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Exercise elicits dynamic changes in extravascular lung water and haemodynamic congestion in heart failure patients with preserved ejection fraction

Heart failure (HF) with preserved ejection fraction (HFpEF) represents about 50% of HF cases, and is a leading cause of morbidity and mortality.[1] Typically, HFpEF patients are asymptomatic at rest but develop dyspnoea and pulmonary congestion with exercise or increased blood pressure, partly driven by impairment of diastolic function. In acute HF, a cascade of events starts with increased left ventricular (LV) filling pressures ('haemodynamic congestion') causing interstitial and alveolar oedema ('pulmonary congestion'), before the appearance of signs and symptoms of congestion.[2] In HFpEF, dynamic changes in diastolic function can be assessed by exercise test[3]; with exercise, diastolic stiffness induces acute elevation in invasively-measured wedge pressure.[4] It is assumed that pulmonary congestion contributes to exercise intolerance; yet, there is no direct evidence of it.

Lung ultrasonography (LUS), being capable of non-invasively scanning the pulmonary interstitium, might be well-suited to investigate this issue.[5] Using standard cardiac transducers on chest echography, typical signals ('B-lines') can be visualized, which are strongly associated with echocardiographic and bio-humoral indices of congestion.[6] Recently, LUS has been shown to reproducibly detect the rapid increase in pulmonary congestion typically seen when HF patients with reduced ejection fraction (HFrEF) exercise, through development or increase of B-lines.[5,7,8] Additionally, stress B-line count correlates with natriuretic peptide concentration and estimated pulmonary pressures.[8] Given the pathophysiological and clinical relevance of exercise response in HFpEF, it would be important to investigate pulmonary congestion also in this setting, as afforded by B-line assessment. However, this issue has remained largely unexplored.

By LUS, we investigated changes in pulmonary congestion in response to exercise stress echocardiography (ESE) in HFpEF patients. B-lines were measured along with echocardiography and laboratory indices of congestion; findings were compared to those obtained in controls without HF.

Methods

Consecutive outpatients with HFpEF, diagnosed according to the European HF guidelines,[9] haemodinamically stable (>8 weeks if previous HF hospitalization), referred to the Cardiology Clinic of the Niska Banja Institut, were enrolled. Controls were recruited prospectively among hypertensive subjects (with other cardiovascular risk factors such as dyslipidaemia, diabetes, or smoking habit) free of history of HF or significant coronary or valvular heart diseases. Inclusion criteria for the entire cohort were: (i) ability to perform a bicycle ESE; (ii) sinus rhythm; (iii) good echocardiographic window; (iv) no pulmonary fibrosis, or other diseases potentially hampering image acquisition (pleural effusion, severe emphysema, previous pneumectomy or lobectomy, pulmonary cancer or metastases). The protocol was approved by the local ethics committee; all subjects gave an informed consent. At baseline, demographic and clinical parameters were collected. After standard transthoracic echocardiography examination (Esaote-MyLab Alpha eHD Crystalline series 7400), patients underwent submaximal ESE (supine decubitus, slightly tilted on the left side) on a tilting table using a cyclergometer, according to the modified Cardiff MEDIA protocol.[3] Exercise started at 15 W workload, with 5 W increments every minute; once heart rate reached >100 b.p.m., workload was kept constant for another ~5 min, to perform echocardiography and LUS; exercise was followed by 10 min recovery. Echocardiography and LUS measurements were repeated during the last 5 min of recovery.

Echocardiographic examination included: LV volumes, LV ejection fraction (LVEF, biplane Simpson's method), Doppler transmitral flow velocities [early filling (E) and atrial (A) peak velocities], LV septal and lateral wall velocities by pulsed-wave tissue Doppler to measure average e' and estimated LV filling pressures by average E/e' ratio, and systolic pulmonary artery pressure [using peak tricuspid regurgitation (TR) velocity]. LUS was performed by the 28-scanning point method,[6] using a 1–4 MHz phased-array probe.

All echocardiographic images were recorded and analysed off-line; the number of B-lines was assessed in real time. All exams were performed by a single operator (D.S.), unaware of group assignment, and who took no part in the clinical management. Scanning sites with missing B-line data were not taken into account and were consequently judged as 'zero B-lines'.

