



Thoracic fluid content: a novel parameter for detection of pulmonary edema in parturients with preeclampsia

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Abstract

Acute pulmonary oedema is a serious complication of preeclampsia. Early detection of pulmonary edema in preeclampsia would improve fluid management and would also allow earlier detection of severe cases. The aim of this work is to evaluate the ability of thoracic fluid content measured by electrical cardiometry for early detection of pulmonary edema in parturients with preeclampsia. A prospective observational study included a cohort of preeclamptic parturients. On admission, lung ultrasound score was calculated, and thoracic fluid content was recorded using electrical cardiometry ICON device. Area under receiver operating characteristic (AUROC) curve was calculated for lung ultrasound score, thoracic fluid content for detection of pulmonary edema. Spearman correlation coefficient was calculated for correlation between lung ultrasound score and thoracic fluid content. Sixty patients were included in the study; of them, 6 patients (10%) required diuretics for pulmonary edema. Patients with pulmonary edema had higher lung ultrasound score and thoracic fluid content compared to other patients. Good correlation was reported between Lung ultrasound score and thoracic fluid content ($r=0.82$). Thoracic fluid content and lung ultrasound score showed excellent diagnostic properties for pulmonary edema {AUROC: 0.941 (0.849–0.986), best cut-off value: 40 k ohm⁻¹}, and {AUROC: 0.961 (0.887–0.994), best cut-off value of 15.7}. In parturients with preeclampsia, both lung ultrasound score and thoracic fluid content showed excellent properties for detection pulmonary edema. The high negative predictive value of both tests makes them useful screening tests to rule out pulmonary edema. The excellent correlation between both measures suggests that electrical cardiometry could be a promising surrogate to ultrasound for assessment of extravascular lung water.

Keywords Preeclampsia · Lung ultrasound · Thoracic fluid content · Electrical cardiometry

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1 Introduction

Preeclampsia (PE) is a serious pregnancy disorder associated with poor outcomes [1]. Pulmonary edema is the most frequent cardiopulmonary complication of PE [2]; thus, preeclamptic patients need meticulous fluid and diuretic management. Under-resuscitation of patients with PE impairs peripheral organ perfusion; whereas, fluid overload aggravates lung congestion [3]. Thus, early detection of lung congestion would allow early management and improve patient outcome.

Ultrasound is a robust method for assessment of extravascular lung water (EVLW) [4]. Lung ultrasound had been considered a useful diagnostic and prognostic tool for evaluation of various lung disorders, especially lung congestion [5]. Lung ultrasound was reported as a useful tool which could detect pulmonary edema in parturients with severe PE [6, 7]. Though it is accurate and non-invasive, ultrasound is a subjective, operator-dependent method.

Thoracic fluid content (TFC) is one of the many variables measured by the ICON electrical cardiometry (EC) device (Osypka Medical, etc.). The ICON device is one relatively new proprietary implementation of impedance cardiography technology, which is also often called “thoracic electrical bio-impedance”. Impedance cardiography is based on measuring the changes in total resistance of the thorax to electric current. The impedance (Z_0) to electric current is determined by the resistance of different tissues such as bone, muscles, and fluids. The fluid compartment is considered the dynamic component that would cause short term changes in thoracic impedance. TFC is calculated as the reciprocal of the total thoracic impedance ($1/Z_0$) [8] and is considered a numerical measure of total (intravascular and extravascular) thoracic fluid. Although TFC is a measure of both extra and intra-vascular thoracic fluid, we hypothesized that it might provide an estimate of the increase in intrathoracic fluids such as to facilitate the risk of pulmonary edema. The aim of this work is to evaluate the accuracy of TFC in detection of pulmonary edema in parturients with PE. The second aim is to evaluate the correlation between lung ultrasound and TFC.

2 Materials and methods

A prospective observational study was conducted for an 8-month period in the obstetric emergency department, Cairo university hospital. The study was approved by research ethics committee (N-28-2017). Written informed consent was obtained from all participants before recruitment.

Included patients were parturients, aged between 18 and 40 years, diagnosed with PE (defined as systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg presenting after 20 weeks of gestation with significant proteinuria) [9], in the first stage of labor (defined as the period starting from the beginning of regular uterine contractions which result in progressive cervical dilatation and effacement till full cervical dilatation). We excluded patients admitted at later stages of labor, patients presenting with postpartum PE, and patients with eclampsia.

