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ORIGINAL ARTICLE

Effect of a Therapeutic Strategy Guided by Lung Ultrasound on 6-Month Outcomes in Patients with Heart Failure: Randomized, Multicenter Trial (EPICC Study)

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Abstract

Introduction and Objectives Pulmonary congestion (PC) is associated with an increased risk of hospitalization and death in patients with heart failure (HF). Lung ultrasound has shown to be highly sensitive for detecting PC in HF. The aim of this study is to evaluate whether lung ultrasound–guided therapy improves 6-month outcomes in patients with HF compared with conventional treatment.

Materials and Methods Randomized, multicenter, single-blind clinical trial in patients discharged from Internal Medicine Departments after hospitalization for decompensated HF. Participants will be assigned 1:1 to receive treatment guided according to the presence of lung ultrasound signs of congestion (semi-quantitative evaluation of B lines and the presence of pleural effusion) versus clinical assessment of congestion. The primary outcome is the combination of cardiovascular death and readmission for HF at 6 months.

Conclusions The results of this study will provide more evidence about the impact of lung ultrasound on treatment monitoring in patients with chronic HF.

Keywords Heart failure · Lung ultrasound · Trial · Therapy

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Introduction

Mortality and readmission rates increase during the first months after hospitalization for heart failure (HF) [1–3]. One of the reasons is the difficulty in assessing pulmonary congestion. In fact, it has been shown that a significant percentage of patients are discharged with a certain degree of residual pulmonary congestion after hospitalization due to acute HF [4, 5].

Pulmonary congestion (PC) is involved in the pathogenesis of HF. In our clinical practice, this parameter is usually evaluated by the patient's signs and symptoms, but the accuracy of clinical parameters alone is poor [5–8]. Chest X-ray, proBNP, echocardiography, and other invasive procedures have been advocated to quantify and evaluate the severity of PC [5, 8, 9]. However, the availability of an accurate clinical-based method to quantify PC status remains an unsolved need in the management of patients with HF.

Lung ultrasound provides a semi-quantitative evaluation of B lines and the presence of pleural effusion that are associated with subclinical congestion in 30–70% of patients with HF [10, 11]. This method has also shown to be useful to predict short- and mid-term prognosis [10, 12, 13] and is sensitive to intravascular volume changes [14, 16].

Previous studies have shown that patients with residual PC could benefit from intensive diuretic treatment without increasing treatment-related side effects [17, 18]. The preliminary results of a clinical trial comparing lung ultrasound–guided ambulatory treatment versus conventional treatment in 96 patients with chronic HF and reduced ejection fraction showed a reduction in hospitalization at 3 months with no influence on mortality [19].

Lung ultrasound–guided treatment could improve prognosis. It is not known if its effectiveness varies with different disease stages, or if it is independent of the ejection fraction. In the current study, we aim to evaluate if lung ultrasound–guided treatment improves 6-month outcomes compared with conventional clinical assessment among patients with HF after an episode of decompensation.

Methods

Study Design

This will be a randomized, multicenter, single-blind clinical trial in patients with HF discharged from Internal Medicine Departments after an episode of decompensation.

Population

Patients older than 18 years with HF will be selected prior to hospital discharge after a decompensation episode. Table 1 shows the inclusion and exclusion criteria.

Management of Patients

Patients will be selected within 36 h prior to hospital discharge. They must meet the inclusion and exclusion criteria and give written consent. Participants will be assigned 1:1 to receive treatment guided according to the presence of congestion evaluated by lung ultrasound or conventional clinical assessment (Fig. 1).