Peripheral venous blood samples for B-type natriuretic peptide (BNP) were obtained both at baseline and at peak exercise (during echocardiographic image acquisition).[10]

Continuous variables are expressed as mean ± standard deviation, or median (25th–75th percentiles), as appropriate. Categorical variables are presented as counts and percentages.

Between-group characteristics were compared by unpaired *t*-test or Mann–Whitney test, as appropriate; within-group measurements at different stages (rest vs. peak exercise, peak vs. recovery, and recovery vs. peak) were compared by Friedman test (for overall significance) and Wilcoxon signed-rank test with Bonferroni adjustment for pairwise comparisons. The relationship between B-line net increase and changes of other indices was assessed by non-parametric Spearman's correlation coefficient analysis. A *P*-value <0.05 was considered statistically significant.

Results

A total of 31 HFpEF patients and 19 controls were studied. *Table 1* shows demographic, clinical, and echocardiographic characteristics. Participants were predominantly female, with a mean age of 60.5 ± 11.1 years. Compared to controls, HFpEF patients were older, with higher body mass index, more likely to have dyslipidaemia, diabetes, or high creatinine values.

With regard to echocardiography parameters, HFpEF patients had higher LV mass index and left atrial volume index; they also showed lower LVEF, E/A ratio, and tricuspid annular plane systolic excursion (TAPSE) (*Table 1*). There were no differences between groups in terms of average exercise test duration (6.8 ± 1 min), and peak heart rate (104.5 ± 4.6 vs. 105.1 ± 4.9 b.p.m.); however, exercise systolic and diastolic blood pressure were higher in HFpEF patients (151.7 ± 11 vs. 139.0 ± 7.9 mmHg and 82.5 ± 5.9 vs. 78.2 ± 4.6 mmHg, respectively; both $P < 0.01$).

Overall, changes in B-lines, E/e' ratio, TR velocities, and BNP were significant across exercise stages ($P < 0.0001$ for all subgroups), except for E/e' ratio in controls ($P = 0.229$).

According to B-line grading,[11] pulmonary congestion was absent (B-lines ≤5) in all participants at rest, although B-lines were detectable in 28 HFpEF patients (92.3%) and 8

