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Diagnostic accuracy of Lung Ultrasound for identification of elevated left ventricular filling pressure

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Abstract: (193 words)

Aims: The current algorithm in transthoracic echocardiography (TTE) proposed in the 2016 ASE/EACVI recommendation for the estimation of left ventricular filling pressure (LVFP) is quite complex and time-consuming. B-lines, in lung ultrasonography (LUS), could constitute an interesting tool for LVFP evaluation in clinical practice, although data regarding their association with invasive haemodynamics are lacking. The purpose of this study was to explore the diagnostic accuracy of B-lines in identifying elevated left ventricular end-diastolic pressure (LVEDP).

Method and results: 81 adults with significant dyspnoea (NYHA \geq 2) were prospectively analyzed by LUS in four areas in each hemithorax and a complete TTE within four hours prior to coronary angiography. Twenty-eight patients had elevated LVEDP. Clinical variables yielded a C-index of 79% to identify elevated LVEDP. The number of total B-lines was higher in the elevated LVEDP group (1.0vs17.0, $p<0.0001$) and significantly increased the diagnostic accuracy (C-index increase=10.5%, $p=0.002$) and net reclassification index (NRI=145.4, 113.0-177.9, $p<0.0001$) on top of clinical variables.

Conclusion: This study demonstrates the substantial diagnostic capacity of B-lines to identify elevated LVEDP, which appears superior to that of classical echocardiographic strategies. This tool should be considered in a multi-parametric approach in patients with heart failure.

Conflicts of interests: None

Running title: B-lines and left ventricular filling pressure

Keywords: B-lines, lung ultrasonography, left ventricular filling pressure, echocardiography

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Introduction

Echocardiography is currently the gold standard in the routine evaluation of left ventricular filling pattern in patients with dyspnoea and/or heart failure. The 2016 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines for the evaluation of left ventricular diastolic function[1] reported a new algorithm to assess the presence and severity (grade 1 to 3) of diastolic dysfunction (DD) and to estimate Left Ventricular Filling Pressure (LVFP). This algorithm, based on the estimation of left atrial volume, E wave, velocity, e' septal and lateral velocity by Tissue Doppler Imaging (TDI), and maximal tricuspid velocity is quite complex and time-consuming.

B-lines (also called “comet-tail artefacts” or “lung comet”) are linear artefacts that are observed during lung ultrasonography (LUS), reflecting extravascular lung water [2]. LUS is simple and can be applied quickly at a patient's bedside with the same probe that is used for echocardiography. The utility of B-line quantification for the diagnosis of acute pulmonary oedema has been demonstrated in multiple studies. B-line number shows a good correlation with chest radiography findings, brain natriuretic peptide levels and E/e' ratio [3–6]. In patients with subclinical pulmonary congestion, the assessment of B-lines allows the diagnosis of subclinical pulmonary congestion and is strongly associated with clinical outcome[7–9]. With regard to the ASE/EACVI joint recommendations which can be difficult to apply in the presence of severe valvulopathy and/or atrial fibrillation, B-line quantification can be performed in these clinical conditions and is associated with clinical outcome regardless of underlying heart disease [10]. Moreover, echocardiographic algorithms are influenced by ageing given its strong association with diastolic function impairment; this may decrease the diagnostic accuracy for elevated LVFP in these patients[11]. B-lines could therefore constitute a valuable bedside tool for LVFP evaluation in routine clinical practice. A previous study[12] reported a good association of B-line count and right catheter haemodynamics although did not

evaluate diagnostic accuracy *per se* and included mostly young patients (a third of the patients were included after heart transplant). Data regarding the association between B-lines and left cardiac haemodynamics in non-transplanted elderly patients are still lacking.

The purpose of this study was to explore the diagnostic accuracy of B-lines to identify elevated left ventricular end-diastolic pressure (LVEDP), as assessed by left heart catheterization (LHC).

Methods

Study sample

We prospectively included 93 adults (≥ 18 years old) with significant dyspnoea (NYHA ≥ 2) who underwent a coronary angiography with left heart catheterization from May 2016 to July 2017. Patients with mitral stenosis (because of significant differences in LVEDP compared to other heart disease), known pulmonary fibrosis, pneumonia, active lung cancer or a history of recent chest trauma were excluded. Patients who had any change in diuretic treatment between Transthoracic Echocardiography (TTE) and LHC were also excluded. These exclusion criteria were chosen among conditions that alter B-line counting[13]. Clinical and demographic data were obtained from the review of medical records. N-terminal Pro-Brain Natriuretic Peptide (NT-ProBNP) testing was performed within routine care prior to the angiography and recorded when available. The study protocol was approved by our local ethics committee (authorization number: 2014-A01331-456).

