University of Szeged
Albert Szent-Györgyi Medical School
Doctoral School of Clinical Medicine

THE PROGNOSTIC VALUE OF LUNG ULTRASOUND IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION AND AORTIC STENOSIS

Blanka Morvai-Illés, M.D.

Summary of Ph.D. thesis

Supervisors: Gergely Ágoston, M.D., Habil., Albert Varga, M.D., Habil.

Szeged
2024

THE THESIS IS BASED ON THE FOLLOWING PAPERS

I. Morvai-Illés B, Polestyuk-Németh N, Szabó IA, Monoki M, Gargani L, Picano E, Varga A, Ágoston G. The Prognostic Value of Lung Ultrasound in Patients With Newly Diagnosed Heart Failure With Preserved Ejection Fraction in the Ambulatory Setting. Front Cardiovasc Med. 2021 Dec 2;8:758147.
doi: 10.3389/fcvm.2021.758147. PMID: 34926610; PMCID: PMC8674474.
Quartile: Q1 (2021)

II. Szabó IA, Gargani L, Morvai-Illés B, Polestyuk-Németh N, Frigy A, Varga A, Ágoston G. Prognostic Value of Lung Ultrasound in Aortic Stenosis. Front Physiol. 2022 Apr 5;13:838479.
doi: 10.3389/fphys.2022.838479. PMID: 35480045; PMCID: PMC9037236.
Quartile: - Physiology (medical): Q1 (2022)
- Physiology: Q2 (2022)

FURTHER RELEVANT PAPERS

I. Morvai-Illés B, Ágoston G, Séllei Á, Kovács L, Varga A. Giant cell arteritis presenting with pericardial effusion, hoarseness, and amaurosis. Anatol J Cardiol. 2020 Mar;23(4):235-237.
doi: 10.14744/AnatolJCardiol.2019.00502. PMID: 32235128; PMCID: PMC7163215.
Quartile: Q3 (2020)

II. Ágoston G, Morvai-Illés B, Pálinkás A, Varga A. The role of stress echocardiography in cardiovascular disorders. Kardiol Pol. 2019 Nov 22;77(11):1011-1019. doi: 10.33963/KP.15032. Epub 2019 Oct 24. PMID: 31647477.
Quartile: Q3 (2019)

III. Morvai-Illés B, Jdid MS, Csadi R, Varga A, Vágó H, Ágoston G. A felnőttkori autoimmun reumatológiai kórképek kardiológiai vonatkozásai. Cardiologia Hungarica. 2023; 53: 619–626.

doi: 10.26430/CHUNGARICA.2023.53.6.619

QUOTABLE ABSTRACTS

I. Ágoston G, Morvai-Illés B, Bencsik P, Szabados T, Monoki M, Hulló D, Kovács L, Varga A
A terheléses echokardiográfia és a biomarkerek szerepe a szisztámás szklerózishoz kacsolódó kardiovaszkuláris szövődmények diagnózisában – Pilot tanulmány = The potential role of exercise echocardiography and biomarkers to assess cardiopulmonary complications in systemic sclerosis – a pilot study. Cardiologia Hungarica 52 : Suppl. C p. C303 (2022)

II. Morvai-Illes B, Burcsar SZ, Monoki M, Varga A, Kovacs L, Balog A, Agoston G, Assessment of the right ventricular-pulmonary circulation unit during stress in ankylosing spondylitis and psoriatic arthritis patients, *European Heart Journal*, Volume 43, Issue Supplement_2, October 2022, ehac544.088. doi:10.1093/eurheartj/ehac544.088

III. Ladóczky-Hulló, D ; Morvai-Illés, B ; Bencsik, P ; Kovács, L ; Ágoston, G. Examination of exercise stress echocardiography and biomarkers in systemic sclerosis patients for the early detection of pulmonary arterial hypertension and myocardial involvement
ANNALS OF THE RHEUMATIC DISEASES 82 : Suppl 1 pp. 1628-1629. , 2 p. (2023)

IV. Morvai-Illés, B ; Hulló, D ; Horváth, R ; Kovács, L ; Ágoston, G ; Varga, A. A terheléses echokardiográfia prognosztikus szerepe szisztémás szklerózisban [The prognostic role of exercise stress echocardiography in systemic sclerosis] CARDIOLOGIA HUNGARICA 53 : Suppl A p. A229 (2023)

Introduction

Both heart failure with a preserved fraction (HFpEF) and aortic stenosis (AS) are common, chronically evolving diseases in everyday practice with considerable mortality and impact on patient's quality of life.

Despite the rising diagnostic possibilities, knowledge and the high prevalence of HFpEF, establishing its diagnosis and prognostication remained challenging.