Table 1 Inclusion and exclusion criteria of EPICC trial

Inclusion criteria	Exclusion criteria
-Age ≥ 18 years	-Life expectancy < 6 months due to a different medical condition
-Decompensated heart failure requiring hospital admission. Heart failure defined as the presence of objective evidence during hospitalization or prior to it, structural anatomy or functional heart anomaly at rest, NT-proBNP > 1.000 pg/ml or BNP > 100 pg/ml or echocardiographic abnormalities consistent with heart failure: left ventricular systolic dysfunction (EF < 50%); left ventricular hypertrophy (defined as a posterior ventricular wall thickness or septum ≥ 12 mm or left ventricular mass index (%) > 104 g/m^2 [females] or 116 g/m^2 [males]); E/e′ > 15 or significant heart valvulopathy (moderate to severe)	-Heart transplant, acute coronary syndrome, coronary revascularization, or valve replacement 3 months prior
	-Pregnancy
	-Restrictive pulmonary disease or severe COPD needing continuous oxygen
	-Serum creatinine > 3 mg/dl or chronic renal insufficiency in dialysis
	-Resynchronization in the prior 3 months
	-Severe valve stenosis
-Met the criteria for hospital discharge	-Participation in another randomized study
-Functional class NYHA ≥ II at inclusion	
-Able to understand and sign the written consent	
-Ambulatory follow-up possible	

Main inclusion criteria

-Age ≥ 18 years

-Decompensated heart failure requiring hospital admission.

-Able to understand and sign the written consent

-Ambulatory follow-up possible

5 centers

Total n=152

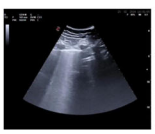
At discharge:medical history, physical examination,NT-proBNP renal function, hemoglobin, sodium and potassium.

Therapy guided by lung ultrasound

N=76

¿Presence of at least one positive anterior region bilaterally and/or the presence of pleural effusion >1 cm?

Yes



increase furosemide doses and/ or add hydrochlorothiazide

No

No change in diuretic dose

Therapy guided by clinical assessment at discharge

N=76

(symptoms or signs of congestion?

Yes

increase furosemide doses and/ or add hydrochlorothiazide

No

No change in diuretic dose

Fig. 1 Flow diagram of the progress through the discharge phase of EPICC trial

Patients assigned to lung ultrasound–guided treatment will follow the treatment algorithm shown in Table 1. In brief, the treatment will be optimized and diuretic doses increased in the presence of at least one positive bilateral pulmonary region and/or significant pleural effusion (> 1 cm) (Figs. 2, 3, and 4). In the group receiving treatment, based on clinical assessment, the diuretic dose will be adjusted according to signs and symptoms of clinical congestion. Ambulatory intravenous administration of a diuretic will be given to patients with signs and symptoms of persistent PC or in those not responding to high oral doses of diuretics. Intravenous administration of furosemide may be implemented in both groups.

Patients in both groups will be treated according to the current European guidelines [20]. In general, all patients with HF and a reduced left ventricular ejection fraction will receive (a) angiotensin-converting enzyme inhibitors if there is no contraindication, or in case of intolerance, an angiotensin-2 receptor antagonist will be prescribed; (b) beta-blockers at the highest dose tolerated; (c) consider anti-aldosterone drugs in patients with an ejection fraction < 35%; (d) ivabradine in patients with an ejection fraction < 35%, sinus rhythm, and heart rate > 70 bpm after reaching the maximum dose of beta-blockers; (e) vasodilator treatment with hydralazine and isosorbide if angiotensin-converting enzyme inhibitors or angiotensin-2 receptor antagonists are contraindicated or not well-tolerated; and (f) sacubitril-valsartan will be used in patients already on angiotensin-converting enzyme inhibitors, with an ejection fraction < 40%, and symptomatic despite optimal treatment.