Transthoracic Echocardiography

All patients underwent a standard TTE prior to LHC using a Vivid S6, E7 or E9 ultrasound system (General Electric Healthcare, Horten, Norway). Images were recorded on a remote station for off-line analysis by dedicated software (EchoPAC PC, version BT 13, General Electric Healthcare, Horten, Norway). Interpretation was blinded from haemodynamic

data. Left ventricular ejection fraction (LVEF) was measured by biplane Simpson's method, and $LVEF \geq 50\%$ was considered to constitute a preserved ejection fraction [14]. Typical diastolic parameters were measured: peak tricuspid regurgitation velocity, right atrial pressure estimated by inferior vena cava diameter and collapsibility, mitral LV inflow early peak (E) with the deceleration time and late peak (A), isovolumic relaxation time (IVRT), septal and lateral diastolic early peak velocity of mitral annulus (e') and left atrial volume index (LAVi)[1].

Lung Ultrasonography

Lung ultrasonography was performed immediately before a comprehensive TTE with patients in supine or near-to-supine position, as previously described [2]. Four different areas for each hemithorax were explored during five seconds (Figure 1, panel B-1). The probe was placed in sagittal orientation, in the intercostal space, at an imaging depth of 10 to 14 cm. Loops were recorded in order to maximize the number of B-lines for each zone by adjusting the gain to allow for optimal visualization of the pleural line and B-lines (Figure 1, panel B-2). The scanning lasted less than 3 minutes. Loops were stored on a remote station to perform off-line analysis with the same tools as those used for TTE. For each lung ultrasound zone, the number of B-lines was quantified from 0 to 10. Consequently, LUS scoring ranged from 0 to 80 (8-zones method). B-line count was used either as a continuous variable or dichotomized using the following cut-offs: 1) 3, which has been reported to be the best cut-off for the prediction of stable heart failure (HF) patient outcomes[7,15], 2) 8, which approximately corresponds to a score of 30 when using the 28-points method, a useful cut-off in patients at discharge from HF hospitalization[16], and 3) the presence of one or two bilateral positive zones (> 2 B-lines on a recording site) as promoted by acute LUS guidelines [13] (Figure 1, panel B-3).

Haemodynamic data

LHC was performed, within four hours after TTE, via a retrograde approach from the radial artery. Before coronary angiography, transducers were calibrated, with a 0-level set at the mid-axillary line. The LVEDP was recorded continuously (25 mm/s) with a 5 French Judkin R4 catheter (ICU Medical, San Clemente, CA, USA) placed at the mid-LV cavity using fluoroscopic screening. Waveform analysis was performed from paper tracings and was blinded from lung and heart ultrasonographic data. The LVEDP was calculated as the mean value of 4 consecutive heart cycles.

An elevated LVEDP was defined by a LVEDP > 20 mmHg[17]. In our experience, a LVEDP cut-off of 16 mm Hg is not strongly associated with symptoms and signs of congestion.

Inter- and intra-observer variability

Interpretation of LUS loops was repeated in 10 random patients (>10% of the total population). An inter-observer reproducibility assessment was performed by 4 independent observers. For the intra-observer reproducibility assessment, the second reading was performed at least 2 months after the initial evaluation. During these repeated measurements, all observers were blinded to previous analysis and were unaware of patient clinical and haemodynamic data.

Statistical analysis

Continuous data are presented as the mean \pm standard deviation, and categorical data are presented as numbers. The distributions of variables were assessed visually. Comparisons between both groups (LVEDP \leq 20 mm Hg or > 20 mm Hg) were performed using an unpaired t-test or a Mann-Whitney test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables, as appropriate. Correlation between parameters and LVEDP was tested by a Spearman test. Receiver operating characteristic (ROC) curves were created and areas

under the curves (AUC) were calculated for the ability of each parameter to identify patients with a LVEDP > 20 mmHg. In addition, continuous net reclassification improvement (NRI) was performed to assess the additional value of ultrasonography parameters on top of clinical variables in predicting LVEDP>20 mmHg. A diagnostic accuracy increase on top of these clinical variables was assessed using C-index differences extracted from logistic models.

Inter- and intra-observer variabilities of B-line counting were expressed by intra-class correlation coefficients.

Tests with p-values less than 0.05 were considered to be statistically significant.

Statistical analysis was performed using SAS (SAS institute, North Carolina, US).

Results

Patient characteristics

Among the 81 analysed patients (Figure 1, panel A), 28 had elevated LVEDP (Table 1). Patients with elevated LVEDP were more likely to have diabetes, chronic obstructive pulmonary disease (COPD) and heart failure. There were no significant differences in the proportion of history of chronic kidney disease, severe heart valve diseases, atrial fibrillation (AF) and coronary disease.

Differences in lung and heart ultrasonography variables according to LVEDP

A marked difference was identified in B-line count according to LVEDP level (median B-line count 1.0 (0.0 - 4.0) in patients with LVEDP<20 vs. 17.0 (9.0 - 24.0) in patients with LVEDP \geq 20 mmHg, $p<0.0001$, Table 2). This significant difference persisted upon dichotomization of B-lines (all $p<0.001$). The 8 B-line cut-offs yielded marginally fewer true positive patients than the 3 B-line cut-offs (78.6% vs. 85.7%, respectively) although with numerous fewer false positives (9.4% vs. 34%, respectively).

