ACTA SCIENTIFIC CARDIOVASCULAR SYSTEM

Volume 1 Issue 2 April 2022

Research Article

# Evaluation of Left Ventricular Filling Pressures in Acute Coronary Syndromes

**Fathia Mghaieth Zghal[1,2]*, Selim Boudiche Selim[1,2], Manel Ben Halima[1,2], Rekik Bassem[1,2], Abdeljelil Farhati[1,2], Khaled Ezzaouia[1,2], Ali Bonkano[1,2], Sana Ouali[1,2] and Mourali Mohamed Sami[1,2]**

[1]*Service of Functional Exploration and Cardio Reanimation, Rabta University Hospital, Tunis, Tunisia*

[2]*Faculty of Medicine of Tunis, University Tunis El Manar, Tunis, Tunisia*

***Corresponding Author:** Fathia Mghaieth Zghal, Service of Functional Exploration and Cardio Reanimation, Rabta University Hospital, Tunis, Tunisia and Faculty of Medicine of Tunis, University Tunis El Manar, Tunis, Tunisia.

**Received:** March 01,2022

**Published:** April 29, 2022



## Abstract

**Introduction**: Left Ventricular (LV) filling pressures (FP) are altered in the setting of acute coronary syndrome (ACS). Many Echocardiographic parameters were found to be correlated with LV FP but not all of them were validated in ACS patients

**Aim**: The objective was first, to assess the validity of individual echocardiographic parameters of LV FP in the setting of ACS. Then to define a concrete and practical strategy of non-invasive LV FP assessment in ACS.

**Methods**: A prospective monocentric study was conducted in the Cardiology department of (*the name was removed to respect anonymity*) in two consecutive steps. In a first prospective cohort of ACS patients, we investigated the effectiveness of all diastolic parameters to predict LV FP as defined by joint ASE and ESC guidelines. This first study permitted a selection of most useful parameters. In a second prospective cohort invasive LVEDP was the reference measurement, it defined elevated LV FP when it was > 18 mmHg and allowed the validation of selected cardiac and lung ultrasound parameters. We finally defined a new algorithm to assess LV FP in the setting of ACS.

**Results**: The first sub study, included 84 patients demonstrated that 91% of them had a diastolic dysfunction Grade I (44%), grade II (33.3%) and grade III (13.1%). Based on American and European guidelines, 27% of patients had high LV FP but 14% of them had undetermined LV FP status. In the second sub study including 40 ACS patietns, we found that classical echocardiographic parameters; E/A ratio, left atrial volume and E' by tissue Doppler were not correlated with LV FP in ACS. Parameters correlated with LVEDP were: B lines (Rho = 080, p < 0.001), TDE (Rho = -0.46, p = = 0.036), E/E' (Rho = 0.43, p = 0.005), TE'-E (Rho = -0.45, p = 0.004), IRT (Rho = -0.69, p < 0.001), GLS (Rho = 0.61, p < 0.01), dAr-Am (Rho = 0.74, p < 0.001), S/D (Rho = -0.53, p < 0.001). B lines (93.1% and 93%) and dAr-Am (94.4% and 95.5%) had the highest sensitivity and specificity for LVEDP prediction. We proposed new algorithm based in a first step on lung ultrasound B lines, when ≥ 5 we could conclude in high LVEDP. If B lines were < 5 we proposed to move to a second step based on Three Doppler echocardiography parameters and was considered positive when 2 or 3 of them were above the cut off value; E/E' (cut off = 12), dAr-Am (cut off = 20 ms) and GLS (cut off = -12%). This algorithm had 100% of sensibility and 86% of specificity for elevated LV FP prediction.

**Conclusion**: Elevation of LV FP occurs at an early stage of ACS. Its detection by echocardiography is crucial. Over reliance on guidelines algorithm can lead to a misdiagnosis of acute elevation of LV FP. We proposed a new algorithm with higher sensitivity and comparable specificity. We encourage its application in ACS patients without previous chronic heart or lung morbid state.

**Keywords**: Left Ventricular; Filling Pressures; Acute Coronary; Syndromes

## Abbreviations

A: Telediastolic Mitral Wave by pulsed Doppler ACS: Acute Coronary Syndrome; Ar: Telediastolic Venous Pulmonary Wave by pulsed Doppler; AUC: Area Under the Curve; ASE: American Society of Echocardiography D: Diastolic Pulmonary Venous Wave; dAr-dAm: Difference Between Mitral and Pulmonary Venous Telediastolic Waves Durations; DTE: Deceleration Time of Mitral E Wave; DTD: Deceleration Time of Diastolic Pulmonary Venous Wave; E: Early Diastolic Mitral Wave by Pulsed Doppler; E': early Diastolic Annular Mitral Wave by Tissue Doppler; ECG: Electrocardiogram; EF: Ejection Fraction; ESC: European Society of Cardiology; FP: Filling Pressure; GLS: Global Longitudinal Strain; HR: Heart Rate; HTA: Hypertension; IRT: Isovolumic Relaxation Time; LA: Left Atrium; LAEI: Left Atrial Expansion Index; LAIV: Left Atrial Indexed Volume; LV: Left Ventricle; LVEDP: Invasive Left Ventricular End Diastolic pressure; NSTEMI: Non-ST Elevation Myocardial Infarction; NYHA: New York Heart Association; PASP: Pulmonary Artery Systolic Pressure; PRVG: Pressions de Remplissage du Ventricule gauche; ROC: Receiver Operating Characteristics; S: Systolic Pulmonary Venous Wave by Pulsed Doppler; S': Systolic Mitral Annulus Wave by Tissue Doppler; Se: Sensitivity; Sp: Specificity; SPSS: Statical Package for the Social Sciences; STEMI: ST-Elevation Myocardial Infarction; TE: Time from the Beginning of Electrocardiogram QRS to E Mitral Wave; TE': Time from QRS to E'mitral Annulus Wave; TE'-E: Difference Between TE and TE'; TTE: Transthoracic Echocardiography; VRT: Maximal Velocity of Tricuspid Regurgitation; WMSI: LV Wall Motion Score Index

## Introduction

Left Ventricular (LV) filling pressures (FP) are frequently altered in the setting of acute coronary syndrome (ACS) [1]. They have an important prognostic value [2], and their assessment is crucial for therapy adjustment and right management of ACS patients. Indeed, early after an ischemic event, meaningful modifications in diastolic then systolic myocardial functions occur, both can increase LV FP, and both should y be detected particularly in early preclinical stages.

Many echocardiographic parameters were correlated to LV FP, however, only few of them were validated in the setting of ACS, which is characterized by acute changes of filling pressures.

## Aim

The objectives of our study were:

- First, to assess the validity of individual echocardiographic parameters of LV FP in patients with ACS. This evaluation included consensual, classical, and novel parameters such as lung water by lung ultrasound (LUS), LV strain and left atrial expansion index (LAEI).
- Second, we aimed to define a new algorithm for a noninvasive structured multiparametric approach of LV FP assessment in the context of ACS.

## Methods

Two consecutive sub studies (respectively named A and B) were conducted in the (the name of the center was removed by authors to respect anonymity), Tunisia. Both were prospective and monocentric. the study global design is illustrated in figure 1.

### Sub study A design

The first study aimed to investigate the feasibility and effectiveness of diastolic parameters as proposed by ASE/ ESC guidelines [3] when applied in an ACS setting. This study tended to be comprehensive and included a board number of parameters (table1), we used this cohort.

