Association between Lung Ultrasound B-lines and Exercise-Induced Pulmonary Hypertension in Patients with Connective Tissue Disease

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ABSTRACT

Background: Identification of elevation in pulmonary pressures during exercise may provide prognostic and therapeutic implications in patients with connective tissue disease (CTD). Interstitial lung disease (ILD) is common in CTD patients and subtle interstitial abnormalities detected by lung ultrasound could predict exercise-induced pulmonary hypertension (PH).

Methods and Results: Echocardiography and lung ultrasound were performed at rest and bicycle exercise in CTD patients (n=41) and control subjects without CTD (n=24). Ultrasound B-lines were quantified by scanning four intercostal spaces in the right hemithorax. We examined the association between total B-lines at rest and the development of exercise-induced PH during ergometry exercise. Compared to controls, the number of total B-lines at rest was higher in CTD patients (0 [0, 0] vs. 2 [0, 9], $p<0.0001$) and was correlated with radiological severity of ILD assessed by computed tomography (fibrosis score, $r=0.70$, $p<0.0001$). Pulmonary artery systolic pressure (PASP) was increased with ergometry exercise in CTD compared to controls (48±14 vs. 35±13 mmHg, $p=0.0006$). The number of total B-lines at rest was highly correlated with higher PASP ($r=0.52$, $p<0.0001$) and poor right ventricular pulmonary artery coupling (tricuspid annular plane systolic excursion/PASP ratio, $r=-0.31$, $p=0.01$) during peak exercise. The number of resting B-lines predicted the development of exercise-induced PH with an area under the curve 0.79 ($p=0.0003$).

Conclusions: These data may suggest the value of a simple resting assessment of lung ultrasound as a potential tool for assessing the risk of exercise-induced PH in CTD patients.

Key Words: lung ultrasound, B-lines, exercise-induced pulmonary hypertension, connective tissue disease

INTRODUCTION

Pulmonary hypertension (PH) is a leading cause of morbidity and mortality in patients with connective tissue disease (CTD), especially those with systemic sclerosis (SSc).[1,2] Pulmonary vascular resistance and pulmonary pressures can remain normal in an earlier phase of the disease because of the remarkable reserve capacity of the pulmonary circulation. An increase in pulmonary artery (PA) pressures during physiologic stress is considered to be a subclinical pulmonary disease.[3–5] This abnormal increase in pulmonary pressure, known as exercise-induced PH, is associated with the development of resting PH, reduced aerobic capacity, worse right ventricular systolic function, and poor clinical outcomes.[6–9] Thus, identification of exercise-induced PH may have important diagnostic, prognostic, and therapeutic implications in patients with CTD.[10,11]

Exercise stress echocardiography provides detailed information on pulmonary hemodynamics and RV function during exercise non-invasively and serves as the primary test to identify exercise-induced PH.[12–14] On the other hand, the risk of exercise-induced PH in individual patients may substantially vary, and it may be necessary to determine the pre-test probability of which patients should undergo the exercise testing. Interstitial lung disease (ILD) is common in patients with CTD and contributes to the development of PH and poor clinical outcomes.[15,16] Increasing evidence has demonstrated that ILD can be reliably detected by lung ultrasound as B-lines in CTD patients.[17–20] It may be that lung ultrasound can identify subtle interstitial abnormalities compared to chest radiography, such as chest computed tomography (CT).[21]

Based on these backgrounds, we hypothesized that ultrasound B-lines associated with ILD could predict the development of exercise-induced PH in patients with CTD. In this preliminary study, we sought to determine the association between ultrasound B-lines measured by a simplified scanning and Doppler echocardiography-derived PA pressures at rest and during bicycle exercise echocardiography.

MATERIALS AND METHODS

Study Population

Consecutive CTD patients who were referred to the echocardiographic laboratory of the Gunma University Hospital for exercise stress echocardiography for exertional dyspnea between September 2019 and July 2020 were prospectively enrolled in this study. Subjects with left ventricular ejection fraction (LVEF) <50%, heart failure (HF), or significant left-sided valvular heart disease (>moderate regurgitation, >mild stenosis) were excluded. Control subjects free of CTD who were also referred to exercise echocardiography because of clinical indication of exertional dyspnea were included as a comparator group (controls). The control subjects were required to display no evidence of the cardiac cause of dyspnea after thorough clinical evaluation and exercise assessment. Data on clinical demographics, past history, current medications, and laboratory and pulmonary function data were collected from a detailed chart review. The study was approved by our Institutional Review Board with the waiver of consent and all authors have read and agreed to the manuscript as written.

CT Assessments for the Severity of Interstitial Lung Disease

CT scans were obtained according to clinical indication within 6 months of exercise echocardiography in a subset of participants (n=47). The severity of ILD was determined by two independent pulmonologists blinded to the patient's clinical and echocardiographic information (K.Y. and S.K) based on the two independent CT findings: the ground-glass opacity (GGO) score and fibrosis score (septal thickening and honeycombing).[22] Three CT levels were manually identified: the mid-aortic arch, left tracheal bifurcation, and 1 cm above the diaphragm. The GGO and fibrosis scores were rated (0-5, higher scores indicate a worse lung condition) in each lobe of the lungs (right upper, middle, and lower, and left upper and lower lobes) and summed (Supplemental Figure).