Overall, LV diastolic parameters were more impaired in the elevated LVEDP group (Table 2): E/A ratio and average mitral E/e' ratio were higher (1.3 vs. 0.8, $p=0.001$ and 15.6 vs. 11.6, $p=0.014$, respectively), and E wave deceleration time and isovolumic relaxation time were shorter (167 vs. 216 ms, $p=0.004$ and 106.3 vs. 125.0 ms, $p=0.035$, respectively). Of note, LAVi was not significantly different across groups (45.7 vs. 49.1 ml.m⁻², $p=0.51$).

The following parameters were significantly higher in the elevated LVEDP group: peak Tricuspid Regurgitation (TR) velocity (2.9 ± 0.6 cm.s⁻¹ vs. 2.5 ± 0.4 , $p=0.002$), inferior vena cava diameter (18.5 mm vs. 11.0, $p<0.0001$) and estimated systolic pulmonary artery pressure (50.0 vs. 30.0 mmHg, $p=0.0007$).

Correlation of lung and heart ultrasonography variables with LVEDP

The correlation between B-line count and LVEDP was higher than that observed for all echocardiographic parameters ($r=0.62$ for B-line count vs. $r<0.50$ for all right- or left-sided echocardiographic parameters, Table 3). Among LV parameters, the highest correlation was observed for E/A ratio ($r=0.338$). Peak tricuspid regurgitation velocity, inferior vena cava diameter and estimated systolic pulmonary artery pressure exhibited correlations with LVEDP ranging from 0.40 to 0.50.

Diagnostic accuracy for elevated LVEDP of lung and heart ultrasonography variables (Figure 1-panel C)

None of the clinical and echocardiographic parameters significantly increased the diagnostic accuracy for elevated LVEDP in addition to clinical variables (namely, age, NYHA class, signs of pulmonary congestion, diabetes, COPD and history of heart failure) except for IVC diameter [C-Index increase of 7.1 (0.3 to 14.0), $p=0.042$, Table 3] and PASP [C-Index increase of 6.3 (0.2 to 12.5), $p=0.043$]. Importantly, NtProBNP was also not associated with a

significant increase in C-index (C-Index increase of 0.8 (-5.6 to 7.2), $p=0.81$). In contrast, B-line count used either as a continuous or dichotomous variable significantly increased the diagnostic accuracy [C-index increase of 10.5 (3.7 to 17.3), $p=0.002$ for total B-line count; 5.9 (-0.1 to 11.9), $p=0.053$ for B-lines ≥ 3 ; 8.6 (2.4 to 14.8), $p=0.007$ for B-lines ≥ 8 , Table 3]. The diagnostic accuracy obtained with the joint use of clinical variables and B-lines was excellent [C-index=95.5 (90 to 100)]. These results remained consistent in subgroup analysis in the AF population or decreased ejection fraction (LVEF < 30%; LVEF<40%) (table in supplementary materials 2).

Reclassification was not significantly increased when using left-sided recorded ultrasonography parameters. In contrast, IVC diameter, peak tricuspid regurgitation velocity and estimated systolic pulmonary arterial pressures as well as lung ultrasonography parameters significantly increased reclassification.

Of note, the integration of the last recommendations in the evaluation of LV pressure did not increase either the reclassification [NRI 45.0 (-5.6 to 95.6), $p=0.081$] or diagnostic accuracy [C-index increase of -0.2 (-1.6 to 1.3), $p=0.82$].

Lastly, intra- and inter-observer reproducibility was excellent, with ICCs > 0.9 for both measurements (graphs in supplementary materials).

Discussion

In this study, B-line count as measured by lung ultrasonography (LUS) was the variable most strongly correlated with invasively measured LVEDP, and significantly increased both diagnostic accuracy and reclassification for elevated LVEDP. Strikingly, none of the left-sided recorded echocardiographic parameters correlated well with LVEDP or were associated with a similarly important increase in diagnostic accuracy for elevated LVEDP. In contrast, peak TR velocity and vena cava diameter were moderately correlated with LVEDP, while IVC diameter

significantly increased the diagnostic accuracy for elevated LVEDP. Taken together, these results suggest the usefulness of LUS and IVC diameter quantification for evaluating LV filling pressures.

Lung ultrasonography to identify elevated filling pressures

Our study is the first to demonstrate an association between elevated LVEDP measured by LHC and B-line count. In a previous study, Platz et al., reported a fair association of B-line count with right-sided haemodynamic variables [12], whereas no significant association was identified with wedge pressures. In contrast, in the present study, we found a moderate association between B-line count and LV filling pressures. The mismatch between wedge pressures and pulmonary congestion observed in some patients [18] could account for these discrepancies. Furthermore, Halpern et al. recently questioned the relevance of wedge pressure to correctly classify pre- and post-capillary hypertension[19]; thereby casting some doubt on the ability of wedge pressure to appropriately identify pulmonary oedema. Consequently, our study strengthens the case of LUS for the correct assessment of heart haemodynamics that are relevant for congestion evaluation (i.e., LVEDP).