- To preselect most useful diastolic parameters in ACS patients
- Then to test and assess the validity of the new algorithm established in the sub study B in a real-life cohort of ACS patients.
    - The reference test for LV FP in this sub study A was the ASE/ESC guidelines algorithm [3]. Individual ultrasound parameters were confronted to this reference test. The ASE/ESC algorithm resulted in a subdivision of this cohort A in patients with presumably elevated FP (group 1) and patients with presumably non-elevated or indetermined filling pressures (group 2).

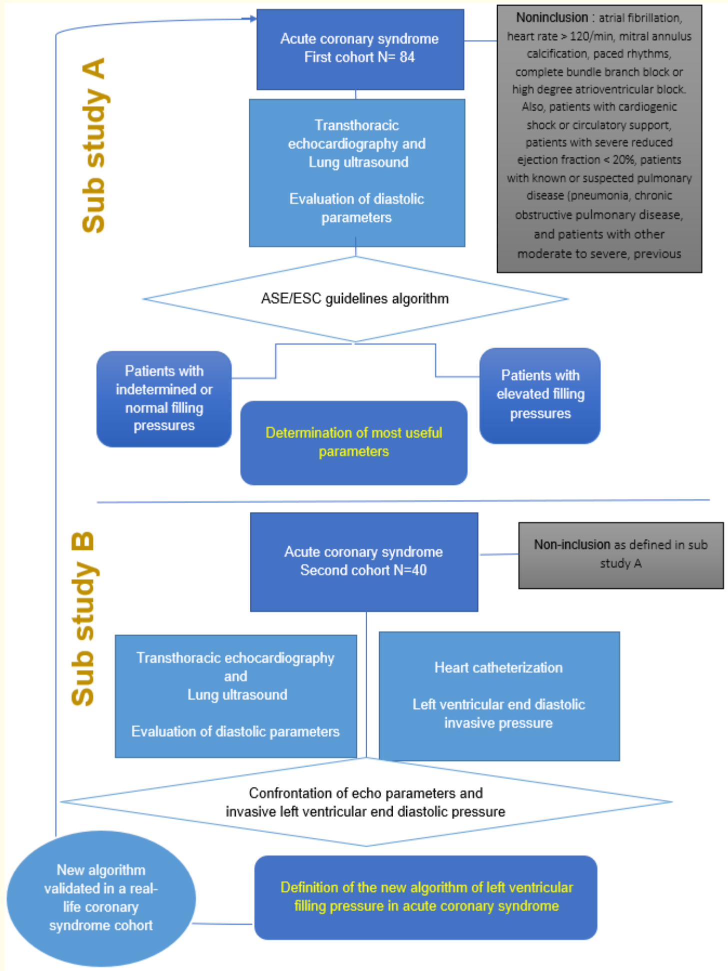



**Figure 1:** Flow chart representing the design of the study

Two consecutive and independent prospective cohorts

Sub study 1 was a non invasive study that tended to be comprehensive and evaluate the maximal number of diastolic transthoracic echocardiography parameters and lung ultrasound B lines. The reference for this study to define elevated elevated filling pressure was the esc guidelines algorithme and it permitted a preselection of useful and feasible parameters.

The sub study B consisted in non invasive and invasive determination of left ventricular filling pressures by ultrasound and heart catheterization. The reference for the definition of left ventricular elevated filling pressure was invasive left ventricular end diastolic pressure measurement. This substudy resulted in the validation of preselected invasive parameters and the definition and validation of a new algorithm for left ventricular non invasive filling pressure assessment.

Finally the new algorithme was applies to the first cohort A to assess its usefulness in a real life cohort.

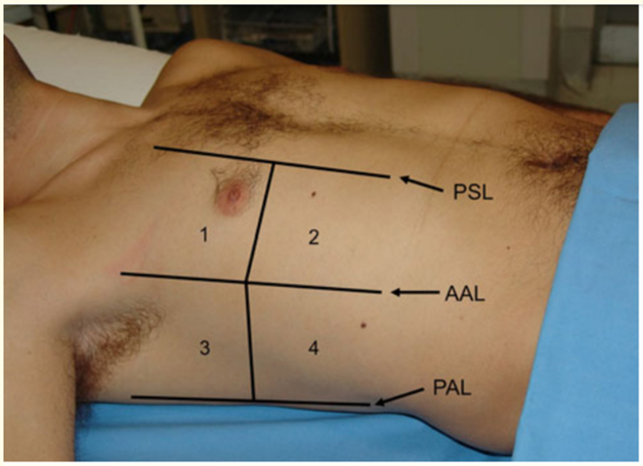



**Figure 2:** Areas of Lung ultrasound for assessing the extrapulmonary water by the 8 zones method. Zones 1 and 2 represent respectively the zones Upper anterior and the lower anterior. 3 and 4 respectively the upper lateral and the basal lateral. PSL parasternal line. AAL anterior axillary line. PAL posterior axillary line.

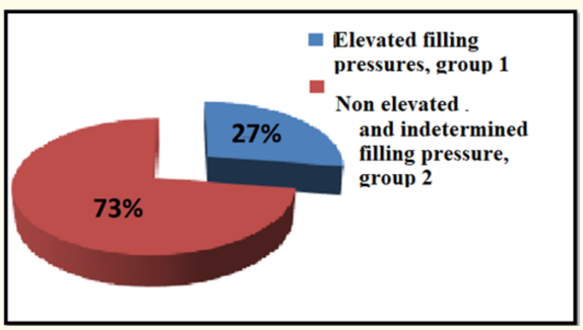



**Figure 3:** Subdivision of cohort 1. in elevated (group 1) and non-elevated or indetermined (group 2) left ventricular filling pressure based on European guidelines algorithm.

We included all patients admitted to the cardiology department for evolving ST elevation (STEMI) or non-ST elevation (NSTEMI) myocardial infarction (< 48 hours from onset of symptoms) in the period between january 2, 2019 and june 30, 2019.

We did not include patients with atrial fibrillation, heart rate > 120/min, mitral annulus calcification, paced rhythms, complete bundle branch block or high degree atrioventricular block. Also, patients with cardiogenic shock or circulatory support, patients with severe reduced ejection fraction < 20%, patients with known or suspected pulmonary disease (pneumonia, chronic obstructive pulmonary disease, and patients with other moderate to severe, previous non-ischemic cardiac disease such as valvular disease grade 2 or more, or congenital heart disease.

We excluded all patients with poor acoustic window.

The material used for transthoracic echocardiography (TTE) and lung ultrasound (LUS) was a General Electric VIVID E9 commercialized machine with a M5S transducer.

The delay from admission to ultrasound examination was less than 24 hours in all patients, and it was performed by the same experienced senior operator.