able 1 Baseline characteristics

	Total cohort ($n = 50$)	Controls ($n = 19$)	HFpEF ($n = 31$)	*P*-value
Demographics				
Male gender, n (%)	20 (40.0)	8 (42.1)	12 (38.7)	0.812
Age (years), mean ± SD	60.5 ± 11.1	56.6 ± 10.7	65.0 ± 10.1	**0.007**
BMI (kg/m^2), mean ± SD	28.4 ± 4.7	26.6 ± 5.0	29.6 ± 4.3	**0.031**
Medical history, n (%)				
Hypertension	46 (100)	15 (100)	31 (100)	N/A
Diabetes	19 (38.0)	2 (10.5)	17 (54.8)	**0.002**
Dyslipidaemia	44 (88.0)	13 (68.4)	31 (100)	**0.001**
Coronary artery disease	6 (12.0)	0 (0.0)	6 (19.4)	N/A
Current smoking	15 (30.0)	8 (42.1)	7 (22.6)	0.144
COPD	5 (10.0)	2 (10.5)	3 (9.7)	0.923
Previous HHF	21 (42.2)	0 (0)	21 (67.7)	**<0.0001**
Previous AF episode	2 (4.0)	0 (0)	2 (6.5)	0.258
NYHA class I	35 (70)	19 (100)	16 (51.6)	**<0.0001**
NYHA class II	15 (30)	0 (0)	15 (48.4)	**<0.0001**
Therapy, n (%)				
ACEi or ARB	49 (98.0)	18 (94.7)	31 (100)	0.197
Beta-blocker	48 (96.0)	17 (89.5)	31 (100)	0.07
Statin	37 (74.0)	10 (52.6)	27 (87.1)	**0.007**
Diuretics	35 (70.0)	8 (42.1)	27 (87.1)	**0.001**
Nitrates	7 (14.0)	1 (5.3)	6 (19.4)	0.163
Aldosterone antagonist	4 (8.0)	0 (0)	4 (12.9)	0.103
Physical examination, mean ± SD				
Systolic BP (mmHg)	122.6 ± 7.8	121.5 ± 6.0	123.3 ± 8.7	0.270
Diastolic BP (mmHg)	75.5 ± 7.1	76.6 ± 5.3	74.8 ± 7.9	0.271
Heart rate (b.p.m.)	66.1 ± 7.0	67.6 ± 6.2	65.4 ± 7.4	0.323
Laboratory, mean ± SD				
Haemoglobin (g/dL)	13.1 ± 1.2	13.4 ± 8.4	13.5 ± 14.3	0.910
Sodium (mEq/L)	143.9 ± 3.4	143.7 ± 4.0	144.1 ± 3.0	0.690
Creatinine (mmol/L)	89.8 ± 22.8	81.0 ± 16.2	95.1 ± 24.8	**0.032**
BNP (pg/mL)	32.8 ± 39.7	9.1 ± 8.5	47.3 ± 44.2	**<0.0001**
Echocardiography, mean ± SD				
LVEF (%)	60.4 ± 7.4	63.4 ± 5.7	58.6 ± 7.7	**0.023**
LVEDV (mL/m^2)	45.1 ± 9.6	42.8 ± 8.4	46.5 ± 10.2	0.254
LV mass index (g/m^2)	111.0 ± 25.6	91.5 ± 20.9	122.8 ± 20.6	**<0.0001**
LA volume index (mL/m^2)	25.6 ± 7.0	22.9 ± 3.5	27.2 ± 8.1	**0.032**
E/A ratio	0.9 ± 0.5	1.2 ± 0.3	0.8 ± 0.5	**0.008**
E/e' average	7.3 ± 2.6	7.0 ± 2.1	7.5 ± 3.0	0.540
TAPSE (mm)	22.0 ± 3.2	23.3 ± 3.5	21.2 ± 2.7	**0.017**
TR peak velocity (m/s)	1.5 ± 0.6	1.2 ± 0.6	1.8 ± 0.5	**<0.0001**
B-lines	1.9 ± 1.6	0.5 ± 0.7	2.7 ± 1.4	**<0.0001**

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BNP, B-type natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; HHF, heart failure hospitalization; LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; N/A, not applicable; NYHA, New York Heart Association; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

control subjects (42.1%), with higher counts in HFpEF [3 (2–4) vs. 0 (0–1), $P < 0.0001$]. In all subjects, B-lines increased upon exercise, and tended to decrease toward baseline upon recovery (*Figure 1A*). However, net increase, and absolute values of B-lines were both markedly higher in HFpEF patients compared to controls (*Figure 1A*).

E/e' ratio at baseline was within the normality threshold of 8[12] in 17 (55%) HFpEF patients, and 15 (79%) controls (*P*=NS; *Figure 1B*). Upon exercise, controls displayed no significant changes, while in HFpEF patients E/e' ratio increased significantly with respect to baseline and to peak value in controls (*Figure 1B*).

At rest, median TR peak velocity was 1.8 (1.4–2.2) in HFpEF, and 1.0 (0.8–1.2) in controls ($P < 0.0001$) (*Table 1*). In all subjects, TR velocities increased upon exercise, and tended to decrease toward baseline upon recovery (*Figure 1C*). However, both net increase and absolute values of TR peak velocities were higher in HFpEF patients compared to controls (*Figure 1C*).

BNP concentrations at baseline were already substantially higher in HFpEF patients compared to controls [31.2 (14.4–61.9) vs. 6.2 (5.0–8.2) pg/mL, $P < 0.0001$]; upon exercise, BNP increased in both groups.