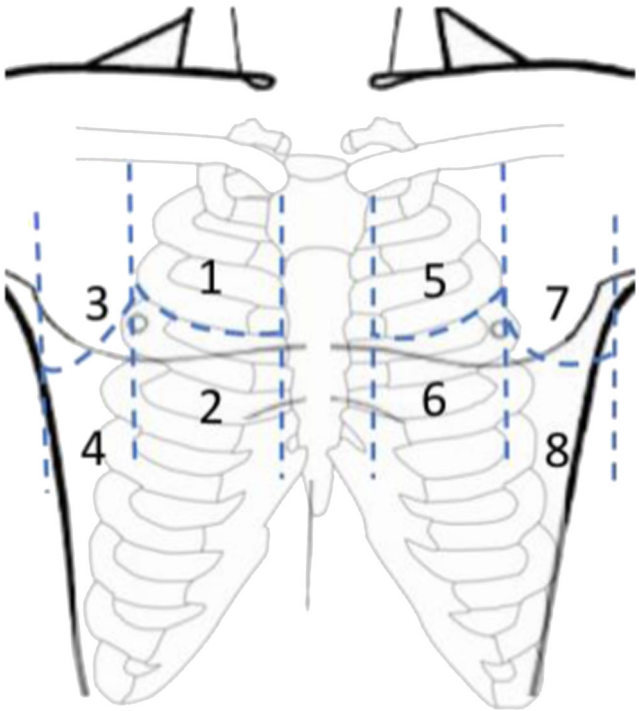


Fig. 2 Pulmonary regions to examine by ultrasound in EPICC study

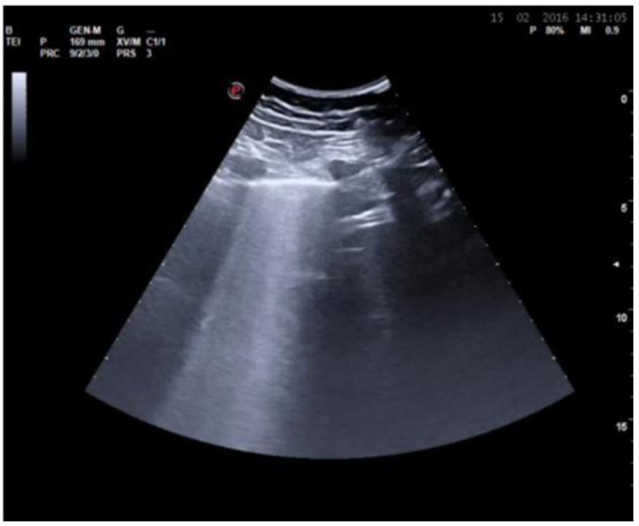


Fig. 3 Detection of B lines with lung ultrasound

In patients with HF and preserved ejection fraction, the treatment will be (a) management of signs and symptoms of PC with diuretics and the addition of spironolactone if there are no contraindications; (b) angiotensin-converting enzyme inhibitors or angiotensin-2 receptor antagonists; and (c) beta-blockers or calcium channel blockers (verapamil and/or diltiazem), especially if the blood pressure is > 130/80 mmHg or the patient presents atrial fibrillation. Other options will include digoxin, anticoagulation, nitrates, and antiarrhythmics according to current guidelines [21].

Follow-up appointments will be set for days 7–14 and 1, 3, and 6 months after the patient is assigned to a group. In both groups, optional appointments will be allowed according to the patient's clinical condition and the clinician's choice, especially if the diuretic dose must be adjusted (in this case, a 1 to 4-day window is recommended for the next consultation). Each consultation will include history, physical examination, review of medical treatment, and laboratory tests.

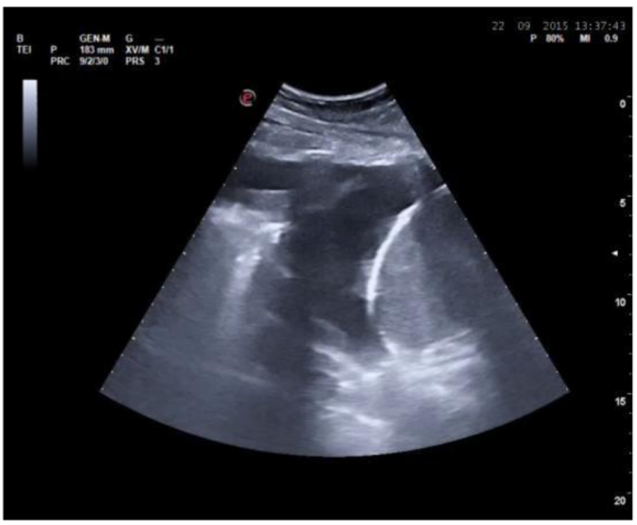


Fig. 4 Evaluation of pleural effusion with lung ultrasound

Lung ultrasound evaluation of PC in patients assigned to that group will be performed according to the protocol described in the literature [11, 16, 20]. A low-frequency convex probe (3.5–5 MHz) with abdominal configuration and 10–15-cm depth will be used. To respect blinding for the control group, a lung ultrasound with the screen not visible to the patient will be performed.