A 28-zone LUS is usually used in ambulatory or hospitalized patients with heart failure during their hospital stay [6,10,16]. In this study, we used a simplified technique using 8 scanning zones, similar to the imaging strategy used by Platz et al. in ambulatory patients[12]. However, B-line quantification using a score graded on a scale of 80 was used as opposed to the diagnosis algorithm used in the emergency department. The strong association and diagnostic accuracy of this semi-quantitative simplified technique, which can be performed in a few minutes, suggest its adequacy for routine clinical practice. The finding of 0.3 B-lines or more per scanning site does appear as a reliable threshold to identify high-risk ambulatory HF patients[7,15,20] (adjusted hazard ratio for death or hospitalization for HF 4.08, 1.95-8.54;

$p < 0.001$). Our study provides the haemodynamic background for this observation as patients with 0.3 B-lines or more are very likely to have a LVEDP higher than 20 mmHg.

On the other hand, the use of 8 B-lines as a cut-off for a 28-point technique (i.e., a similar 0.3 B-lines per scanning site) could provide similar diagnostic accuracy with a reduced risk of misclassification[15], but at the expense of a moderately longer acquisition time.

Echocardiography to identify elevated filling pressures

IVC diameter and peak TR velocity were found to be relevant markers of elevated LVEDP. Ommen et al. demonstrated a clear correlation between IVC diameter and right atrial pressure [21] that could be increased as a result of LV diastolic dysfunction, hypervolemia or both. Peak TR velocity is a marker of elevated pulmonary artery systolic pressure (PASP). Transthoracic echocardiography ascertains the pre- or post-capillary status of pulmonary hypertension [22]; however, postcapillary hypertension is the most frequent in patients with HF and/or LV diastolic dysfunction [23]. When associated with LUS, and based on the results of our study, IVC does appear to be the best candidate to identify elevated LVEDP since it was the only parameter to significantly increase diagnostic accuracy on top of clinical variables.

Weaknesses of traditional LV echocardiographic parameters to identify LVEDP

Typical markers of LV diastolic dysfunction that are used as individual markers did not effectively identify elevated LVEDP. In addition to an international study by Sato et al. [24], Lancellotti et al., in a recent multicentre European study [25], reported concurring results. Most importantly, the algorithm recommended in the 2016 ASE/EACVI recommendations yielded only a moderate performance for elevated LVEDP (C-index 0.78). In our study, the diagnostic accuracy of clinical variables (C-index 0.79) was similar to that of clinical variables and the

2016 ASE/EACVI algorithm (C-index 0.79), suggesting that the algorithm has no additional clinical relevance to better assess congestion in patients with HF. This result further adds to the ongoing debate regarding the usefulness of current algorithms to identify elevated LV filling pressures [26,27].

The poor diagnostic capacity of the aforementioned algorithm in our cohort could be the consequence of the limitations of echocardiographic evaluation: high E-wave velocity can be observed in patients with mitral regurgitation, e' can be altered by mitral annulus calcifications rather than LV filling pressures, etc. For LA volume, numerous confounding factors could increase atrial size including AF (approximately 30% of the study population), mitral insufficiency or aortic stenosis. LA volume seemingly constitutes more of a LV remodelling marker than a LV filling marker, except for a highly selected population. In contrast, LUS is not influenced by these cardiac conditions, which in turn could translate into better diagnostic accuracy.

Clinical implications

B-lines are an efficient marker of elevated LVFP. Consequently, they should be more frequently implemented in the assessment of LV diastolic function and LVFP. Their implementation could moreover be extremely easy in routine practice, either prior to or immediately after transthoracic echocardiography, and could be completed within less than 3 minutes.

In addition, because of the portability of recently introduced hand-held devices, LUS could further be easily performed throughout the course of in-hospital management or in the outpatient setting. We do believe, as other authors [10,28,29], that LUS is more accurate than lung auscultation [30,31] and should thus be routinely performed in patients with HF as an

extension of clinical examination. Whether this powerful diagnostic tool can help better tailor HF treatment and improve clinical outcomes remains to be tested in clinical trials.

Limitations

Limitations of this study include its single-centre nature and moderate sample size. Results herein should therefore be interpreted with caution and warrant confirmation in larger multicentre studies.

LVEDP was considered to be the gold standard in our study although some authors consider that the mean LAP provides a better estimation of pulmonary congestion [32]. However, rather than including patients with AF in whom LAP usefulness is questionable, LVEDP was preferentially used as the outcome of our study. In addition, patients with mitral stenosis were excluded in order to decrease the risk of error in filling pressure estimation using LVEDP.

B-lines can have non-cardiogenic origin. Although patients with a high risk of false positive LUS exams (pulmonary fibrosis, etc.) were excluded, we cannot rule out the possibility that some of the patients included in this cohort had B-lines of non-cardiac origin. However, despite these potential measurement caveats, LUS yielded an excellent diagnostic accuracy for elevated LVEDP.