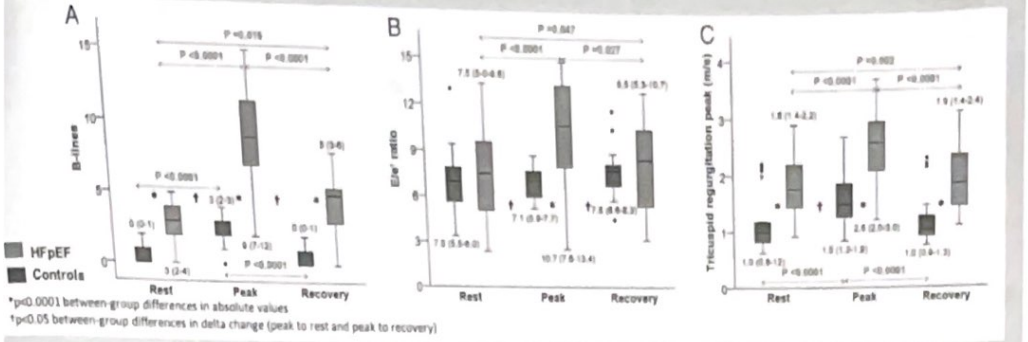

Figure 1 Dynamic changes of B-lines (A), E/e' ratio (B), and tricuspid regurgitation velocity (C) during submaximal exercise stress echocardiography in heart failure with preserved ejection fraction (HFpEF) patients and controls.

owever, net increase [19.8 (5.5–51.3) s. 6.5 (4.6–8.6) pg/mL, $P=0.004$] and bsolute values [56.8 (36.7–94.2) vs. 13.5 10.4–18.0) pg/mL, $P<0.0001$] of BNP were both markedly higher in HFpEF patients compared to controls. B-line net increase was significantly correlated with changes in BNP ($R=0.61$, $P<0.0001$) and E/e' ratio ($R=0.49$, $P<0.0001$).

Discussion

A distinguishing feature of HFpEF patients is reduced tolerance to exercise, with sudden increase in pulmonary congestion. Here, we describe for the first time dynamic changes in pulmonary congestion elicited by submaximal ESE—as easily detectable by lung ultrasounds—which markedly increased and promptly returned toward baseline during recovery. B-line behaviour was mirrored by changes in estimated LV filling pressure and pulmonary artery pressure. BNP concentrations also significantly increased with exercise. Interestingly, those various indices showed a similar temporal pattern in control subjects, in whom however all values remained markedly and significantly lower compared to HFpEF patients.

B-line assessment at rest has demonstrated diagnostic and prognostic usefulness to detect pulmonary congestion in different settings and HF phenotypes,[2,5] as it is a simple procedure able to overcome limitations of Doppler-derived indices (sample volume placement, high respiratory rate, poor acoustic window, age dependence).[12]

Recently, LUS has been successfully employed to monitor the acute effects of exercise on pulmonary congestion in HF,[7,8] showing a prompt increase in B-line count. However, our study is novel, and it differs in several major aspects. First, those studies primarily[7] or exclusively[8] focused on HFrEF, not HFpEF; secondly, B-line assessment was performed only at one point, namely peak exercise[8] or recovery,[7] whereas we explored the whole behaviour, from baseline throughout recovery; finally, we also demonstrated that increase in B-line count occurred simultaneously with BNP increment during exercise.

Submaximal ESE is feasible in HFpEF patients and thought to reproduce efforts patients may experience during daily activities[5,13]; by targeting heart rate around 100–110 b.p.m., merging of Doppler velocity signals was avoided, in line with recommendations.[14]

Our data also suggest that exercise LUS in HFpEF patients, who are often asymptomatic at rest, may potentially represent a simple and useful means to better identify patients at higher risk. Furthermore, being HFpEF a population in which trials of conventional HF medications have been inconclusive, and identification of proper patient population problematic, it may represent a powerful tool to aid conducting large randomized trials. Further studies are warranted to prove these aspects.

Exercise LUS represents a useful extension of standard ESE, easily performed in routine clinical practice; additionally, given the low level of required training, it might be envisioned as the first step of functional testing that every cardiologist is capable of carrying out, as opposed to the specific expertise required for standard ESE.

In conclusion, our data show that submaximal ESE coupled with pulmonary B-line assessment unveils development of pulmonary congestion in HFpEF patients. This occurs concomitantly with increase of other echocardiographic markers of congestion and of natriuretic peptides, all requiring more technical or logistical efforts. Thus, LUS may represent a simple tool in both clinical practice and clinical research.

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