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Prognostic value of the ultrasonic determination of the degree of interstitial edema in patients with intermediate ejection fraction of the left ventricle after treating acute decompensation of heart failure

Aim To study ultrasonic characteristics of lung tissue in patients with heart failure with left ventricular (LV) mid-range ejection fraction (HFmEF) and predictive value of these characteristics after reversing acute decompensated heart failure (ADHF).

Material and methods Ultrasonic characteristics of lung tissue were studied by prospective observation in 71 patients (mean age, 65.2±3.6 years; men, 64.3%) with HFmEF (LVEF from 40 to 49%) following ADHF reversal. Semiquantitative evaluation of B-lines was performed by the E. Picano (2016) method at 5+2 days after hospitalization and on discharge from the hospital. The distance between B-lines was 3 mm (B3 lines) and 7 mm (B7 lines). Patients' catamnesis was studied for determining the predictive value of lung tissue ultrasonic characteristics for two years since the index hospitalization. Statistical analysis was performed using the McNemar's χ^2 test (for evaluation of linked samples and of changes in the presence / absence of B-lines as determined by lung ultrasound examination (USE)) and the Wilcoxon test (for evaluation of quantitative changes). Differences were considered significant at $p<0.05$.

Results B7-lines characteristic of interstitial component of pulmonary parenchymal edema prevailed in patients with HFmEF. B3-lines characteristic of alveolar edema were found in a small amount. In the anterior-superior segment, B7-lines predominated over B3-lines (80% vs. 20%, $p<0.01$) on the right; however, on the lest, significant differences were not observed (64% vs. 36%, $p>0.05$). In the anterior-inferior segment, B7-lines prevailed over B3-lines on the right (75% vs. 25%, $p<0.05$); however, on the left, the difference was not significant (67% vs. 33%, $p=0.05$). In the lateral superior segment on the right, B7-lines predominated over B3-lines (75% vs. 25%, $p<0.01$); in contrast, on the left, there were no differences (67% vs. 33%, $p>0.05$). In lateral-basal segments on both sides, significant differences were present (73% vs. 27% on the right, $p<0.05$; 72% vs. 28% on the lest, $p<0.05$). The results of lung ultrasound were also used for evaluation of the B-line predictive value in patients with ADHF and mid-range EF on discharge from the hospital after reversal of X-ray and clinical symptoms of pulmonary congestion. In the next two years, 35 patients (49.2% of sample) were rehospitalized with signs of ADHF (39 hospitalizations, 1.1 hospitalizations per patient). The rehospitalized patients were divided into two subgroups, with an increased number of B-lines and small congestion on discharge (6–15 B-lines) and without signs of congestion (<5 B-lines). For patients with a minimal (small) congestion on pulmonary ultrasound but regression of clinical and X-ray congestion, the number of rehospitalizations was 25 vs. 11 in patients with the number of B7-lines <5. In the ROC-analysis, the area under the curve was 0.706, which corresponded to the expert assessment as «good». The position sensitivity was 78.6% and the specificity was 79.7%.

Conclusion «Ultrasonic pulmonary edema syndrome» in patients with LV mid-range ejection fraction after reversing ADHF was characterized by predomination of the interstitial component, despite the absence of X-ray congestion, correlated with the blood level of NT-proBNP measured at the same time, and was associated with rehospitalizations.

Keywords Acute decompensated heart failure; mid-range ejection fraction; lung ultrasound; interstitial edema; alveolar edema; prediction of rehospitalization

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Pulmonary vascular congestion, one of the most common causes of hospitalization for patients with symptoms of decompensated heart failure, is caused by the transudation of fluid into pulmonary parenchyma resulting in increased blood pressure in the left atrium, pulmonary veins, and capillaries, as well as filtration into the interstitium. While increased vascular resistance due to the activation of the renin-angiotensin-aldosterone and sympathoadrenal systems leads to decreased filtration, it also results in impaired hemodynamics [1]. In cases of severe pulmonary vascular congestion, clinical and radiological symptoms are comparatively easy to detect. However, if the interstitial pulmonary edema is mild, clinical and radiological examination methods may fail to provide a conclusive diagnosis. In such cases, lung ultrasound (LUS) can be used to aid the visualization of even subclinical signs of vascular congestion along B-lines that correspond with sub-pleural thickened interlobular septa [2].