Once PE was diagnosed in the obstetric emergency room, full investigations were obtained, and baseline hemodynamic measures (arterial blood pressure and heart rate) were recorded in the supine position. Within 30 min of admission, lung ultrasound examination was performed, and EC measures were also reported. Both lung ultrasound and EC records were reported three times with 5 min intervals, and then, the average value was calculated. The physician who performed the ultrasound examination was blinded to the EC records. The physicians who performed anesthetic and obstetric management were blinded to the results of lung ultrasound and EC. Patients were observed for development of symptomatic pulmonary edema starting from hospital admission till 48-h after delivery. Patients who developed symptomatic pulmonary edema {defined as shortness of breath (dyspnea or orthopnea), and tachypnea, and audible crepitations, and/or hypoxemia (oxygen saturation < 90% on room air)} were admitted to intensive care unit and managed by diuretic therapy [6].

2.1 Ultrasound examination

The 12-region technique for lung assessment was performed by an expert (of more than 70 previous examinations) using Mindray device (DC-N6, with a phased array transducer, model P4-2, 3–6 MHz). B-line was defined as laser like vertical hyperechoic artefact which extends between the pleural line and the bottom of the screen, and moves with respiratory movements [10]. Two types of B-lines were evaluated: (1) B-7 lines: which are 7 mm apart denoting interstitial oedema [10] (2) B-3 lines: which are 3 mm apart denoting alveolar oedema [4]. Lung consolidation was defined as “sub-pleural, hypoechoic, wedge-shaped, tissue-like structure” [6, 11].

Lung ultrasound score (LUS) was calculated for each patient as follows:

- The 12 inter-rib spaces were scanned vertically starting up and moving downwards.
- Each hemithorax was divided into six zones: two anterior zones (between parasternal and midaxillary lines), two lateral zones (between midaxillary and posterior axillary

lines), and two posterior zones (behind the posterior axillary lines).

- A B-line score was calculated for each zone as follows: zero: no lines, 1: B-7 lines, 2: B-3 lines, 3: consolidation.
- The total LUS was calculated as the sum of all lung zones (from 0 to 36).

2.2 EC

EC ICON^R monitor (Osypka Medical, Inc., La Jolla, California and Berlin) was applied to the patients through four ECG electrodes. The electrodes were placed over the bare skin of patients at the following sites: (1) on the left neck below the ear; (2) directly superior to the midpoint of the left clavicle; (3) along the left mid-axillary line at the level of the xiphoid process; (4) two-inches caudad from the third electrode.

2.3 Outcomes

Our primary outcome is the area under receiver operating characteristic (AUROC) curve for TFC {measured on patient admission to obstetric emergency department} to detect pulmonary edema. Secondary outcomes included: LUS {measured on patient admission to obstetric emergency department}, demographic data {age, parity, gestation, and body mass index (BMI)}, history of previous PE, hemodynamic data (SBP, DBP, and heart rate), laboratory investigations (hemoglobin, proteinuria, platelets, serum urea, creatinine, and albumin), lung congestion, and pulmonary edema needing diuretic therapy.

2.4 Statistical analysis

We calculated our sample size using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium) to detect the accuracy of TFC in detection of pulmonary edema. The AUROC curve for lung ultrasound was previously reported to be 0.9 [6]. We made a more conservative sample size assumption to detect AUROC of 0.85. Considering that null hypothesis for AUROC was 0.5, a minimum number of 28 parturients was needed to have a study power of 80% and alpha error of 0.05. Taking in consideration that the incidence of lung congestion in PE is about 17.5% [12, 13], a minimum number of 5 positive cases should be present.

Statistical package for social science (SPSS) software, version 15 for Microsoft Windows (SPSS inc., Chicago, IL, USA) was used for data analysis. Categorical data were presented as frequency percentage. Continuous data were tested for normality using Shapiro–Wilk test and were presented as mean (standard deviation) or median (quartiles) accordingly. Comparison between patients with and patients without pulmonary edema was performed using Chi square test, unpaired t-test, or Mann–Whitney test as appropriate.

AUROC was calculated for LUS and TFC for detection of pulmonary edema. Positive predictive values (PPV), negative predictive values (NPV), and best cut-off values for all parameters were also calculated. MedCalc version 12.1.4.0 (MedCalc Software bvba, Mariakerke, Belgium) generated values with the highest sensitivity and specificity (Youden index). The AUC of the ROC curves were compared using a Hanley–McNeil test. Correlation between LUS and TFC was performed using Spearman's correlation coefficient. P value of 0.05 or less was considered significant.