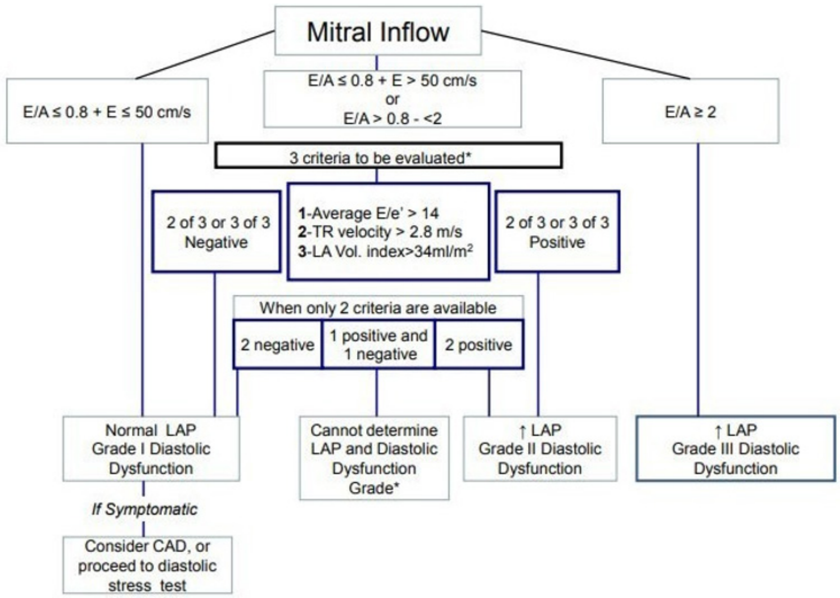
Acquisitions and measurements were done according to ASE recommendations. All LV FP parameters are summarized in table 1.

LUS was performed previously to TTE in patients in supine position in 8 different zones: 4 on each right and left hemi thorax (Figure1). The B lines were visualized as vertical hyperechoic artifacts arising from the pleural line and diverging through the sector depth. The operator counted manually the B lines in each area and considered the sum of all B lines in the 8 areas. B lines ≥ 5 were considered pathological.

We adopted the algorithm proposed by ESC [3] for the evaluation of LV FP by echocardiography to assess diastolic dysfunction. This algorithm graded diastolic function as follows (Annex 1): the first analyzed parameter was trans mitral flow with E velocity and E/A ratio. If E/A ≤ 0,8 and E ≤ 50 cm/s, LV FP were considered normal (grade I diastolic dysfunction). If E/A was ≥ 2, LV FP were considered elevated (grade III diastolic dysfunction). If the case of an E/A was between 0,8 and 2 (or E/A ≤ 0,8 but E > 50 cm/s), three discriminative criteria were considered: average E/e' > 14, tricuspid regurgitation (TR) velocity > 2,8 m/s and indexed LA volume > 34 ml/$m^2$. If 2 or 3 out of these 3 criteria were positive, then LV FP were considered elevated (grade II diastolic dysfunction). In mitigate cases, other criteria were used such as the duration of mitral A wave-pulmonary A wave > 20 ms, the presence of 5 B lines or more in LUS and altered longitudinal global strain (LGS > -16%).

| Echocardiographic parameters | Methods | Units |
|---|---|---|
| Left Atrial (LA) volumes | Biggest LA volume at the frame before mitral valve closure and end systolic biggest LA volume at the frame before Mitral Valve opening in apical 4 and 2 chambers views. | ml/m2 |
| Left atrial expansion index (LAEI) | (End systolic Volume-end diastolic Volume)/end diastolic volume [* 100%] in apical 4 and 2 chambers views. | % |
| Left Ventricular ejection fraction (LVEF) | by Biplane Simpson Method. LVEF > 50% was characterized as normal. | % |
| Mitral Inflow velocities, E/A ratio and E wave<br><br>deceleration time (DTE) | -Determination of peak of the early diastolic E wave late diastolic A wave<br><br>-from the summit of E wave to the baseline<br><br>E/A<br><br>Using Doppler PW in apical 4 chambers view. | cm/s<br><br>cm/s<br><br>msec |
| Mitral annulus early diastolic pulsed tissue Doppler imaging waves and E/E' ratio | In apical 4 chambers view, we considered the average velocity of the two waves E'(cm/sec) by placing the sample volume in the mitral annulus in lateral and septal zones.<br><br>And then we determined E/E' ratio | cm/s |
| Time to E' and time to E difference (TE'-E). | Exploitation of Doppler pulsed and Doppler tissue patterns to get time between the peak of R QRS complex and the E wave TE and then Time peak of R to E' wave<br><br>And then the time difference TE'-TE | msec<br><br>msec<br><br>msec |
| Pulmonary venous flow | Obtained by Doppler pulsed wave guided by color in apical 4 chambers view to get: The Systolic (S), diastolic (D) waves and reverse Pulmonary venous A wave (Ar) velocities.<br><br>AS well as time deceleration time of D (DTD).<br><br>The difference between mitral and pulmonary A wave durations (dAm-dAr)<br><br>And S/D ratio | cm/s<br><br>msec<br><br>msec |
| Tricuspid regurgitation velocity and pulmonary artery systolic pressure (PASP) | After detecting the regurgitant flow and after alignment obtaining the peak of tricuspid systolic regurgitation.<br><br>PASP was calculated by the Bernoulli equation. | m/s<br><br>mmHg |

**Table 1:** Summary of noninvasive ultrasound LV FP parameters.




**Annex 1**: Approach to diastolic dysfunction and left ventricular filling pressure assessment 2016 in joint American and European guidelines.

Pulmonary artery systolic pressure (PASP) was assessed using Bernouilli equation $4*VTR^2$.

### Sub study B design

The second sub study was conducted from july first, 2019 to September 30, 2019.

We included 40 adult patients with ACS admitted within the 48 first hours of symptoms onset of an ACS, and who had invasive angiographic exploration during the first 48 hours of their hospitalization. Non-inclusion and exclusion criteria of sub study A were applied in sub study B.

The delay of ultrasound examination performance was similarly less than 24 hours from admission for all patients and it was carried out by the same sub study A experienced operator which used the same echo machine.

Invasive measurement of LVEDP joint to coronary angiography were performed in less than 12 h from ultrasound examination.

Heart catheterization was obtained by retrograde approach from the radial artery before the coronary angiogram a 6Fpigtail/5F Judkin R 3.5 catheter was placed in the middle of the left ventricle. LVEDP was obtained in the beginning of the QRS. The pressure was measured after four complete cycles.

### A high LVEDP was defined by a LVEDP > 18 mmHg regardless to symptoms or signs of heart failure

Patients were divided according to the level of LVEDP, in Group E for patients with elevated LVEDP > 18mHg and group NE for patients with non-elevated LVEDP ≤ 18 mmHg. This invasive classification of FP was considered the reference test in this sub study and allowed the validation of individual ultrasound parameters as well a new defined algorithm based on individual validated parameters.

### Statistical analysis

In our descriptive part, we expressed the continuous variables as means +/- SD in the overall study population or in the two groups. The categorical variables were expressed as absolute frequencies and percentages.

For the analytic part, comparisons of continuous variables were performed using Mann–Whitney U-test. Spearman's methods assessed correlations between continuous variables. Correlation coefficient (Rho) has -1 and 1 limits values. A Rho coefficient higher than zero indicated a positive correlation while values under zero indicated negative relationship.

For all tests a P value < 0.05 indicated that statistical significance was reached. To determine cutoff values of each parameter correlated to elevated LV FP. Receiver Operating Characteristics (ROC) curves were established and the value with the highest sensitivity-specificity sum was considered.

### Ethical considerations

The study was approved by the ethics committee of (the name of the hospital was removed by authors to respect anonymity) Hospital.

All patients provided informed consent for the data collection and participation to the study.

## Results

### Sub study A

Our cohort A included 84 patients. Diastolic dysfunction was found in of 90.5% patients against 9.5% with normal diastolic function. Based on their diastolic parameters, patients were classified grade I in 44% cases, grade II in 33.3% and grade III in 13.1%. 19.1% of grade II patients remained with indetermined filling pressures, thus the cohort was subdivided into 23 patients with elevated filling pressures (group1) and 61 patients with non-elevated or indetermined filling pressure (group 2).