LUS is a rapidly developing technique used to assess the extent and character of lung lesions; here, B-lines are the primary diagnostic sign used to assess the pattern of congestive changes, whose pathophysiology can be described as follows: the distance between B-lines formed by the reflection of ultrasound that penetrates into the interlobular partition corresponds either to alveolar (3 mm) or interstitial edema (7 mm) [3]. Meta-analysis carried out by Altaie and Khalifa [2] showed that patients with reduced left ventricular ejection fraction (LVEF) are at a higher risk of death than patients with mid-range LVEF. In the guidelines describing chronic heart failure (CHF) and acute decompensated heart failure (ADHF), the evidence level of an ultrasound study is defined as IIB, Class C. However, several ultrasound studies refer positively to its beneficial non-invasive nature and diagnostic accuracy [3–6].

While there have been no individual investigations into the prognostic value of LUS in patients with preserved and mid-range LVEF, numerous studies have shown the predictive value of LUS in patients with reduced LVEF. In the population of patients with stable CHF, it has been demonstrated that LUS has a good predictive value for mortality and repeated hospitalizations [2].

For the purposes this study, the lung structure forms an anatomical substrate: interlobular structures are located 7 mm apart (B7 lines), while intralobular structures are located 3 mm apart (B3 lines). Moreover, B7 lines are shown to correlate with Kerley lines (type 2) since these lines correspond to thicker interlobular spaces (approximately 550 lobules in the right lung and 450 lobules in the left lung) [7]. Although the LUS quantifies B-lines, the present study is characterized by a significant variation of 7–10% [8].

Our objective was to study the ultrasound characteristics of pulmonary tissue in patients having suffered heart failure with mid-range LVEF (HFmrEF) and their prognostic value for repeat hospitalizations following ADHF.

Material and Methods

The study design was prospective. Following the admission of patients, their management was determined based on hemodynamic profiles using the Forrester and Stevenson classification [4]. Following N-terminal pro-brain natriuretic peptide (NT-proBNP) determination, an echocardiographic study was performed (repeated on day 5±2 and at discharge) in order to identify patients with mid-range LVEF. Mid-range LVEF (40–49%) was verified echocardiographically in all patients. Lung X-rays were also carried out and repeated on reduced lung congestion. During this period, usually on day 5±2 (95% of patients), LUS was performed; the ultrasound profile was studied in 71 patients (mean age of the study sample 66.4 ± 5.6 years; 64.3% of males, 35.7% of females) following reduction in ADHF. Reducing ADHF implied the achievement of a stable condition with the greatest possible reduction in the severity of the patient's congestive syndrome, the best-possible hemodynamics, and the absence of severe functional impairment of kidney function during the administered therapy within 24 hours. Ultrasound examination was performed using the Picano technique according to the BLUE protocol with PLAPS points [2–7]. Of all the assessed parameters, attention was primarily focused on the B-lines. These were divided into two groups: B3 lines characteristic of alveolar edema and B7 lines typical of interstitial edema [7].

A combination of coronary artery disease and arterial hypertension (67.6%) prevailing in the disease's etiological structure was followed by persistent atrial fibrillation (32.4%). We used the mean

values of ten heart cycles to estimate LVEF in patients with atrial fibrillation. During the estimation of LVEF, mean heart rate was between 65 and 80 beats per minute. The diagnosis of ADHF was established in the presence, rapid development and aggravation of at least two of the following signs: dyspnea, neck vein swelling, hepatomegaly, clinically and/or radiologically evident hypostatic congestion in the lungs, and peripheral edema [4]. All patients exhibited structural changes in the form of linear calcification of the valves. The echocardiographic signs of pulmonary hypertension were evaluated by half-quantitative methods: mild (<20 mmHg), moderate (20–60 mmHg), and severe (>60 mmHg).