Conclusion

This study demonstrates the important diagnostic capacity of B-lines in identifying elevated left ventricular end-diastolic pressure. This tool should be considered in a multi-parametric approach of patients with HF. The simplicity of LUS and IVC diameter measurement allows the use of a hand-held device to quickly, easily and adequately evaluate LV filling pressure.

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Tables and Figures

Figure 1:

Panel A: Flow chart

Panel B: Method of B-line quantification.

Panel 1: The four explored areas on the right hemithorax; Panel 2: Example of a frozen loop of lung ultrasonography with B-lines; Panel 3: The different analysed cut-offs. A: one bilateral positive zone (defined by ≥ 3 B-lines in the same zone); B: two bilateral positive zones; C: Simplified B-line count: sum of all B-lines in the eight zones using two different cut-offs: ≥ 3 or ≥ 8 B-lines.

Panel C: ROC curves of the best indices and ASE/EACVI algorithm for the diagnosis of elevated LVEDP.

Table 1: Baseline characteristics

	Overall n=81	LVEDP < 20 mmHg n=53	LVEDP ≥ 20 mmHg n=28	p-value
Age (years)	75 (67 - 80)	75 (70 - 80)	75 (64 - 79)	0.49
Sex, male	55 (67.9%)	34 (64.2%)	21 (75.0%)	0.32
BMI (kg.m ²)	26 (23 - 30)	26 (22 - 30)	26 (23 - 30)	0.65
Smoking	31 (38.3%)	20 (37.7%)	11 (39.3%)	0.89
Hypertension	56 (69.1%)	37 (69.8%)	19 (67.9%)	0.86
Dyslipidaemia	37 (45.7%)	24 (45.3%)	13 (46.4%)	0.92
Diabetes mellitus	17 (21.0%)	6 (11.3%)	11 (39.3%)	0.003
Heart Failure	41 (50.6%)	21 (39.6%)	20 (71.4%)	0.007
Coronopathy	40 (49.4%)	28 (52.8%)	12 (42.9%)	0.39
Severe Valvulopathy	35 (43.2%)	24 (45.3%)	11 (39.2%)	0.96
<i>Severe Aortic Stenosis</i>	24 (29.6%)	17 (32.1%)	7 (25.0%)	
<i>MR ≥ 3/4</i>	9 (11.1%)	5 (9.4%)	4 (14.3%)	
<i>AR ≥ 3/4</i>	2 (2.5%)	2 (3.8%)	0 (0.0%)	
AF history	25 (30.9%)	18 (34.0%)	7 (25.0%)	0.41
<i>paroxysmal</i>	12 (14.8%)	8 (15.1%)	4 (14.3%)	1.0
<i>permanent</i>	13 (17.3%)	10 (20.8%)	3 (10.7%)	0.36
COPD	6 (7.4%)	1 (1.9%)	5 (17.9%)	0.017
Renal insufficiency	24 (29.6%)	13 (24.5%)	11 (39.3%)	0.17
Biology				
MDRD (mL.min ⁻¹)	68.2 ± 21.3	69.6 ± 19.8	65.5 ± 24.0	0.41
Hb (g.dL ⁻¹)	13.5 (12.2 - 14.8)	13.6 (12.4 - 14.8)	13.4 (12.2 - 14.6)	0.69
NT-ProBNP (pg.mL ⁻¹)	2013.9 ± 2448.7	1248.1 ± 1603.2	3332.7 ± 3079.6	0.014
Medications				
B-blockers	47 (58.0%)	30 (56.6%)	17 (60.7%)	0.72
Calcium channel blocker	4 (4.9%)	2 (3.8%)	2 (7.1%)	0.61
ACEi/ARAI	50 (61.7%)	35 (66.0%)	15 (53.6%)	0.27
Thiazide diuretic	2 (2.5%)	1 (1.9%)	1 (3.6%)	0.49
Spironolactone	9 (11.1%)	7 (13.2%)	2 (7.1%)	0.49
Physical examination				
Heart rate (bpm)	73 ± 15	71 ± 13	75 ± 19	0.34
SBP (mmHg)	135 ± 22	137 ± 22	131 ± 22	0.25
DBP (mmHg)	74 ± 13	74 ± 13	74 ± 14	0.91
NYHA				0.0001
2	59 (72.8%)	46 (86.8%)	13 (46.4%)	
3 - 4	22 (27.2%)	7 (13.2%)	15 (53.6%)	
Angina	18 (22.2%)	15 (28.3%)	3 (10.7%)	0.070
Right heart failure clinical signs	13 (16.0%)	5 (9.4%)	8 (28.6%)	0.052
Left heart failure clinical signs	10 (12.3%)	2 (3.8%)	8 (28.6%)	0.003