- Demographic characteristics of sub study A patients are summarized in table 2. The mean age was 61.7±12.4 years (76.1% males), smoking was the most frequent risk factor followed by hypertension and Diabetes. ACS consisted in STEMI in 56% of patients and NSTEMI in 44% of them.
- Ultrasound parameters are summarized in table 3.

mean LV ejection fraction (EF) in this cohort was 46.7 ± 10.5 and mean GLS was -13.3 ± 4.2.

The principal parameters used in ASE algorithm, namely E, E/A, E/E', LAIV and VTR had all significant differences between group 1 and group 2 patients. B lines was 12 [5;30] in group1 and 0 [0;0] in group 2 (p < 0.001).

Durations of mitral and reverse telediastolic left venous flow was feasible (98%) and showed a significant difference (p = 0.02) between group 1 and 2

| Parameter | Cohort A N = 84 | Group 1 N = 23 | Group 2 N = 61 | P |
|---|---|---|---|---|
| Age (years) mean ± SD | 61.7 ± 12.4 | 61.2 ± 12.7 | 61.9 ± 12.4 | 0.94 |
| Males (%) | 76.1 | 73.9 | 77.0 | 0.49 |
| Smoking (%) | 70.2 | 78.3 | 67.2 | 0.24 |
| Hypertension (%) | 44.0 | 39.1 | 45.9 | 0.38 |
| Diabetes (%) | 33.3 | 30.4 | 34.4 | 0.47 |
| Dyslipidemia (%) | 26.2 | 21.7 | 27.9 | 0.39 |
| History of coronary disease (%) | 25 | 17.4 | 27.9 | 0.24 |
| STEMI (%) | 56 | 78.3 | 47.5 | 0.01 |
| Anterior ACS (%) | 41.7 | 60.9 | 34.4 | 0.03 |
| Systolic pressure (mmhg)mean ± SD | 120.2 ± 22.7 | 121.1 ± 21.9 | 119.8 ± 23.2 | 0.67 |
| Diastolic pressure (mmhg)mean ± SD | 74.4 ± 12.1 | 74.4 ± 14.4. | 74.3 ± 11.2 | 0.75 |
| Heart rate (bpm) mean ± SD | 82.6 ± 13.8 | 78.9 ± 19.5 | 79.5 ± 17.6 | 0.85 |
| Pulmonary rales (%) | 11.0 | 21.7 | 6.8 | 0.05 |
| Hemoglobin(g/dL) mean ± SD | 13.6 ± 2.0 | 13.6 ± 1.8 | 13.6 ± 2.1 | 0.63 |
| Glycemia (g/l) mean ± SD | 1.7 ± 0.9 | 1.91 ± 1.08 | 1.57 ± 0.8 | 0.42 |
| Glomerular filtration rate (ml/min/1.73m2) mean ± SD | 76.8 ± 13.6 | 76.2 ± 10.9 | 77.5 ± 17.8 | 0.92 |
| Coronary status | | | | 0.89 |
| One vessel lesions (%) | 49.3 | 52.4 | 48.1 | |
| Two vessel lesions (%) | 32.9 | 28.6 | 34.6 | |
| Three vessel lesions (%) | 17.8 | 19.0 | 17.3 | |
| Thrombolysis (%) | 22.4 | 33.3 | 17.4 | 0.13 |
| Transcutaneous angioplasty (%) | 84.5 | 86.4 | 82.1 | 0.47 |

**Table 2:** General characteristics of sub study A population.

| Parameter | Cohort A N = 84 | Group 1 N = 23 | Group 2 N = 61 | P |
|---|---|---|---|---|
| LVEF (%), Mean ± SD | 46.7 ± 10.5 | 41.9 ± 10.3 | 48.5 ± 10.00 | 0.008 |
| WMSI, Mean ± SD | 2.4 ± 0.7 | 2.6 ± 0.6 | 2.3 ± 0.7 | 0.12 |
| GLS (%) Mean ± SD | -13.3 ± 4.2 | -10.2 ± 2.9 | -14.4 ± 4.1 | < 0.001 |
| LV EDV (ml) Mean ± SD | 11.2 ± 36.7 | 122.4 ± 44.9 | 108.5 ± 32.7 | 0.19 |
| LAIV ($ml/m^2$) Mean ± SD | 31.5 ± 10.3 | 39.6 ± 11.1 | 28.4 ± 8.3 | < 0.001 |
| LAEI, Mean ± SD | 0.6 ± 0.4 | 0.5 ± 0.35 | 0.7 ± 0.4 | 0.03 |
| E (cm/s), Mean ± SD | 73.8 ± 22.3 | 91.5 ± 20.9 | 67.2 ± 19.1 | < 0.001 |
| A (cm/s), Mean ± SD | 71.5 ± 22.3 | 58.4 ± 23.6 | 76.4 ± 19.8 | < 0.001 |
| TDE (ms), Mean ± SD | 172.9 ± 59.6 | 144.0 ± 53.6 | 183.6 ± 58.5 | 0.001 |
| E/A, Mean ± SD | 1.2 ± 0.6 | 15.8 ± 4.9 | 8.2 ± 2.9 | < 0.001 |
| E'(cm/s), Mean ± SD | 7.7 ± 2.3 | 6.3 ± 2.2 | 8.2 ± 2.1 | 0.001 |
| E/E', Mean ± SD | 10.3 ± 4.9 | 15.8 ± 4.9 | 8.2 ± 2.9 | < 0.001 |
| TE'-E(ms), Mean ± SD | 35.1 ± 14.1 | 35.6 ± 10.4 | 34.9 ± 15.4 | 0.06 |
| IRT (ms), Mean ± SD | 73.9 ± 23.1 | 67.4 ± 29.2 | 76.4 ± 20.0 | 0.03 |
| IRT/TE-TE', Mean ± SD | 2.9 ± 2.0 | 2.2 ± 1.8 | 3.2 ± 2.5 | 0.03 |
| S (cm/s), Mean ± SD | 52.7 ± 13.6 | 47.8 ± 19.4 | 54.6 ± 10.3 | 0.20 |
| D (cm/s), Mean ± SD | 49.3 ± 22.6 | 50.1 ± 16.1 | 48.9 ± 24.8 | 0.21 |
| TDD (ms), Mean ± SD | 223.1 ± 62.6 | 211.5 ± 64.6 | 227.5 ± 61.8 | 0.02 |
| S/D, Mean ± SD | 1.2 ± 0.5 | 1.0 ± 0.5 | 1.3 ± 0.5 | 0.04 |
| dAr (ms), Mean ± SD | 131.1 ± 30.2 | 126.7 ± 25.9 | 132.7 ± 31.7 | 0.09 |
| dAr-dA (ms)Median [interquartile interval] | 17 [-11 ;35] | 31 [10;46] | 12 [-15;31] | 0.02 |
| VTR, Mean ± SD | 2.2 ± 0.8 | 2.8 ± 0.8 | 2.0 ± 0.8 | < 0.001 |
| PASP (mmHg), Mean ± SD | 26.8 ± 14.5 | 36.0 ± 19.4 | 23.4 ± 10.5 | 0.001 |
| B lines Median [interquartile interval] | 0 [0 ;5] | 12 [5 ;30] | 0 [0 ;0] | < 0.001 |

**Table 3:** Echocardiographic parameters in sub study A population.

- Prediction of left ventricular noninvasive filling pressure by individual ultrasound parameters

As displayed in table 4. B lines (figure 4) had the highest specificity (91%) to predict elevated LV FP, followed by S/D (89.1%) and TDE (85.6%). B lines showed also one of the highest sensitivities (85.2%) after TE'-E (91%).