AS is the most common degenerative valve disease. The indication for surgery relies mainly on the quantitative assessment of the severity of stenosis. However, these measurements may not always show prognostic significance. Quantifying the cardiac damage caused by AS may result in a more reliable prognosis estimation.

Pulmonary congestion (PC) is fluid accumulation in the lungs, impairing gas exchange. PC is a frequent and almost universal pathophysiological phenomenon in patients with heart failure. It is frequently seen in severe AS patients, developing as a consequence of the constantly elevated afterload leading to compensatory left ventricular hypertrophy, and later to systolic and diastolic dysfunction. The elevated left ventricular filling pressure leads to elevated capillary hydrostatic pressure and to PC. PC is responsible for the development of postcapillary pulmonary hypertension and, thus, the occurrence of

dyspnea. PC is also connected with worse prognosis in acute and chronic heart failure regardless of the EF.

During lung ultrasound (LUS), B-lines are „discrete laser-like vertical hyperechoic reverberation artefacts that arise from the pleural line, extend to the bottom of the screen without fading, and move synchronously with lung sliding" (Gargani, 2014), and are present in lung interstitial syndrome. LUS evaluation of B-lines has been proposed as a simple, noninvasive, radiation-free, semi-quantitative tool to assess PC.

Methods

The study population of the HFpEF study

A total of 131 consecutive patients were screened at our cardiology outpatient clinic (University of Szeged, Hungary) between January 2018 and December 2019. General practitioners referred all patients with mild or moderate HF symptoms. None of the patients had a previous diagnosis of HF. Data collection was based on a standardised clinical questionnaire by a researcher blinded to clinical records. Our inclusion criteria were: (1) age ≥ 18 years; (2) diagnosis of HFpEF defined in the 2016 ESC guideline. The following patients were excluded: (1) atrial fibrillation with >80/min ventricular rate at rest; (2) prior history of interstitial lung disease, moderate or severe COPD (Chronic Obstructive Pulmonary Disease), or pulmonary hypertension; (3) moderate or severe aortic or mitral valve disease on

the screening echocardiogram; (4) history of cardiomyopathy; (5) severe kidney failure or anaemia (eGFR ≤35 ml/min, Hgb ≤100 g/l); (6) malignancy (except localised basal cell carcinoma of the skin or localised prostate cancer). Data handling and publication respected the Declaration of Helsinki. The registration number of ethical approval is 131/2019/SZTE.

Study population of the aortic stenosis study

Seventy-five consecutive patients with AS from two sites (University Of Szeged, Hungary, Clinical County Hospital Târgu Mures, Romania) were enrolled. The inclusion criteria were: (1) moderate degenerative AS with mean gradient of 20-40 mmHg and aortic valve area (AVA) 1–1.5 cm^2; or severe degenerative AS with mean gradient >40 mmHg and AVA <1 cm2; (2) age >18 years. We enrolled patients with severe symptomatic AS only if the patient refused surgery or it was contraindicated. The exclusion criteria were: (1) low flow-low gradient AS (mean gradient <40 mmHg, AVA <1 cm2, LVEF<50%); (2) concomitant moderate or severe aortic regurgitation; (3) concomitant moderate or severe mitral regurgitation; (4) severe, decompensated HF, requiring urgent hospitalisation (NYHA class IV); (5) severe interstitial lung disease; (6) active pneumonia or acute lung injury; (7) malignancy (except localised skin basal cell carcinoma or localised prostatic cancer); (8) cardiomyopathies—dilated, hypertrophic or infiltrative

cardiomyopathy. All patients were evaluated in ambulatory settings in stable conditions. None of the patients required hospitalisation at the time of transthoracic echocardiography (TTE) and LUS. The patients signed informed consent before inclusion in the study. Data handling and publication respected the Declaration of Helsinki. The registration number of ethical approval is 131/2019/SZTE.

Echocardiographic assessment

A comprehensive TTE was performed using a Vivid-S70 (GE Vingmed, Horten, Norway) ultrasound machine with a 3S probe (1.5–3.6 MHz). An experienced cardiologist with EACVI-TTE certification performed all measurements according to the recommendations of the European Association of Cardiovascular Imaging.

Myocardial deformation was analysed with GE EchoPAC (version v202) software. LV strain was measured according to EACVI recommendations. QRS complex was used as a time reference. LA strain parameters were recorded per the EACVI consensus document and were post hoc analysed by two experienced physicians. An electrocardiography (ECG) trigger was used as a time reference, using the upslope of the R wave as a surrogate of end-diastole. In case of any uncertainty, the strain pattern provided support (and mitral inflow pattern in patients with sinus rhythm). From apical four- and two-chamber views with a frame rate of 40–80 frames per second, three consecutive cardiac cycles were acquired and averaged in each patient.