3 Results

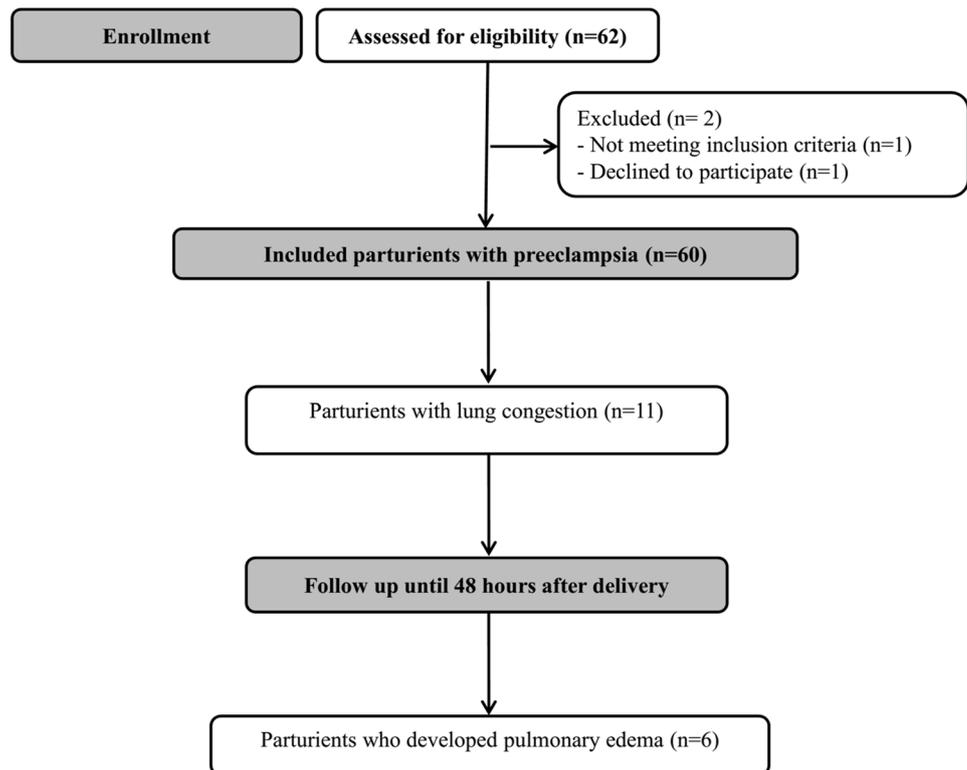
Sixty-two parturients with PE were evaluated for eligibility. Two parturients were excluded, and 60 parturients with PE were available for final analysis (Fig. 1). Baseline demographic, hemodynamic, and laboratory data are presented in Table 1. Eleven parturients had lung congestion (by auscultation) on hospital admission; of them, 6 parturients (10%) developed symptomatic pulmonary edema and received diuretic therapy. All cases with pulmonary edema were diagnosed before or during delivery of the fetus. The median LUS was 2.6 with interquartile range of (2–3.6); whilst, the median TFC was 29 k ohm⁻¹ with interquartile range of (27–40) k ohm⁻¹.

Both LUS and TFC showed the excellent ability to detect pulmonary edema {AUROC: 0.961 (0.887–0.994), best cut-off value of 15.7}, and {AUROC: 0.941 (0.849–0.986), best cut-off value: 40 k ohm⁻¹} (Table 2; Fig. 2) with good correlation between both parameters {spearman correlation coefficient *r* (95% confidence interval): 0.816 (0.709–0.886)} (Fig. 3). There was no significant difference between the AUROC of both parameters in detection of pulmonary edema. On comparing patients with and patients without pulmonary edema, patients with pulmonary edema had higher age, LUS, TFC, SBP, DBP, and lower serum albumin compared to patients without pulmonary oedema (Table 3).

4 Discussion

We reported two main findings: (1) Both TFC and LUS showed excellent properties for detection of pulmonary edema in parturients with PE. (2) There is an excellent correlation between TFC and LUS.

TFC is a parameter that had been previously measured by thoracic bio-impedance; and recently, it had been introduced with the newer EC technology. The bio-impedance-derived TFC had been previously used for assessment of the hemodynamic effect of diuretics [14]; it had been also used for evaluation of thoracic fluid in heart failure [15]. Bio-impedance derived TFC had