LVEDP: Left Ventricular End Diastolic Pressure; BMI: Body Mass Index; MR: Mitral regurgitation; AR: Aortic Regurgitation; AF: Atrial Fibrillation; COPD: Chronic Obstructive Pulmonary Disease; MDRD: Creatinine clearance by the MDRD formula (Modification of Diet in Renal Disease); Hb: Haemoglobin; NT-ProBNP: N-terminal-Pro Brain Natriuretic Peptide; ACEi: Angiotensin Conversion Enzyme inhibitors; ARAII: Angiotensin Receptor II Antagonists, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 2: Ultrasonographic and catheterization characteristics

	Overall n=81	LVEDP < 20 mmHg n=53	LVEDP ≥ 20 mmHg n=28	p-value
AF during TTE	19 (23.5%)	12 (22.6%)	7 (25.0%)	0.81
Total B-lines	3.0 (0.0 - 12.0)	1.0 (0.0 - 4.0)	17.0 (9.0 - 24.0)	< 0.0001
≥ 3 B-Lines	45 (51.9%)	18 (34%)	24 (85.7%)	< 0.0001
≥ 8 B-lines	27 (33.3%)	5 (9.4%)	22 (78.6%)	< 0.0001
1 positive zone in each side*	16 (19.8%)	1 (1.9%)	15 (53.6%)	< 0.0001
2 positive zones in each side*	10 (12.3%)	0 (0.0%)	10 (35.7%)	< 0.0001
LV systolic function				
Preserved LVEF	44 (54.3%)	34 (64.2%)	10 (35.7%)	0.015
LVEF (%)	52.0 (34.0 - 61.4)	53.0 (43.0 - 62.0)	39.0 (30.0 - 55.3)	0.027
GLS (%)	-12.8 (-18.0 - -8.6)	-14.7 (-18.4 - -10.0)	-10.1 (-16.6 - -7.8)	0.054
LVESVi (ml.m ⁻²)	31.8 (19.5 - 50.6)	27.8 (18.8 - 46.0)	46.2 (29.5 - 63.3)	0.043
LVEDVi	69.0 (50.4 - 86.7)	63.3 (47.6 - 81.0)	74.0 (59.6 - 92.8)	0.103
Mitral S average (cm.s ⁻¹)	6.0 (4.5 - 7.5)	6.0 (5.0 - 7.5)	5.5 (4.0 - 6.0)	0.015
LV diastolic function				
Mitral E (cm.s ⁻¹)	81 (66 - 102)	79 (63 - 94)	92 (74 - 108)	0.078
Mitral A (cm.s ⁻¹) (n=62)	75 (56 - 104)	87 (65 - 104)	62 (34 - 78)	0.003
E/A ratio (n=62)	0.9 (0.7 - 1.6)	0.8 (0.6 - 1.3)	1.3 (1.0 - 2.9)	0.001
E wave, deceleration time (ms)	186.0 (148.4 - 259.0)	216.0 (164.0 - 305.0)	167.0 (118.8 - 190.5)	0.004
e' septal (cm.s ⁻¹)	5.8 ± 2.5	6.0 ± 2.3	5.5 ± 2.7	0.39
e' lateral (cm.s ⁻¹)	7.0 (5.0-10.0)	8.0 (5.0-10.0)	6.5 (4.5-8.5)	0.31
Mitral e' average (cm.s ⁻¹)	6.5 (4.5 - 8.0)	7.0 (5.0 - 8.5)	5.8 (4.3 - 7.8)	0.18
Mitral E/e' septal	15 (11-21)	13 (10-19)	20 (14-26)	0.017
Mitral E/e' lateral	11 (8-17)	10 (8-15)	13 (10-20)	0.021
Mitral E/e' average of annuli	12.5 (9.3 - 18.3)	11.6 (8.6 - 15.9)	15.6 (11.4 - 22.0)	0.014
LV isovolumic relaxation time (ms)	118.0 ± 36.6	125.0 ± 35.6	106.3 ± 35.7	0.035
LAVi (ml.m ⁻²)	48.5 (33.4-62.3)	45.7 (33.3 - 62.3)	49.1 (36.4 - 62.6)	0.51
RV systolic and diastolic functions				
RAVi (ml.m ⁻²)	25.5 (19.5 - 34.7)	23.6 (18.9 - 31.2)	28.7 (20.4 - 51.1)	0.046
RV area change (%)	42.0 ± 12.9	45.2 ± 11.4	36.0 ± 13.7	0.002
TAPSE	22.0 (18.0 - 25.0)	23.0 (19.0 - 26.0)	20.5 (16.0 - 24.5)	0.14
RV free wall strain (%)	-21.6 ± 7.0	-22.5 ± 6.6	-20.0 ± 7.4	0.15
RV IVA	1.4 (0.9 - 2.1)	1.3 (0.9 - 2.1)	1.4 (0.9 - 1.8)	0.94
Peak TR velocity (m.s ⁻¹)	2.6 ± 0.5	2.5 ± 0.4	2.9 ± 0.6	0.0019
IVC dimension (mm)	13.0 (8.5 - 17.0)	11.0 (7.0 - 15.0)	18.5 (15.0 - 20.0)	<0.0001
PASP (mmHg)	34.0 (26.0 - 45.0)	30.0 (25.5 - 36.5)	50.0 (30.0 - 60.0)	0.0007
Catheterization				
LVEDP (mmHg)	16.0 (12.0 - 22.0)	14.0 (10.0 - 16.0)	25.0 (21.5 - 30.0)	< 0.0001
LV-PreA (mmHg) (n=62)	10.0 (6.5 - 15.5)	8.0 (5.0 - 10.0)	16.5 (13.0 - 18.0)	< 0.0001
LVESP (mmHg)	153.9 ± 33.1	155.6 ± 33.2	150.6 ± 33.4	0.53