Clinical characteristics of patients with ADHF with mid-range LVEF were as follows: dyspnea (100%), edema (35.2%), ascites (16.9%), long-term permanent congestive changes in the lower lung segments (25.3%).

Patient treatments following the ADHF management protocol included the administration of angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, loop diuretics (first intravenous injections with further transfer to tablets), and antithrombotic therapy as indicated in case of coronary artery disease and after percutaneous coronary intervention. All patients were allocated two-year follow-up by structured telephone surveys (in 6, 12, and 24 months).

The results were processed using Microsoft Office Excel 2013 and IBM-SPSS 23. Age data were expressed as M±SD. Given the non-parametric distribution (verified by the Shapiro–Wilk test), the number of B-lines represented a median expressed as the percentage. The study results were processed using non-parametric statistics (χ^2) followed by quantitative data verification using the Mann–Whitney test. The linked samples were assessed by applying the McNemar and Wilcoxon tests. ROC-analysis was used to verify the positions presented. The statistical significance threshold was $p<0.05$.

The study was conducted following the Declaration of Helsinki and approved by the ethics committee at the Research Institute of Emergency Medicine n.a. Janelidze in 2017. All patients signed an informed consent form to be included in the study.

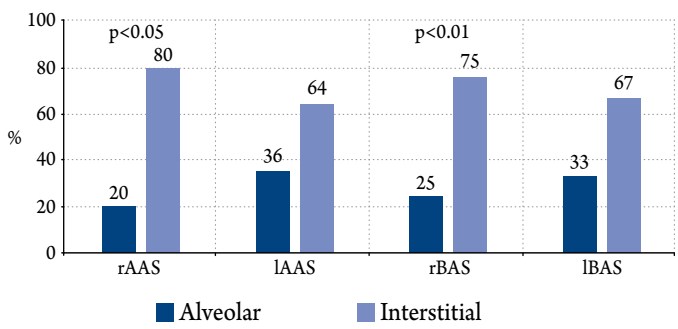
Results

Following stabilization of a patient's condition with the greatest possible reduction in the severity of congestive syndrome, best possible hemodynamics, and no severe impairment of kidney function during the administered therapy within 24 hours, along with regression of congestive changes according to the clinical (fewer bubbling rales in the lungs) and radiological pictures, the LUS profile was estimated on day 5±2. However, in 5% of patients, it took longer to reduce ADHF; these underwent LUS on day 10–12.

The ratio of interstitial (B7-line) to alveolar (B3-line) vascular congestion components in the anterior lungs is shown in Figure 1; the corresponding ratio in the lateral lungs is shown in Figure 2.

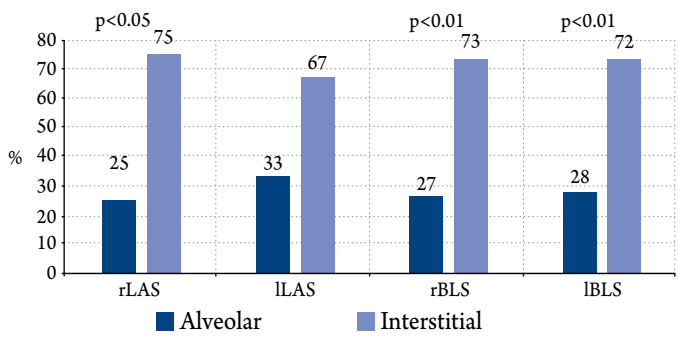
The interstitial component of lung vascular congestion (B7-lines) prevailed over the alveolar component (B3-lines) in both anterior and lateral segments of the lungs; here, the differences were statistically significant on the right. A similar profile was observed despite reduced ADHF and regression of the radiological pattern of congestive changes. The estimation of B-line dynamics detected the following changes in pulmonary vascular congestion, see Figure 3. Blood levels of NT-proBNP were 3215.2±107.4 pmol/L and were correlated with the number of B-lines on day 5±2 ($r=0.52$, $p=0.04$).