Fig. 1 CONSORT chart showing patient recruitment**Table 1** Patient characteristics and Hemodynamic data

| Characteristic | Value |
|--------------------------------------|----------------|
| Age (years) | 26.8 ± 4.5 |
| BMI (kg/m ²) | 29 (27, 31) |
| Heart rate (Bpm) | 80 (76, 90) |
| Parity [median (quartiles)] | 2 (1, 3) |
| Gestation (weeks) | 35 (32, 37) |
| History of preeclampsia [number (%)] | 12 (20%) |
| SBP (mmHg) | 149 (142, 160) |
| DBP (mmHg) | 84.6 ± 8 |
| Laboratory investigations | |
| – Serum urea (mg/dL) | 19 (17–21) |
| – Serum creatinine (mg/dL) | 0.65 (0.5–0.8) |
| – Serum albumin (mg/dL) | 2.9 ± 0.35 |
| – Hemoglobin (mg/dL) | 10.7 ± 0.84 |
| – Platelets (mg/dL) | 264 ± 75 |
| – 24-h urinary protein (mg) | 900 (600–1400) |
| Fetal complications [number (%)] | 2 (3%) |
| Maternal hemorrhage [number (%)] | 2 (3%) |

Data are presented as mean ± standard deviation, median (quartiles), and number (percentage)

been a valuable dynamic monitor in hemodialysis where the changes in TFC showed good correlation with the change in both weight and ultrafiltrate removed [16]. TFC showed high correlation with fluid balance during cardiac surgery [17]. The newly developed EC-derived TFC

had been only investigated for evaluation of the volume status during autologous blood transfusion [8]. In our study, we introduced the use of EC-derived TFC in PE. Our findings introduce TFC as a novel, objective, hands-free, continuous, accurate, and user-friendly parameter. EC could be applied by a junior physician or even by a trained nurse; moreover, its interpretation is so simple as it provides numerical values.

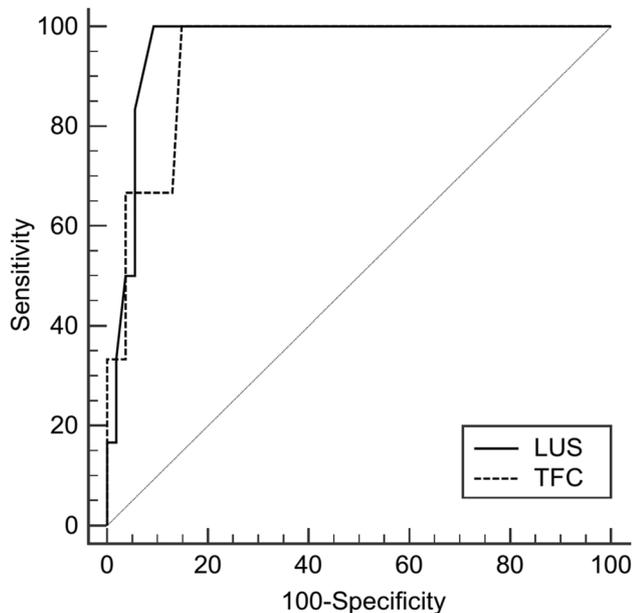
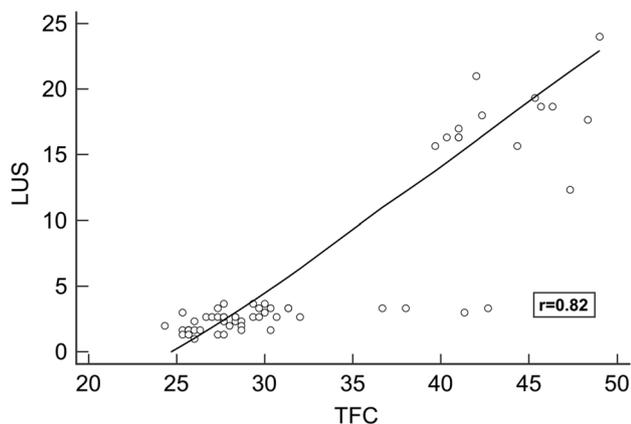
Lung ultrasound is a robust method for evaluation of extravascular lung water [4, 5, 7]. Zieleskiewicz et al. had reported excellent properties for lung ultrasound in detection of pulmonary edema in parturients with severe PE [6]. Though ultrasound is considered a valuable tool for lung assessment, its use is limited by the need to an expert operator. Lung ultrasound had been reported to have a good inter-observer variability [6, 7]; however, it is still considered a subjective operator-dependent method. Other limitations of lung ultrasound include subcutaneous emphysema, and the presence of surgical dressings. All these limitations could be avoided by the use of TFC for assessment of lung congestion in PE.