The thoracic regions that will be explored are shown in Fig. 2, and the pulmonary examination will be performed as follows: patient position, the patient will be placed in the supine position at an angle of 30° (according to clinical tolerance). It is important to examine the patient in the same position during all of the following visits; pulmonary pattern, line B is defined as a reverberation artifact that generates a vertical hyperechoic image with a narrow origin in the pleural line that extends to the base of the image and that moves synchronously with the pleural slip; pleural effusion, the presence of pleural effusion will be defined as an anechoic band that separates the pulmonary parenchyma and the visceral pleura from the parietal pleura and the diaphragm. The presence of an effusion > 1 cm will be defined as significant; exploration areas, each hemithorax will be divided into three zones (anterosuperior, anteroinferior, and lateral). The planes will be obtained by means of a longitudinal section taken from the midclavicular line in the apical and mamillary area of both hemithoraces. The lateral plane will be obtained in the mid-axillary line through a longitudinal section in the last intercostal spaces (Fig. 2). In each 8 planes, a 3-s clip will be recorded. The number of B lines in that clip will be counted. The presence of at least three B lines will be considered as a positive anterior zone. Pulmonary congestion will be defined as the presence of at least one positive anterior region bilaterally and/or the presence of pleural effusion > 1 cm.

All investigators participating in the trial will use the same methodology. Each investigator will have performed at least 20 previous pulmonary lung ultrasound examinations. All 3-s clips will be recorded for later review by the investigators as a whole to achieve maximum consensus regarding the results. A pilot study will be conducted among the investigators to establish the degree of inter-observer agreement in the detection of B lines and pleural effusion with pulmonary ultrasound [9].

Result Variables

The primary outcome is the combination of cardiovascular death and readmission for HF at 6 months. Cardiovascular mortality will be defined as a composite of death, HF, acute myocardial infarction, pulmonary embolism, stroke, sudden cardiac death, cardiovascular procedures, and life-threatening arrhythmia. Death during in-hospital and out-hospital follow-up will be considered. Readmission for HF is defined as unplanned hospitalization requiring a stay > 24 h and caused by a substantial worsening of the signs and/or symptoms of HF requiring new administration of intravenous treatments for HF, including inotropes, diuretics, or vasodilators. To determine the outcomes, all available medical records will go through a blinded checkup by two independent physicians.

Variables to Be Collected During Visits

Demographic variables: age, sex (only in the first visit); past medical history: hypertension, diabetes, chronic obstructive pulmonary disease, chronic renal failure, ischemic cardiomyopathy, and smoking status (only first visit); heart failure characteristics: etiology, left ventricular ejection fraction (only first visit); electrocardiogram; comorbidities: Modified Charlson score (only first visit); physical examination and clinical variables: height, weight, presence of rales, edema in lower limbs and degree, presence of ascites, jugular vein distension, hepatojugular reflux, and pleural effusion. The congestion scale will be recorded as described in the EVEREST study; biological variables: hemogram, sodium, potassium, serum creatinine and glomerular filtration, liver function tests, and natriuretic peptides; echographic variables: Pulmonary congestion will be defined in the presence of at least one positive anterior region bilaterally and/or the presence of pleural effusion > 1 cm [26, 27]; treatment: drugs and doses and modifications during follow-up; side effects (subjective): symptomatic hypotension (defined as systolic blood pressure < 90 mmHg associated with symptoms justifying medical treatment adjustment), worsening of renal failure requiring adjustment of treatment (diuretics, angiotensin-converting enzyme, angiotensin-2 receptor antagonist, sacubitril-valsartan, anti-aldosterone, or beta-blockers); quality of life scale: Kansas City Cardiomyopathy Questionnaire at visits 1, 3, and 6.

A Data Safety Monitoring Board (DSMB) constituted by two external independent investigators will review the data collected from EPICC clinical trials on a regular basis. They will evaluate the safety, validity, and scientific merit of the trial.

Sample Size Calculation

Based on previous studies on lung ultrasound in HF in Spain [25], we would consider 43% for the combined variable in the group not managed by lung ultrasound–guided echography versus 20% in the group of patients receiving lung ultrasound–guided treatment with a statistical power of 90% ($\beta = 0.10$), with an expected drop-out rate of 10% and a level of significance $\infty = 0.05$ bilaterally. A sample size of 152 patients will be needed for this study (76 patients in each arm).