Figures 1. Ratio of interstitial and alveolar congestion in the anterior lung segments



AAS, anterior apical section; BAS, basal anterior section; r, right; l, left.

Figures 2. Ratio of interstitial to alveolar congestion in the lateral lung segments



LAS, lateral apical section; BLS, basal lateral section; r, right; l, left.

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The follow-up assessment established long-term mortality to be 35.2% (25 patients). Forty-six patients (64.8% of the total sample) successfully completed the study. Due to 39 repeat hospitalizations of 35 (49.2%) patients (54.9% of the total sample, 1.1 hospitalizations per 1 readmitted patient) with manifested ADHF, the prognostic value of the B-lines determined at discharge to predict repeat hospitalizations was studied. All patients were divided into two subgroups depending on the severity of vascular congestion at discharge after the index hospitalization. The threshold was 5 B-lines (minimal vascular congestion) and less than 5 B-lines (no vascular congestion) as having the highest sensitivity and specificity in the pilot study defined using the ROC analysis. The findings are shown in Figure 4.

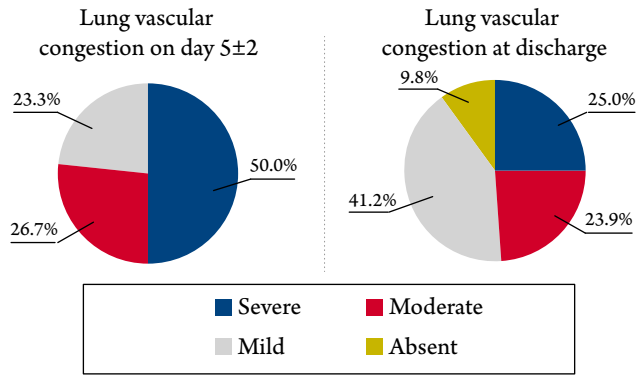
On the basis of the ultrasound study, it was established that the group of patients with minimal pulmonary congestion (6–15 B-lines) had a higher number of repeated hospitalizations versus the sample without congestive changes. This position was verified using the ROC-analysis (Figure 5). The AUC of 0.706 was categorized as «very good» in terms of the AuROC expert score. The sensitivity and specificity of the method were 78.6% and 89.7%, respectively.

Discussion

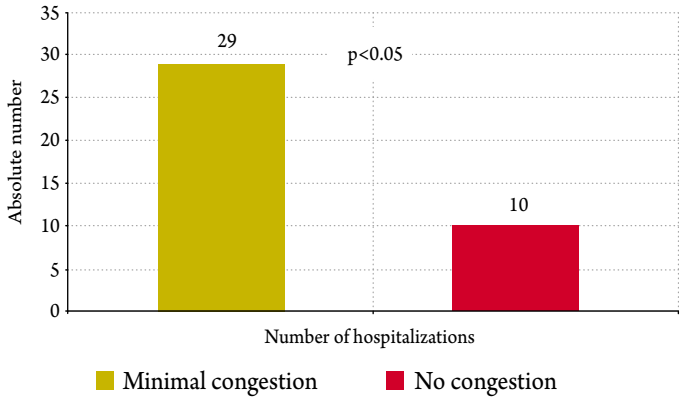
Being more sensitive than X-ray, the ultrasound technique was used to show resolving vascular congestion in the continuing presence of rales and signs of interstitial congestion. More severe vascular congestion in the right lung as compared to the left is associated with blood supply via three lobar arteries and the right pulmonary artery, being longer than the left one, arising from the pulmonary trunk at an angle. The study also demonstrated that, despite the prevalence of interstitial component over the alveolar components in all PLAPS points, its statistical significance is characteristic only of the right lung. This may be explained in terms of the relationship between bronchus (B), artery (A), and vein (V): BAV in the right and ABV in the left lung. If patients have a dilated pulmonary artery, the vein is constricted (blood outflow is impaired). Since there was no frank pulmonary edema at the time of the ultrasound study, the alveolar component was less pronounced than the interstitial component. The ultrasound technique is more sensitive to the morphological changes in the lungs (edema).