We defined a cut-off value of 16.7 for LUS to detect pulmonary edema. Interestingly, many authors reported cut-off values which are very near to our cut-off value. Enghard et al. reported that LUS of 18.5 accurately detected severely increased EVLW in critically ill ventilated patients [18]. Miglioranza et al. had found that B-line score of 15 is a reliable sign of decompensation in

Table 2 Receiver operating characteristic, sensitivity, specificity, and cut-off value for prediction of pulmonary edema

| | AUROC (95% CI) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Cut-off value |
|-----|---------------------|-----------------|-----------------|---------|---------|--------------------------|
| LUS | 0.961 (0.887–0.994) | 100 | 90.7 | 54 | 100 | > 15.7 |
| TFC | 0.941 (0.849–0.986) | 100 | 85.2 | 43 | 100 | > 40 k ohm ⁻¹ |

AUROC area under receiver operating characteristic, LUS lung ultrasound score, NPV negative predictive value, PPV positive predictive value, TFC total fluid content

**Fig. 2** Receiver operating characteristic curve for the ability of different parameters to predict pulmonary oedema. LUS lung ultrasound score, TFC total fluid content**Fig. 3** Scatter dot graph showing correlation between LUS and TFC. Spearman correlation coefficient (r)=0.82. LUS lung ultrasound score, TFC total fluid content

outpatients with heart failure [19]. Zhao et al. reported that LUS of 16.5 is a very useful prognostic marker in patients with ARDS [20].

LUS is a measure of EVLW; whilst, TFC is a measure of both intravascular and extravascular fluid compartments. Despite the clear physiological difference between both parameters, we reported excellent correlation between TFC and LUS; thus, TFC could be used as a simple and non-invasive surrogate for LUS in evaluation of the lung.

Pulmonary edema is a common and serious complication of PE. The most challenging aspect when a physician is dealing with pulmonary edema is fluid management. Under-resuscitation impairs peripheral organ perfusion; whereas, fluid overload results in lung congestion. Early detection of pulmonary edema would guide fluid management and allow early diuretic therapy. TFC and LUS could also act as early screening measures before further meticulous cardiac evaluation. High TFC values could be an early alarming sign for the need of high dependency unit.

Our study had some limitations: (1) It is an observational study. these findings need to be confirmed by randomized controlled trials. (2) It is a single-center study. (3) We reported an excellent NPV and a moderate PPV for TFC and LUS; thus, we suggest that both measures could be useful screening tests to rule out rather than diagnostic tests to rule in pulmonary edema. We recommend more studies which include more positive cases to for more precise evaluation of both parameters. (4) The absence of ante-natal data is considered another limitation; thus, future studies are warranted that include patients during earlier stages of pregnancy. We should also clarify that TFC could be affected by changes in cardiac output, pleural disorders, and arrhythmias; none of these conditions was present in our patients. This should be taken in consideration before generalization of our findings. We also suggest studies that validate EC in other patient groups such as cardiac and critically ill patients.

In parturients with preeclampsia, both LUS and TFC showed excellent properties for detection of pulmonary edema. The high negative predictive value of both tests makes them useful screening tests to rule out pulmonary edema. The excellent correlation between both measures suggests that EC could be a promising surrogate to ultrasound for assessment of extravascular lung water.

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Table 3 Comparison between parturients with and without pulmonary edema

| | Patients with pulmonary edema (n=6) | Patients without pulmonary edema (n=54) | P value |
|----------------------------|-------------------------------------|---|---------|
| Age (years) | 31 ± 3.5 | 26 ± 4.2 | 0.01 |
| BMI (kg/m ²) | 30 (29–33) | 29 (27–31) | 0.2 |
| Previous PE (%) | 6 (100%) | 6 (10%) | <0.001 |
| SBP (mmHg) | 163 (152–169) | 148 (141–157) | 0.01 |
| DBP (mmHg) | 92 ± 3 | 84 ± 8 | 0.001 |
| Heart rate (Bpm) | 80 (76–91) | 80 (76–90) | 0.9 |
| Albumin (mg/dL) | 2.5 ± 0.2 | 2.92 ± 0.3 | 0.04 |
| 24-h urinary protein (mg) | 1300 (875–2325) | 900 (600–1325) | 0.15 |
| TFC (k ohm ⁻¹) | 47 (42–49) | 29 (27–33) | <0.001 |
| LUS | 19 (17–20) | 3 (2–3) | <0.001 |

BMI body mass index, *DBP* diastolic blood pressure, *LUS* lung ultrasound score, *PE* preeclampsia, *SBP* systolic blood pressure, *TFC* total fluid content. Statistical significance: $P < 0.05$

Data are presented as mean ± standard deviation, median (quartiles), and frequency (percentage)

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest with this work.

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