Statistical Analysis

Quantitative variables will be expressed as means and standard deviation, or median and interquartile range if they do not comply with the principles of normality. The comparison of the treatment groups will be carried out with the Student *t* test for unpaired data or with the Mann-Whitney *U* test depending on the distribution of the variable. Discrete variables will be compared with the chi-square test or Fisher's exact test as appropriate.

All statistical comparisons will be made according to the intention-to-treat principle. The time to the first event of the composite variable will be considered. The difference between the treatment groups will be represented graphically with the Kaplan-Meier method and evaluated by the log rank test.

Univariable risk ratios will be estimated with a Cox proportional hazards regression test; however, the multivariable Cox regression analysis will be used only in case there are important prognostic factors or baseline characteristics of the patients that show a significant imbalance between the two groups established by randomization.

Analyses will consider a possible grouping effect among the centers. A bilateral p value < 0.05 in all analyses will be considered statistically significant. The statistical analysis will be carried out using the SPSS 17.0 software program.

Ethical Aspects

This study will be carried out in compliance with the standards of Good Clinical Practice, Declaration of Helsinki of 2002. All patients or guardians will sign the written consent. The study was approved by the Ethical Committee of Puerta de Hierro University Hospital in Madrid.

Discussion

Pulmonary congestion evaluated by lung ultrasound has been shown to be a strong predictor of hospital readmissions and mortality in patients with HF [9–11]. A recent study by Pellicori et al. suggested that lung ultrasound could detect subclinical congestion in patients with HF whom no alterations were observed on physical examination. Lung ultrasound could therefore complement the data provided by the clinical history and physical examination for detecting PC in patients with HF [22].

The detection of artifacts known as B lines in lung ultrasound is related to congestion in HF. The integration of lung ultrasound with clinical assessment for the diagnosis of acute HF seems to be more accurate than the current diagnostic approach based on chest radiography and natriuretic peptides such as NT-proBNP [23]. Thus, some studies have shown a correlation between the number of B lines and the presence of high levels of B-type natriuretic peptide [24]. Indeed, Hubet et al. demonstrated the important diagnostic capacity of B lines in identifying elevated left ventricular end-diastolic pressure [25].

The persistence of B lines after hospital discharge for HF is associated with a worse prognosis, including a greater than fivefold risk of hospital readmission and mortality [10]. Pulmonary decongestion is one of the treatment objectives in patients with HF. Inadequate decongestion leads to an increase in dyspnea and the risk of hospitalization and associated mortality [21]. In addition, some prospective studies have shown that the presence of B lines may decrease when depletive treatment is administered. These results suggest that lung ultrasound can be a useful tool to guide diuretic treatment in HF. However, most of the evidence available regarding the usefulness of lung ultrasound in the treatment of HF has been obtained from open, prospective, non-randomized trials with small sample sizes [12–17].

It would be useful to design clinical trials focussing on safety and efficiency of lung ultrasound in diuretic-guided treatment in heart failure. We do not know if B line congestion distribution would be important in diuretic-guided therapy. Patients with reduced and preserved ejection fraction will probably not respond the same way to lung ultrasound–guided therapy. Therefore, the EPICC study could provide with further information in this respect. The EPICC study will include all patients despite their left ventricular ejection fraction but with high comorbidity which may provide important evidence regarding the efficacy and safety of the use of pulmonary ultrasound in the management of HF in this subgroup of patients not previously evaluated in other clinical trials.

This study might have some limitations as the results could be influenced by inter-observer variability and patient anatomy when performing the procedure. Patients with a high body mass index are known to have a worse acoustic window. Detection of B lines could vary from one center to another as the equipment could be different.

The results of this study might lead to a change in PC management in HF in daily medical practice. At present, PC is evaluated by patient history, physical examination, chest X-rays, and natriuretic peptides, but these evaluations have not shown to be as sensitive as lung ultrasound. In this respect, if ultrasound-guided treatment is shown to be beneficial in PC, it will represent a new tool in the treatment of patients with HF.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All the procedures involving human participants performed in this study are in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki.

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