Our findings are very much consistent with the data obtained by Miglioranza et al., which showed that the evaluation of B-lines in patients with reduced LVEF

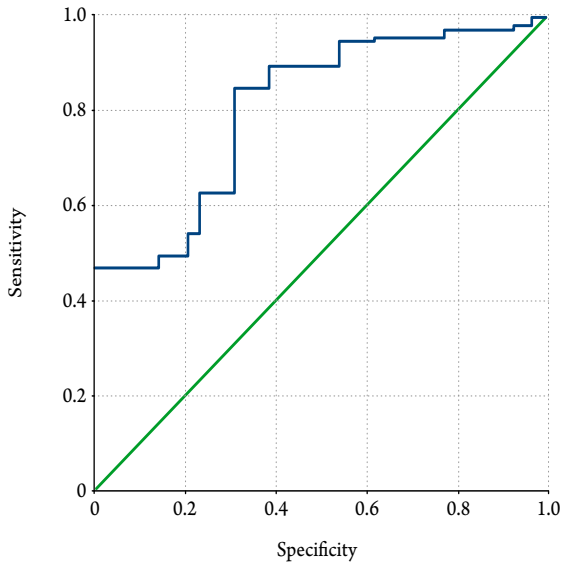
Figures 3. Ratio of B7 lines on day 5±2 and at discharge



Figures 4. Correlation of B-lines with the rates of repeated hospitalizations



Figures 5. ROC-curve to verify prognostic value of B-lines



could predict repeated hospitalization for ADHF within 4 months following LUS [8]. Although Platz et al. also demonstrated a moderate correlation between mortality and repeated hospitalizations for ADHF in the long-term follow-up period [9], it should be noted

that all these examinations were conducted in patients with reduced LVEF.

Since there are no references in the current literature to ultrasound examinations of lungs in patients with ADHF and mid-range LVEF, we compared our findings with the conclusions of the pilot study by Skorodumova et al. (2018) in patients with mid-range LVEF [10]. Although the findings on the predictive value of B-lines are mainly consistent with each other, some differences are observed. While the pilot study identified 25 cases of hospitalization of patients with mild pulmonary vascular congestion (35.2% of the total sample) and an estimated 12-month period, our study identified 35 such cases (49.2% of the total sample). It is also worth noting that there were 39 repeated hospitalizations (1.1 repeated hospitalizations per patient) within the two-year follow-up period. Pivetta et al. (2015) showed that LUS significantly improved the accuracy of HF diagnosis as compared to physical examination – AuROC 0.95 vs 0.88 ($p < 0.01$). The same is true for the combination of LUS with NT-proBNP and lung X-ray examination – AuROC 0.95 vs. 0.88. However, radiological examinations of the lungs and NT-proBNP without LUS did not offer advantages in diagnosing HF over physical examination – AUC 0.87 and 0.85, respectively ($p > 0.05$) [11].

Limitations

Although radiological signs of interstitial pulmonary edema may also be determined by computed tomography, this was not used in the present study.

Summary

Despite the absence of x-ray signs of vascular congestion following a reduction in acute decompensated heart failure in patients with mid-range left ventricular ejection fraction, ultrasound pulmonary edema syndrome is characterized by a predominance of interstitial component and correlates with simultaneously determined NT-proBNP blood levels.

Interstitial venous congestion of the lung shown by ultrasound study at discharge may be a factor associated with repeat hospitalization.

Ultrasound estimation of the interstitial component of pulmonary vascular congestion in patients with mid-range left ventricular ejection fraction in acute decompensated heart failure has 78.6% sensitivity and 89.7% specificity for association with repeat hospitalizations.

No conflict of interest is reported.

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