Among diastolic parameters GLS, LAVI, LAEI, DTE, E/A, IRT, IRT/TE'-TE, E/E', S/D, DTD, dAr-Am, VTR, PASP and B lines were chosen to be focused on in sub study B

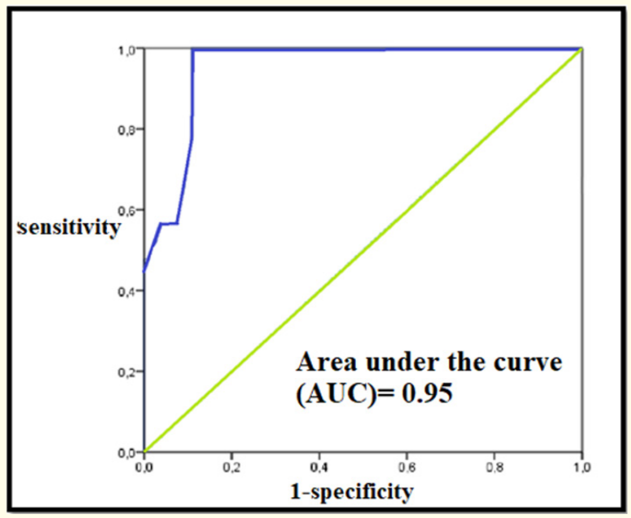



**Figure 4:** ROC curve; prediction of elevated filling pressures by lung ultrasound B lines.

### Sub study B

Cohort B consisted in 40 ACS patients. 18 patients had a LVEDP > 18mmHg (group E) and 22 represented LVEDP ≤ 18mmHg (group NE)

- General characteristics of this population are summarized in table 5. Mean age was 57.1±10.2 years in this populations (76% males), cigarette smoking was also the predominant risk factors and proportions of STEMI and NTEMI were comparable to substudy A (55.6% and 44.4%). There were no significant differences of demographic characteristics between group E and group NE. Group E had a higher mean heart rate and had more frequently pulmonary rales.
- Ultrasound parameters in cohort B and their correlation to LVEDP

| Parameter | AUC | P | cut-off | Se (%) | IC95% Se (%) | Sp (%) | IC95% Sp (%) |
|---|---|---|---|---|---|---|---|
| GLS (%) | 0.79 | < 0.001 | -12 | 73.9 | [64 - 84] | 67.2 | [57 - 77] |
| LAIV (ml/m$^2$) | 0.81 | < 0.001 | 32.7 | 69.5 | [59-79] | 70.5 | [61 - 80] |
| LAEI | 0.66 | 0.03 | 0.49 | 65.2 | [59 - 79] | 67.2 | [57 - 77] |
| TDE (ms) | 0.83 | 0.001 | 153 | 80.2 | [74 - 86.2] | 85.6 | [75 - 91] |
| E/A | 0.87 | < 0.001 | 1.2 | 77 | [68 - 86] | 78 | [69 - 87] |
| E/e' | 0.71 | < 0.001 | 12 | 65.2 | [55 - 75] | 77 | [68 - 86] |
| IRT (ms) | 0.66 | 0.04 | 66 | 65 | [55 - 75] | 60 | [50 - 71] |
| TE'-E (ms) | 0.86 | 0.03 | 35 | 91 | [85 - 97] | 80 | [70 - 90] |
| IRT/ TE'-E | 0.65 | 0.02 | 1.9 | 68.9 | [59 - 79] | 52 | [41 - 63] |
| TDD (ms) | 0.67 | 0.29 | 196.5 | 60.9 | [50 - 72] | 60.7 | [50 - 71] |
| S/D | 0.83 | 0.004 | 1.18 | 70.5 | [60 - 80] | 89.1 | [82 - 96] |
| dAr-Am (ms) | 0.91 | 0.01 | 21 | 75.2 | [65 - 85] | 80 | [70 - 90] |
| VTR (m/s) | 0.77 | < 0.001 | 2.5 | 69.2 | [59 - 79] | 70.5 | [61 - 80] |
| PASP (mmHg) | 0.74 | < 0.001 | 30 | 73.9 | [64 - 84] | 68.9 | [59 - 79] |
| B lines | 0.96 | < 0.001 | 5 | 85.2 | [78 - 88] | 91 | [85 - 97] |

**Table 4:** sensitivity and specificity of ultrasound parameters to predict noninvasive filling pressures.

| Parameter | Group E N = 18 | Group NE N = 22 | P |
|---|---|---|---|
| Age (years, mean ± SD) | 57.6 ± 11.6 | 56.5 ± 8.6 | 0.74 |
| Cigarette smoking (%) | 66.3 | 77.3 | 0.34 |
| Hypertension (%) | 48.9 | 48.2 | 0.11 |
| Dyslipidemia (%) | 33.3 | 38.2 | 0.23 |
| Diabetes (%) | 40.9 | 50 | 0.39 |
| history of coronaropathy (%) | 16.7 | 4.5 | 0.23 |
| STEMI (%) | 55.6 | 31.8 | 0.11 |
| Consultation delay (hours, mean ± SD) | 5.3 ± 3.6 | 4.7 ± 1.2 | 0.40 |
| Systolic blood pressure (mmHg, mean ± SD) | 131.1 ± 19.7 | 121.8 ± 14.3 | 0.09 |
| Diastolic blood pressure (mmHg, mean ± SD) | 82.5 ± 14.4 | 73.4 ± 4.1 | 0.03 |
| Heart rate (bpm, mean ± SD) | 98.2 ± 16.9 | 74.2 ± 10.8 | < 0.001 |
| Rales (%) | 44.4 | 0.0 | < 0.001 |
| Hemoglobin (g/dL, mean ± SD) | 13.8 ± 2.2 | 12.8 ± 1.6 | 0.09 |
| Troponin (ng/L, mean ± SD) | 17296 ± 18382 | 8907.2 ± 18624 | 0.12 |
| Glomerular filtration rate (ml/min/1.73m2) | 77.5 ± 17.8 | 76.2 ± 10.9 | 0.92 |
| Mean number of coronary arteries with significant lesions (mean ± SD) | 1.56 ± 0.4 | 1.95 ± 0.5 | 0.94 |

**Table 5**: Comparison of general characteristics between E and NE cohort B groups.

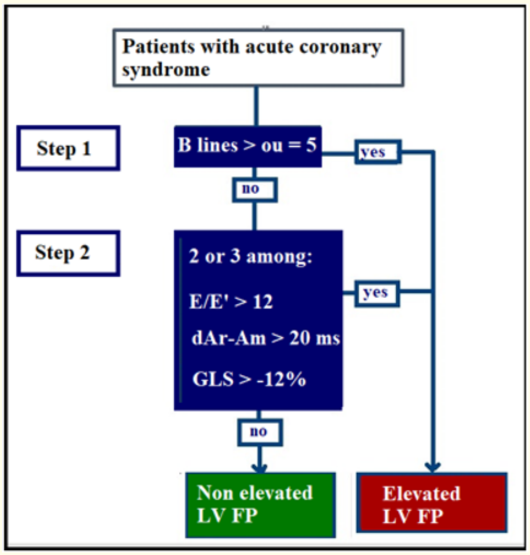



**Figure 5:** Ccentral illustration; new algorithm for the assessment of left ventricular filling pressures in acute coronary syndrome. Approach in two simple steps; step 1 lung ultrasound. if B lines are = or > to 5 then left ventricular filling pressures are elevated without need to other parameters. if there are no or only few B lines. step 2 is based on 3 common echo Doppler parameters E to E' ratio. the difference between Ar and A durations and global longitudinal strain with respective cut offs 12. 20 ms and -12%. when the majority are pathological filling pressures are elevated.