Region of Interest (ROI) was defined using a point-and-click approach for tracking the endocardial border. Longitudinal strains were calculated as strains in the direction tangential to the endocardial atrial border. Atrial strain values during the reservoir phase (LASr) were evaluated.

LUS assessment

Immediately after TTE, all patients underwent LUS performed by the same cardiologist, who obtained the echocardiographic measurements to assess B-lines using the same probe and echocardiography machine. We screened the anterior and lateral hemithoraces, scanning along the parasternal, midclavicular, anterior axillary and midaxillary lines from the second to the fifth intercostal space on the right hemithorax and the second to the fourth intercostal space on the left, adding up to a total of 28 zones. A B-line was defined as a discrete, comet-like vertical hyperechoic reverberation artefact starting from the pleural line, extending to the bottom of the screen and moving synchronously with lung sliding. An experienced operator who had completed a dedicated training previously and was blind to the NT-proBNP value, acquired and analysed all LUS studies.

NT-proBNP measurement

Within 1 hour of the cardiac and lung ultrasound, peripheral venous blood samples were obtained from each patient in the HFpEF

study. NT-proBNP analysis was performed using the Elecsys 2010 analyser (Roche Diagnostics, Mannheim, Germany).

Follow-up data

Follow-up data were collected every three months via phone calls to monitor clinical status and adverse outcomes. Outpatient visits were performed 6-monthly when clinical status and adverse events were recorded. A composite HF endpoint was created, including death (any cause), hospitalisation for acute decompensation of HF, and worsening HF (defined as the intensification of loop diuretic therapy). Information about the endpoint events was retrieved from medical records.

Statistical analysis

Our data are expressed as numbers and percentages for categorical, and mean ± standard deviation, or median with interquartile range for continuous variables. Univariate comparisons were made by chi-square or independent samples T-test, as appropriate. One-way ANOVA was used to compare continuous data of different NYHA functional class. A p-value <0.05 was accepted as statistically significant. Correlations between parameters were assessed with parametric Pearson or nonparametric Spearman correlation coefficient analysis, as appropriate. The prognostic performance was determined by means of receiver-operating

characteristic (ROC) curves. The corresponding area under the curves (AUC) was reported. Univariate and multivariate (Backward LR method) Cox regression analysis was used to assess the prognostic capacity of parameters. Collinearity had been excluded using variance inflation factor <3 before the analysis. Results were reported as Hazard Ratios. Event-free survival was calculated using Kaplan-Meier curves and the log-rank test to determine the significance between groups. Data were analysed using IBM SPSS 22 statistical software.

Results

Results of the HFpEF study

One hundred thirty-one consecutive patients were screened from January 2018 to December 2019. Fifty-six patients were excluded: 14 patients had moderate or severe mitral and/or aortic valve disease, 2 patients had atrial fibrillation with heart rate above 80/min at rest, 10 patients had an EF below 50%, 4 patients had moderate or severe COPD or pulmonary disease, 2 patients had eGFR below 35 mL/min/1.73 m^2, 3 patients had ischemic heart disease (where subsequent examinations were confirming significant coronary artery disease, and in 21 patients, we could not confirm any considerable disorder that could support the referral diagnosis. Finally, 75 patients (age: 70.33 ± 6.85, 73.3% female) met our inclusion criteria. Ten patients had atrial fibrillation with normal ventricular rate during the enrollment, and others were in sinus rhythm.

The feasibility of lung ultrasound was 100%, and the mean duration of the examination was 2.5±0.47 min. We found a strong correlation between the number of B-lines and NT-proBNP levels ($r = 0.636$, $p < 0.001$) and a moderate correlation between B-lines and LASr ($r = -0.487$, $p < 0.001$). B-lines significantly correlated with estimated pulmonary artery systolic pressures (PASP; $r = 0.471$, $p < 0.001$) and left atrial volume index (LAVI; $r = 0.243$, $p < 0.05$), too.

During the 26 [22,32] months follow-up, we detected 11 events: 4 patients were treated at an emergency department for an acute HF episode, 2 patients were admitted to the cardiology ward due to severe HF symptoms, 3 patients needed ambulatory intensification of loop diuretic treatment due to worsening of HF symptoms and 2 patients died (1 unknown cause, 1 patient during HF event). Patients with adverse clinical events more frequently had hyperlipidemia, diabetes mellitus, ongoing digoxin therapy, higher NT-proBNP levels, more B-lines, lower LASr, DCT and systolic myocardial velocity measured with tissue Doppler imaging at the tricuspid annulus (S') than the event-free group.

The performance of the number of B-lines in the prediction of HF events was similar to the performance of NT-proBNP levels, with the best cut-off value at 16 B-lines (sensitivity 91%, specificity 79%), which corresponds with the widely used cut-off for moderate PC. LASr's predictive value was weaker, with the best cut-off at 13.75%

(sensitivity 71.4%, specificity 70%). The feasibility of the LASr measurements was 92%.