LVEDP: Left Ventricular End Diastolic Pressure; AF: Atrial Fibrillation; TTE: Trans-Thoracic Echocardiography; LVEF: Left Ventricular Ejection Fraction; GLS: Global Longitudinal Strain; LVESVi: Left Ventricular End Systolic Volume index; LVEDVi: Left Ventricular End Diastolic Volume index; LAVi: Left Atrial Volume index; RV: Right Ventricle; RAVi: Right Atrial Volume index; TAPSE: Tricuspid Annular Plane Systolic Excursion; IVA: IsoVolumic Acceleration; TR: Tricuspid Regurgitation; IVC: Inferior Vena Cava; PASP: Pulmonary Artery Systolic Pressure; LV-PreA: Left Ventricular pressure just before A-wave; LVESP: Left Ventricular End Systolic Pressure.

*A positive zone is defined by ≥ 3 B-lines in the same zone.

Table 3: Correlations with LVEDP and AUC in predicting an elevated LVEDP

	Spearman's rho	AUC1* (CI 95%)	ΔAUC** (CI 95%)	P-value ΔAUC	NRI (CI 95%)	p-value NRI
NT-ProBNP (n=49)	0.355	86.7 (74.1 to 99.4)	0.8 (-5.6 to 7.2)	0.81	85.3 (33.7 to 136.9)	0.001
Lung ultrasonography						
Total B-Lines	0.621	95.5 (90.0 to 100.0)	10.5 (3.7 to 17.3)	0.002	145.4 (113.0 to 177.9)	<0.0001
≥ 3 B-Lines	0.506	90.9 (83.7 to 98.1)	5.9 (-0.1 to 11.9)	0.053	89.2 (49.5 to 128.9)	<0.0001
≥ 8 B-lines	0.633	93.6 (86.0 to 100.0)	8.6 (2.4 to 14.8)	0.007	145.4 (113.0 to 177.9)	<0.0001
1 positive zone in each side	0.553	91.7 (83.8 to 99.7)	6.7 (0.4 to 13.1)	0.037	117.7 (80.7 to 154.6)	<0.0001
2 positive zones in each side	0.514	91.0 (83.0 to 99.0)	6.0 (0.3 to 11.7)	0.039	99.2 (59.9 to 138.5)	<0.0001
LV parameters						
LVEF	-0.117	84.5 (74.8 to 94.2)	-0.5 (-1.2 to 0.3)	0.22	-12.8 (-58.5 to 32.9)	0.58
GLS	0.000	84.1 (74.3 to 93.9)	-0.1 (-0.5 to 0.3)	0.73	-8.2 (-54.3 to 37.9)	0.73
Mitral E	0.209	85.4 (76.1 to 94.8)	0.5 (-2.1 to 3.0)	0.72	11.1 (-32.2 to 54.3)	0.62
E wave, deceleration time	-0.116	85.6 (76.8 to 94.5)	0.7 (-3.2 to 4.6)	0.74	16.2 (-29.3 to 61.7)	0.49
E/A ratio (n=62)	0.338	85.9 (74.5 to 97.3)	2.7 (-0.5 to 5.9)	0.097	65.2 (16.5 to 113.9)	0.009
Ea lateral	-0.153	84.8 (75.3 to 94.4)	-0.1 (-0.9 to 0.6)	0.73	39.2 (-5.7 to 84.1)	0.087
Ea septal	-0.147	85.1 (75.6 to 94.6)	0.1 (-1.1 to 1.4)	0.84	44.7 (1.8 to 87.7)	0.041
Mitral Ea average	-0.164	84.8 (75.3 to 94.4)	-0.1 (-0.6 to 0.3)	0.57	-20.8 (-66.2 to 24.7)	0.37
Mitral annular E/Ea average	0.316	85.8 (76.5 to 95.2)	0.9 (-1.6 to 3.3)	0.48	24.1 (-21.4 to 69.6)	0.30
LV isovolumic relaxation time	-0.282	87.9 (78.9 to 96.9)	2.1 (-3.2 to 7.4)	0.44	53.3 (7.7 to 99.0)	0.022
LAVi	0.088	84.9 (75.3 to 94.5)	-0.1 (-1.3 to 1.2)	0.91	-2.7 (-47.9 to 42.6)	0.91
RV parameters						
RV fractional area change	-0.152	84.9 (74.7 to 95.1)	0.9 (-3.1 to 5.0)	0.65	21.4 (-25.0 to 67.7)	0.37
TAPSE	0.010	84.8 (75.3 to 94.4)	-0.1 (-0.9 to 0.6)	0.73	8.6 (-36.8 to 54.1)	0.71
RV free wall strain	0.012	86.9 (78.3 to 95.6)	0.1 (-0.3 to 0.6)	0.59	-15.1 (-63.9 to 33.6)	0.54
Peak TR velocity	0.405	89.2 (80.1 to 98.2)	4.9 (-1.1 to 10.9)	0.11	102.0 (61.8 to 142.2)	<0.0001
IVC diameter	0.347	90.5 (82.1 to 98.8)	7.1 (0.3 to 14.0)	0.042	135.9 (100.2 to 171.6)	<0.0001
PASP	0.397	90.6 (82.3 to 98.8)	6.3 (0.2 to 12.5)	0.043	101.4 (62.8 to 140.0)	<0.0001
2016 ASE/EACVI algorithm	0.175	83.0 (70.9 to 95.2)	-0.2 (-1.6 to 1.3)	0.82	45.0 (-5.6 to 95.6)	0.081