In the table 6 displaying the comparison of echocardiographic parameters between E and NE groups. We noted that E/A (Rho = 0.06, p = 0.71) as well as left atrial parameters (indexed volume and extension index (Rho = 0.33, p = 0.056) did not show significant differences between E and NE patients and no significant correlation to LVEDP. While pulmonary venous flow dAr-Am had a significant difference between the two groups. Similarly, the difference was significant for E/E', GLS and PASP (and VTR).

In the table 7 showing the sensitivity and specificity of ultrasound parameters to predict LVEDP > 18 mmHg. Parameters correlated to were LVEDP: B lines (Rho = 080, p < 0.001), TDE (Rho = -0.46, p = = 0.036), E/E' (Rho = 0.43, p = 0.005), TE'-E (Rho = -0.45, p = 0.004), IRT (Rho = -0.69, p < 0.001), GLS (Rho = 0.61, p < 0.01), dAr-Am (Rho = 0.74, p < 0.001), S/D (Rho = -0.53, p < 0.001). We remarked that B lines (93.1% and 93%) and dAr-Am (94.4% and

| Echocardiographic parameters (mean ± SD) | Group E N = 18 | Group NE N = 22 | P |
|---|---|---|---|
| LVEF (%) | 44.83 ± 6.35 | 55.63 ± 0.29 | < 0.001 |
| GLS (%) | -11.35 ± 2.98 | -16.60 ± 2.22 | < 0.001 |
| LAIV (ml) | 28.24 ± 12.89 | 21.12 ± 5.70 | 0.054 |
| LAEI (ml) | 93.78 25 ± 0.36 | 122.68 ± 54.85 | 0.118 |
| DTE (ms) | 187.78 ± 70.32 | 213.86 ± 69.65 | 0.115 |
| E/A | 1.06 ± 0.41 | 0.95 ± 0.30 | 0.295 |
| IRT (ms) | 60.11 ± 13.25 | 82.27 ± 20.04 | 0.001 |
| IVRT/TE'-TE | 4.27 ± 2.69 | 2.29 ± 1.74 | 0.002 |
| E/E' | 9.84 ± 4.04 | 7.08 ± 1.99 | 0.015 |
| TE'-TE | 20.28 ± 14.31 | 46.41 ± 19.86 | < 0.001 |
| IRVT/TE'-TE | 4.27 ± 2.69 | 2.29 ± 1.744 | 0.002 |
| S/D ratio | 1.08 ± 0.38 | 1.67 ± 0.56 | < 0.001 |
| DTD (ms) | 275.61 ± 70.06 | 296.00 ± 59.78 | 0.276 |
| dAr-Am (ms) | 44.22 ± 29.14 | -37.86 ± 47.42 | < 0.001 |
| VTR (m/s) | 2.78 ± 0.54 | 2.34 ± 0.36 | 0.007 |
| PASP (mmHg) | 18.00 ± 32.11 | 22.42 ± 7.42 | 0.004 |
| B lines | 7.33 ± 3.04 | 0.09 ± 0.43 | 0.001 |

**Table 6:** Comparison of Echocardiographic parameters group E and group NE of the cohort B.

95.5%) had the highest sensitivity and specificity among described parameters LVEDP.

### New Algorithm of LV FP determination in patients with ACS

A new algorithm was designed, based on the above validated parameters. It consisted in two steps. The first step was lung ultrasound, if B lines are superior or equal to 5, we concluded in elevated FP. The second step relayed on 3 parameters: average E/E' > 12, GLS > -12% and dAr-Am > 20 ms, if 2 or 3 of these parameters are positive, we concluded in elevated LV FP.

The validation of this algorithm relayed the comparison of its results to LVEDP in each cohort B patient. Table 8 shows a comparison of the sensitivity and specificity of the new algorithm to predict LVEDP > 18 mmHg in comparison to ASE/ESC guideline algorithm. The new algorithm showed a 100% sensitivity and 86% specificity. When comparing confidence intervals, we remarked a higher sensitivity of the new algorithm while there was no significant difference of specificities of the two algorithms.

| Parameter | AUC | P | cut-off | Se (%) | IC95% Se (%) | Sp (%) | IC95% Sp (%) |
|---|---|---|---|---|---|---|---|
| GLS (%) | 0.91 | < 0.001 | -12% | 92 | [83-100] | 89 | [79-99] |
| DTE (ms) | 0.64 | 0.001 | 180 | 61.1 | [45-77] | 68.6 | [53-83] |
| IRT (ms) | 0.92 | < 0.01 | 72.5 | 88.9 | [79-99] | 90.8 | [82-100] |
| E/E' | 0.75 | 0.07 | 12 | 55.6 | [40-72] | 84.1 | [72-89] |
| TE'-TE | 0.86 | < 0.001 | 24ms | 83.3 | [71-95] | 91.0 | [82-100] |
| IRVT/TE'-TE | 0.78 | 0.047 | 1.9 | 88.9 | [79-99] | 31.8 | [16-46] |
| S/D ratio | 0.83 | 0.001 | 1.1 | 72.2 | [58-86] | 91.0 | [82-100] |
| dAr-Am (ms) | 0.95 | < 0.001 | 20 | 94.4 | [86-100] | 95.5 | [88-100] |
| PASP (mmHg) | 0.76 | P = 0.02 | 25 | 66.3 | [51-80] | 75.2 | [61-89] |
| B lines | 0.93 | < 0.001 | 5 | 93.1 | [85-100] | 93.0 | [85-100] |

**Table 7:** Prediction of Elevated left ventricular end diastolic pressure by selected ultrasound parameters.

| Algorithm | Patients with high filling pressure (Group E) | Patients with normal filling pressure (Group NE) | Sensitivity IC 95% | Specificity IC 95% |
|---|---|---|---|---|
| ASE-ESC algorithm | 8/17 | 21/21 | 47% [CI]: [24-71%] | 100% [CI]: [80-100%] |
| New Proposed algorithm | 17/17 | 18/21 | 100% [CI]:[ 77-100%] | 86% [CI]:[63-96%] |

**Table 8:** comparison of the new algorithm to ASE/ESC algorithm to predict LVEDP > 18 mmHg in cohort B patients**.**

### The new algorithm applied in cohort A

We applied the new algorithm to the first cohort A, we found that it could be applied retrospectively in 98.8% of patients. We found that it was correlated to heart rate (r = 0.7, p = 0.001) and to pulmonary rales (r = 0.76, p = 0.001), two clinical parameters that found to be with significant differences between groups 1 and 2. The new algorithm reclassified 52% of patients put in the high LV FP group of cohort A by the ASE/ESC algorithm.

## Discussion

This study aimed to validate individual ultrasound parameters of LV FP assessment and to define a new practical multiparametric strategy to assess these LV FP in the setting of ACS which is characterized by acute changes of LV FP levels. It consisted into two consecutive prospective studies a large sub study A with a broad non-invasive exploration followed by a more focused sub study B with an invasive reference test. We emphasize that our population did not include patients with pulmonary diseases or advanced heart failure and non-ischemic cardiomyopathies that can lead to chronic pulmonary circulation congestion or fibrosis or other anatomic alterations.