Having >15 B-lines significantly increased the risk of the endpoint events and proved it to be an independent predictor of endpoint events during the multivariate analysis.

The event-free survival was significantly worse among patients with >15 B-lines ($p < 0.001$, log-rank: 16.804). The probability of cumulative event-free survival at 20 and 40 months in patients with ≤15 B-lines was 100 and 97.3%, respectively, while in patients with >15 B-lines, it was 72% at 20 and 58.2% at 40 months.

Results of the AS study

97 patients were screened from May 2019. to October 2020. 22 patients were excluded from the initial population (4 patients had concomitant moderate aortic regurgitation, 6 patients had concomitant moderate or severe mitral regurgitation, 4 patients had dilated cardiomyopathy with moderate AS, 4 patients had low-flow, low-gradient AS, 3 patients had severe chronic obstructive pulmonary disease, and 1 patient had active lung cancer). Finally, 75 patients (39 women, mean age 73.85±7.7 years) were enrolled in the study. According to the 2021 ESC guideline categorisation, the enrolled patient population included 30 patients with high-gradient AS, 22 patients with low-flow, low-gradient AS with a preserved EF, 8 patients with normal-flow, low-gradient AS with preserved EF, and 15

patients with moderate AS. During the 13.4±6 months follow-up, we detected 28 events: 19 patients had hospitalisations due to HF (2 of them underwent urgent aortic valve repair-AVR), and seven required ambulatory intensification of loop diuretic therapy. Two patients died (the exact cause of death is unknown).

All patients with events were already in NYHA class II-III, but only 66.67% of the event-free group were symptomatic. More patients in the event group had pulmonary rales, whereas the presence of peripheral oedema was not different.

Pressure gradients measured above the aortic valve differed significantly between the two groups (peak gradient: 54.74±19.3 vs. 67.79±24 mmHg, mean gradient: 34.45±12.6 vs. 42.89±13.2 mmHg). LV EF was significantly worse in the event group (67.67±7.4% vs. 56.02±11.2%, $p < 0.001$). The pulmonary artery systolic pressure (PASP) was higher (31.00±11.5 mmHg vs. 45.79±17.4 mmHg, $p < 0.001$), and the tricuspid annular plane systolic excursion (TAPSE) was lower in the event group (24.54±47mm vs. 21.25±4.6 mm, $p = 0.006$). RV-pulmonary artery (PA) coupling, expressed by TAPSE/PASP ratio, was also significantly different in patients with and without events (0.55±0.29 mm/mmHg vs. 0.87±0.33 mm/mmHg, $p < 0.001$).

We found a severe degree of PC (B-lines≥30) in 29.33% of all patients. Significantly more B-lines occured in the event group (29±18 vs. 18±23, $p = 0.028$) and in this group more patients had 30 or more

B-lines (50% vs. 17%, p = 0.002). The number of B-lines increased significantly along with the worsening of NYHA functional classes, from 13±12 in NYHA Class I, through 19±15 in Class II, to 43±34 in Class III ($p<0.05$, rho=0.383).

Patients with severe AS had significantly more B-lines than patients with moderate AS (14±13 vs. 25±24; $p<0.05$). We also found that the number of B-lines was correlated with LV EF ($R=-0.325$, $p<0.05$) and PASP ($R=0.574$, $p<0.001$). We did not find a significant correlation between E/e' and B-lines or LAVI and B-lines.

Having ≥30 B-lines meant lower event-free survival (log rank 8.619; $p < 0.05$) and significantly increased the risk of endpoint events [HR (95% CI): 2.79 (1.03–7.54), $p<0.05$)]. During multivariable modelling, B-lines and mean aortic gradient were the independent predictors of events.

Discussion

In our study of newly diagnosed HFpEF patients, having more than 15 B-lines at the time of diagnosis was highly suggestive of a worse prognosis. It better predicted HF events than NT-proBNP and the other clinical and echo parameters. That finding is comparable to the results of other, earlier published studies.

We also found that the number of B-lines is related to LA volume and estimated systolic pulmonary artery pressures. In our

study, B-lines showed a close relationship with left atrial dysfunction represented by decreased LASr, which is a new observation.

To the best of our knowledge, this is the first study to address the prognostic value of B-lines for predicting adverse events in patients with AS. Our results show that assessing B-lines in AS adequately reflects patients' functional class and the haemodynamic consequences caused by AS. Presence of severe congestion marked by B-lines ≥30 strongly predicts adverse events.

Conclusion

LUS is a radiation-free, fast, highly feasible and noninvasive method and seems to be an excellent aid for prognostication in HFpEF and moderate-to-severe AS as well.