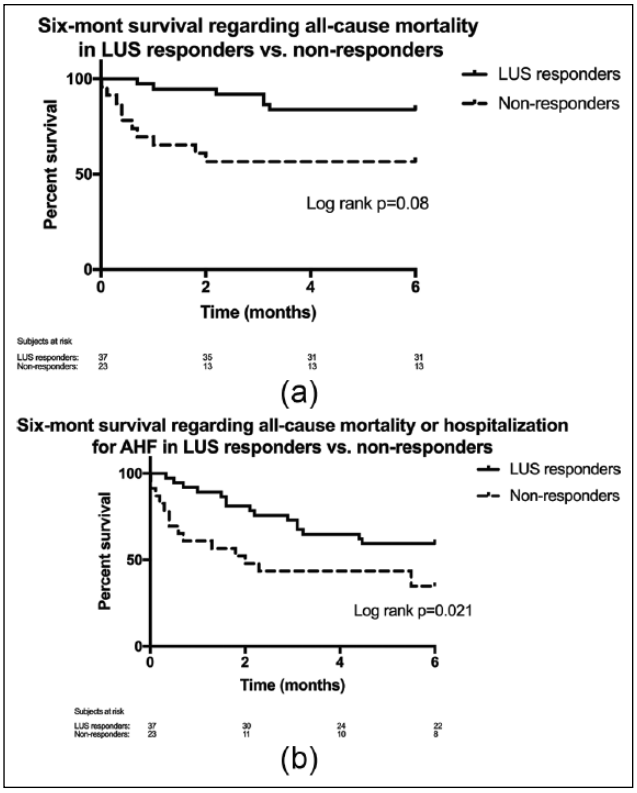

Figure 3. (a) Six-month survival regarding all-cause mortality in lung ultrasound responders compared to non-responders. (b) Six-month survival regarding the composite endpoint of all-cause mortality or hospitalization for acute heart failure in lung ultrasound responders compared to non-responders.

AHF. Although no single parameter is considered optimal for evaluating left-sided cardiac pressures alone,[26] E/e' has been studied in a wide variety of patient groups[27] and has the advantage of also being feasible in patients with non-sinus rhythms.[26,28] Atrial fibrillation is very common among AHF patients, and fewer than 50% of our patients presented with a sinus rhythm. Thus, E/e' seemed like a rational choice for estimating left-sided filling pressures within the CaTUS protocol. Furthermore, an initial decrease in E/e' seemed to be a result of both a decreased E wave and an *increased* e' wave. Since e' is considered to be a rather pre-load-independent marker of diastolic function,[29] this suggests that diastolic function also improves with pharmacological AHF therapy. Thus, using the E wave or the E/A ratio alone might have underestimated treatment efficacy in our population.

Study limitations

This was a single-centre, single-investigator study and the ultrasound examinations were performed by a single investigator. They were, however, blindly validated with good inter-observer correlations, as discussed above. The population was small, and hence the study was underpowered for more complex prognostic calculations.

Conclusions

E/e' seemed to be the fastest and most useful objective marker for monitoring early treatment response, predicting prognostically relevant resolution of pulmonary congestion. An unfavourable treatment response was very unlikely in case of a substantial early decline in E/e'. Future randomised treatment trials will be needed in order to confirm whether rapidly initiated, ultrasound-guided AHF treatment could improve treatment results in AHF compared to standard treatment.

Conflict of interest

The authors declare that there is no conflict of interest.

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