## Our main findings

- Parameters correlated with LVEDP were: B lines, pulmonary venous flow parameters especially dAr-Am, relaxation parameters; IRT, TDE and TE'-E, combined parameters ; E/E', and GLS.
- Parameters related to LA volume or function were not correlated with LV FP in ACS
- The proposed new algorithm was more sensitive (100% CI95% [77-100%] vs 47% CI 95% [24-71]) for detecting elevated LVEDP in ACS without being less specific 86% CI 95% [63-96%] vs 100% CI 95% [80-100%].
- The use of LUS in this algorithm allowed rapid detection of high LV FP in one step in 40% of patients.

## The limitations of this study

- The sample size of the cohort with invasive reference test was limited, this could result in some underpowered parameters (like LA functional parameters), but, on the other hand, this also permitted to highlight most powerful ones.
- The chosen parameters to establish the new algorithm relayed on our objective results, but it did not include all significant identified parameters, it selected variables validated also in the literature and routinely feasible. If the process was somewhat subjective, the validity, feasibility and accuracy of the algorithm were indeed objectively validated by its confrontation to invasive LV FP assessment in the whole cohort.
- Finally new parameters like LA strain were not measured, but LA strain remains high expertise demanding, and our objective was to define a strategy that could be widely adopted.

### Left ventricular filling pressures in acute coronary syndrome and their assessment

The elevation of LVFP in ACS patient is very common and was estimated to 54.3% [4]. Its detection is very important for the management of these patients [5].

Even if in our study revealed that tachycardia and the presence of rales were significantly associated to elevated LV FP, it must be recognized that clinical signs have a weak sensitivity to detect elevated LV FP in ACS. On the other hand, reference invasive measurements of LVEDP cannot be achieved on a repetitive basis to appreciate rapid fluctuations of LV FP in this context. Noninvasive estimation of LV FP by Doppler TTE remains the most suitable and widely used tool [3].

### Ultrasound parameters non predictive of LV FP in ACS

In our study main parameters of the ESC algorithm ASE/ESC [3], E/A ratio, E' and LAVI were not significantly correlated to LVEDP.

- Richardson-Lobbedez., *et al*. reported that higher E/A ratio was associated with an elevation of LV FP and to poor ACS prognosis [6]. However, this parameter was questionable in Seong Choi and., *et al*. [7] study which assessed invasively and non-invasively LV hemodynamic changes of LVEDP in 181 patients in the early phase of heart failure with preserved ejection of fraction, and found no difference in E/A ratios in the two groups of raised and normal LVEDP (0.82 ± 0.22 Vs 0.83 ± 0.23, p = 0.86). Similarly a study led in healthy and myocardial infarction groups of patients, it was remarked that normal E/A ratio could be found in patients with severe diastolic dysfunction [8]. Previous studies have demonstrated that increased LVEDP was associated with increased E/A in animals [9] in dilated cardiomyopathy [10], and in chronic ischemic heart diseases [11]. The divergence of these findings is probably explained by the several factors that affect transmitral flow assessment; such as tachycardia when the two waves E and A merges, the difficulty of placing the sample volume at the suitable site and respiration influences [12] and hypertension and advanced age which increase late diastole contribution. Near half of our population had hypertension and the most represented age group was between 60 to 70 years. As a result, E/A ratio may not be a reliable parameter to assess acute elevation of LVEDP in case of ACS.
- LAIV seemed not adapted to detect the acute change hemodynamics in ACS. LAIV was a reported to be a barometer indicator of LVEDP in chronic situations. Furthermore, this parameter was influenced by age and sex [13].

LA distensibility (LAEI) could be an alternative tool in acute heart failure [14] but it was not significantly influenced by LV FP in our study. Therefore, other studies are needed for this issue.

This study did not assess LA strain, even if recent trials showed a very good correlations of all of reservoir, conduit and contraction LA functions with diastolic dysfunction grade III or II. This parameter may be very useful in echo labs with a high strain expertise [15].

- The use of average of E' wave as recommended in the ASE/ESC algorithm [3] was not convincing in ischemic patients in whom basal septal or lateral myocardial functions could be impaired. Hence, this parameter might not reflect global but regional myocardial performance [14].

### Ultrasound parameters predictive of LV FP in ACS

- E/E' ratio, a combined parameter was a powerful predictor of LV FP in our study. In the descriptive study of Rogéiro., *et al*. [16] including a large series of ACS patients, E/e' > 14 was the best echo parameter correlated with elevated LVEDP and it predicted poor clinical outcome. Similarly, Shih-Hung Hsiao and., *et al*. [14] found a linear correlation between E/e' ratio and the LVEDP (R = 0.22, P < 0.001). E/E' is largely used in critical care departments in various settings of acute LV FP alterations regardless of LV EF; it was found in one study to be the best predictor of mortality in patients with septic shock [17].

- In our study dAr-Am > 20 ms was feasible in all patients and was the most powerful parameter and predicted LVEDP > 18 mmHg with 94.4% Se and 95.5% Sp. This telediastolic parameter changes instantaneously by the hemodynamic fluctuations and balance between LV and pulmonary veins respective resistances when LV stiffness increases. Appleton., *et al*. [18] measured echo parameters in 70 patients with coronary artery disease and found that dAr-Am had the closer correlation with LVEDP (R = 0.75, P < 0.001). in another cohort dAr-Am > 0 predicted high LVEDP (> 15mmHg) with a Se of 85% and a Sp of 79% [19].
- Early diastolic parameters, DTE, TE'-E, IRT were significantly correlated with LVEDP in our study. Relaxation is, indeed, affected first by acute ischemia. Poulsen and., *et al*. [20] found that shortened DTE was associated to congestive heart failure during the first week of myocardial and was shorter in elevated LVEDP group (110±17 vs 187 ± 37ms, p = 0.001). Kusinose., *et al.* [21] demonstrated the superiority of TE'-E to other parameters such as E/E,' a cutoff value of 38ms predicted LVEDP > 16 mmHg with 85% Se and 91% Sp, in our study the best couple (Se, Sp) was obtained by a cut off value of 24ms. We noted that this parameter can be biased the heart rate variations.
- GLS is an established prognostic marker in ACS [22]. Recently a large animal study proved an impairment of GLS in pigs with high LV mean and end diastolic pressures, 1 to 4 weeks after induction of a large myocardial infarction [23]. GLS is charge dependent and increased an LVEDP affects this parameter. GLS allows, in addition, the determination of systolic myocardial infarction, asynchronism, prediction viable/non-viable myocardium in ACS. patients.
- B lines by LUS was a central parameter in our study, it measures lung extravascular water, and detects sub clinical pulmonary congestion. Learning curve of LUS is fast, and variability intra and interobserver is low [24]. It was logical for us to propose it as a first step in our algorithm as lung congestion is a marker of significantly high LV FP. Nevertheless, one should be aware that our population did not include patients with chronic heart or pulmonary diseases, such patients might have pulmonary oedema, infiltration or fibrosis that result in B lines without any LV FP elevation. In their recent trial, Parras., *et al.* [25] proposed to update Killip and Kimball heart failure classification in acute myocardial infarction by using B lines and they found that the "best cut-off value was 5 B-lines, it predicted heart failure (AUC = 0.91) with a sensitivity of 88% (IC95% 68,8-97,5) and specificity of 81% (IC95% 73,9-86,2)". These findings were very similar to ours. Araujo., *et al*. [26], performed LUS on admission and could reclassify patients' mortality prediction thanks to the additive prognostic value of B lines.