*AUC1: AUC of clinical variables + parameter; **ΔAUC: Difference between AUC1 and AUC of clinical variables alone

NRI: Net Reclassification Index; AUC: Area Under the Curve; NT Pro-BNP: N-terminal pro Brain Natriuretic Peptide; LVEF: Left Ventricular Ejection Fraction; GLS: Global Longitudinal Strain; LAVi: Left Atrial Volume index; RV: Right Ventricle; TAPSE: Tricuspid Annular Plane Systolic Excursion; IVA: IsoVolumic Acceleration; TR: Tricuspid Regurgitation; IVC: Inferior Vena Cava; PASP: Pulmonary Artery Systolic Pressure

ACCEPTED MANUSCRIPT

Highlights

Diagnostic accuracy of Lung Ultrasound for identification of elevated left ventricular filling pressure

ASE/EACVI recommendation for the estimation of left ventricular filling pressure is quite complex and time consuming. B-lines, in lung ultrasound, could constitute an interesting tool for LVFP evaluation in clinical practice, but data regarding their association with invasive hemodynamics are lacking. The purpose of this study is to explore the diagnostic accuracy of B-lines to identify elevated left ventricular end-diastolic pressure (LVEDP).

About 81 adults with significant dyspnea (NYHA \geq 2) were prospectively analyzed. Clinical variables had a C-index of 79% to identify elevated LVEDP. Total B-lines number was higher in the elevated LVEDP group (1.0vs17.0, $p<0.0001$) and significantly increased diagnostic accuracy (C-index increase=15.5%, $p=0.004$) and a net reclassification index (NRI=142.0, 108.5-175.6, $p<0.0001$) on top of clinical variables. In contrast, the 2016 ASE/EACVI recommendations did not significantly increase neither the reclassification nor the diagnostic accuracy. There is an important diagnostic capacity of B-lines to identify elevated elevated filling pressure and that is probably something to consider in our clinical routine.

A

93 patients included

5 significant mitral stenosis
 1 pulmonary fibrosis
 6 patients did not undergo left heart catheterization

81 patients analyzed

LVEDP < 20mmHg
 53 patients

LVEDP ≥ 20mmHg
 28 patients

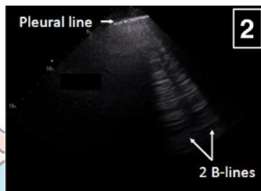
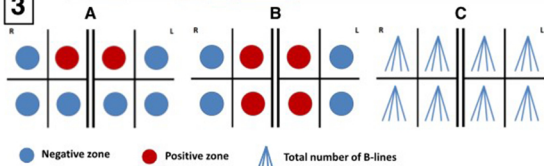
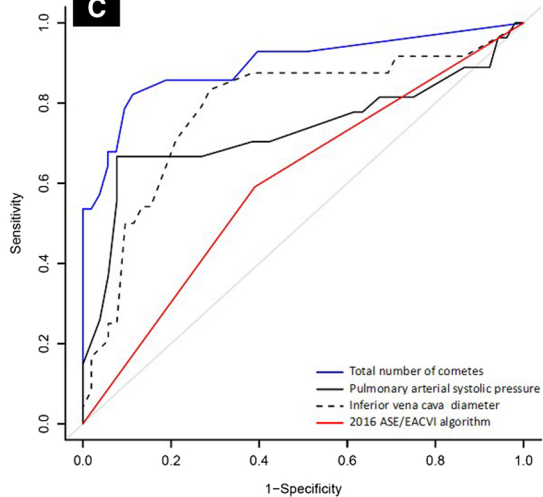
1**B****3****C**

Figure 1