### New proposed algorithm for LV FP assessment in ACS

The finality of this study was to define a new approach of non-invasive LV FP evaluation.

- Defining a new approach was needed due to numerous limitations of ASE/ESC algorithm, among them: the non-applicability of its parameters in acute LV FP alterations, its low sensitivity in ACS patients, and the high proportion of undetermined diastolic function and LV FP.
- Our approach was multi-parametric based on most powerful and feasible predictors of LV FP
- In the new algorithm, the first step consisted in LUS; the presence of pulmonary congestion, in the absence of previous pulmonary or heart diseases, is highly specific of elevated LV FP and can be easily assessed in the bedside, in supine position. It has by itself useful therapeutic and prognostic consequences.
- The second step used three echo parameters widely used with hemodynamic information, prognostic information, and systolic function information by GLS, placing LV FP determination in an integrative evaluation approach.
- The new algorithm was validated by its confrontation to a reference invasive test, was demonstrated to be more sensitive and similarly specific to ASE/ESC algorithm and was demonstrated to be feasible.

## Conclusion

Left ventricular filling pressures are abruptly affected in ACS and therapeutic interventions may lead to their rapid improvement. Noninvasive assessment of LV FP in the early phase of acute coronary syndrome and repetitively during hospitalization is crucial for therapeutic decision and prognostic prediction. The current recommendations are on based on parameters that were not fully validated in acute settings and rapid LV FP changes. Our study found the absence of correlation between a number of these parameters and LF FP in ACS. This study assessed a wide number of diastolic variables. We proposed a new practical approach for

LV FP evaluation in ACS. Our algorithm was made by two simple steps, the first step was B lines by LUS. This only parameter could detect several patients with high LV FP. LUS is easy to master and can be applied in bedside. The second step consisted in three echocardiography robust parameters with close correlation with LV FP in ACS and a high prognostic value. Our algorithm was validated by confrontation to invasive LVEDP measurement, we propose its implementation to allow an improvement of sensitivity and accuracy of LV FP assessment. However, one should be aware about its limitations particularly in case of chronic heart of lung disease associated to increased B lines without LV FP elevation. In all cases, an integrative approach taking into account clinical, biological and all available patient's data leads to the best conclusions.

## Bibliography

1. Bursi F., *et al*. "Diastolic dysfunction grade in acute coronary syndromes: Application of 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations". *International Journal of Cardiology* 305 (2020): 18-24.

2. Bateman RM., *et al*. "36th International Symposium on Intensive Care and Emergency Medicine: Brussels, Belgium". *Critical Care* 20.2 (2016): 94.

3. Nagueh SF., *et al*. "Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging". *European Heart Journal: Cardiovascular Imaging* 17 (2016): 1321-1360.

4. Brienesse S., *et al*. "Prognostic Value of LVEDP in Acute Myocardial Infarction: a Systematic Review and Meta-Analysis". *Journal of Cardiovascular Translational Research* 11.1 (2017): 33-35.

5. Prakash S., *et al*. "TCT-250 Left Ventricular End-Diastolic Pressure Predicts Early Myocardial Recovery in Patients with Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention". *Journal of the American College of Cardiology* 62.18 (2013): B82.

6. Richardson-Lobbedez M., *et al*. "Prognostic importance of tissue Doppler-derived diastolic function in patients presenting with acute coronary syndrome: a bedside echocardiographic study". *European Journal of Echocardiography* 9.5 (2008): 594-598.

7. Choi S., *et al*. "Two Distinct Responses of Left Ventricular End-Diastolic Pressure to Leg-Raise Exercise in Euvolemic Patients with Exertional Dyspnea". *Korean Circulation Journal* 46.3 (2016): 350.

8. Chenzbraun A., *et al*. "Doppler echocardiographic patterns of left ventricular filling in patients early after acute myocardial infarction". *The American Journal of Cardiology* 70.7 (1992): 711-714.

9. Myreng Y., *et al*. "Left ventricular filling at elevated diastolic pressures: Relationship between transmitral Doppler flow velocities and atrial contribution". *American Heart Journal* 119.3 (1990): 620-626.

10. Lavine S and Arends D. "Importance of the left ventricular filling pressure on diastolic filling in idiopathic dilated cardiomyopathy". *The American Journal of Cardiology* 64.1 (1989): 61-65.

11. Kuecherer HD., *et al*. "Determination of left ventricular filling parameters by pulsed Doppler echocardiography: A noninvasive method to predict high filling pressures in patients with coronary artery disease". *American Heart Journal* 116.4 (1988): 1017-1021.

12. Uiterwaal C., *et al*. "The effect of respiration on diastolic blood flow velocities in the human heart". *European Heart Journal* 10.2 (1981): 108-112.

13. Nikitin NP., *et al*. "Effect of age and sex on left atrial morphology and function". *European Journal of Echocardiography* 4 (2003): 36-42.

14. Hsiao S., *et al*. "Left Atrial Distensibility and E/e' for Estimating Left Ventricular Filling Pressure in Patients with Stable Angina". *Circulation Journal* 75.8 (2011): 1942-1950.

15. Fernandes RM., *et al*. "Association between left atrial strain and left ventricular diastolic function in patients with acute coronary syndrome". *Journal of Echocardiography* 17.3 (2019): 138-146.

16. Teixeira R., *et al*. "Left ventricular end diastolic pressure and acute coronary syndromes". *Arquivos Brasileiros de Cardiologia* 97.2 (2011): 100-110.

17. Rolando G., *et al*. “Prognostic value of ventricular diastolic dysfunction in patients with severe sepsis and septic shock”. *Revista Brasileira de Terapia Intensiva* 27.4 (2015): 333-339.

18. Appleton C., *et al*. “Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease”. *Journal of the American College of Cardiology* 22.7 (1993): 1972-1982.

19. Rossvoll O and Hatle L. “Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: Relation to left ventricular diastolic pressures”. *Journal of the American College of Cardiology* 21.7 (1993): 1687-1696.

20. Poulsen S., *et al*. “Evaluation and prognostic significance of left ventricular diastolic function assessed by Doppler echocardiography in the early phase of a first acute myocardial infarction”. *European Heart Journal* 18.12 (1997): 1882-1889.

21. Kusunose K., *et al*. “Interval from the Onset of Transmittal Flow to Annular Velocity Is a Marker of LV Filling Pressure”. *JACC: Cardiovascular Imaging* 6.4 (2013): 528-530.

22. Iwahashi N., *et al*. “Impact of three-dimensional global longitudinal strain for patients with acute myocardial infarction”. *European Heart Journal: Cardiovascular Imaging* (2021): 241.

23. Aikawa T., *et al*. “Impaired left ventricular global longitudinal strain is associated with elevated left ventricular filling pressure after myocardial infarction”. *The American Journal of Physiology-Heart and Circulatory Physiology* 319.6 (2020): H1474-H1481.

24. Wolstenhulme S and McLaughlan JR. “Lung ultrasound education: simulation and hands-on”. *The British Journal of Radiology* 94.1119 (2021): 20200755.

25. Araujo GN., *et al*. “Admission Bedside Lung Ultrasound Reclassifies Mortality Prediction in Patients With ST-Segment-Elevation Myocardial Infarction”. *Circulation: Cardiovascular Imaging* 13.6 (2020): e010269.

26. Parras JI., *et al*. “Lung ultrasound in acute myocardial infarction. Updating Killip and Kimball”. *Indian Heart Journal* 73.1 (2021): 104-108.