Exercise Stress Echocardiography

Comprehensive resting echocardiography was performed by experienced sonographers using a commercially available ultrasound system (Vivid E95, GE Healthcare, Horten, Norway). LV volumes and EF were determined using apical 4-chamber views.[23] LV systolic function was assessed based on the EF and the systolic mitral annular tissue velocity at the septal annulus (mitral s'). LV diastolic function was assessed using the early diastolic mitral inflow velocity (E), early diastolic mitral annular tissue velocity at the septal annulus (e'), and the E/e' ratio. Left atrial (LA) volume was determined using the biplane method of disks. Stroke volume (SV) was determined from the LV outflow dimension and pulse wave Doppler profile. Cardiac output (CO) was calculated from the product of heart rate and SV. RV systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE) and systolic tissue velocities at the lateral tricuspid annulus (TV s'). Right atrial (RA) pressure was estimated from the diameter of the inferior vena cava and its respiratory change. PA systolic pressure (PASP) was calculated as 4 × (peak tricuspid regurgitation [TR] velocity)^2 + estimated RA pressure. The mean PA pressure (mPAP) was calculated as 0.61 × PASP + 2.[24]

Subjects underwent supine cycle ergometry echocardiography, starting at 20 W for 5 minutes, increasing 20W increments in 3-minute stages to subject-reported exhaustion. Exercise-induced PH was defined as mPAP > 30 mmHg with a total pulmonary resistance (i.e., mPAP/CO) of >3 mmHg·min/l, as previously described.[25,26] Echocardiographic images were obtained at baseline and during all stages of exercise. All Doppler measures represent the mean of ≥ 3 beats. All studies were interpreted offline and in a blinded fashion by a single investigator (M.O.).

Lung Ultrasound Imaging

Lung ultrasound was performed using the same cardiac transducer, which was placed perpendicular to the ribs. The sonographic signs of ILD are ultrasound B-lines which present as vertical, hyperechoic lines that originate from the pleural line and extend to the bottom of the ultrasound screen while moving synchronously with respirophasic motion.[17,27,28] Because B-lines may also be caused by pulmonary congestion due to elevation in left-sided filling pressure during exercise, lung ultrasound was performed at rest and immediately after echocardiography at each stage of exercise to assess changes in B-lines with exercise.[29] In this study, B-lines were measured in a simplified approach by scanning four intercostal spaces in the right hemithorax (right third and fourth spaces along the mid-axillary and mid-clavicular lines) because of the time constraints for imaging during the exercise.[30–32] The number of B-lines was assessed off-line in a single observer (T.I.) unaware of patients' information, and the total of B-lines in the four predefined zones was used for the primary analyses.

Statistical Analysis

Data are reported as mean (SD), median (IQR), or number (%) unless otherwise specified. Between-group differences were compared by unpaired t-test, Wilcoxon rank-sum test, or chi-square test, as appropriate. Pearson's or Spearman's correlation coefficients were used to assess relationships between two variables of interest, as appropriate. Receiver operating curves (ROC) were constructed to evaluate the predictive performance of B-lines. All tests were 2-sided, with a value of $P<0.05$ considered significant. All statistical analyses were performed with JMP 14.0.0 (SAS Institute, Cary, NC, USA).

RESULTS

Subject Characteristics

We included 41 CTD patients and 24 control subjects. SSc was the dominant underlying cause of CTD (78%), followed by Sjogren's syndrome (17%) and rheumatoid arthritis (12%). Clinical characteristics between CTD and controls are shown in Table 1. Age, gender, and prevalence of coronary artery disease, diabetes, and systemic hypertension were similar between patients with CTD and controls. As compared to control subjects, body mass index was lower and the prevalence of ILD was higher in CTD patients. Compared to controls, patients with CTD were less treated with diuretics, but other medication use was similar between groups. Levels of B-type natriuretic peptide (BNP) and hemoglobin were similar in CTD and controls. As compared to control subjects, patients with CTD displayed lower predicted vital capacity and diffusion capacity of carbon monoxide (DLCO) on pulmonary function tests. LV dimension, mass index, and EF, LA volume index, and RV systolic function were similar between groups.

Non-invasive Lung Imaging

Given the higher prevalence of ILD, patients with CTD displayed worse total GGO and fibrosis scores than controls (Table 1). Both GGO and fibrosis scores were less severe in the right upper region compared to those rated in the whole lungs (Table 1). Compared to control subjects, CTD patients displayed a greater number of total B-lines obtained from the 4 lung sites in the right upper region (Figure 1). As expected, patients with ILD had more B-lines than those without (0 [0, 0] vs 5 [1, 13], $p<0.0001$). The number of total B-lines at rest was correlated with both GGO and fibrosis scores obtained in the whole lungs ($r=0.43$, $p=0.003$ and $r=0.70$, $p<0.0001$) and in the right upper lobe ($r=0.26$, $p=0.09$ and $r=0.63$, $p<0.0001$).

Resting Left and Right Heart Hemodynamics, Lung Ultrasound, and CT Findings

At rest, heart rate, systolic blood pressure, LV systolic and diastolic function, CO, and RA pressure were similar between patients with CTD and control subjects (Table 2). Compared to controls, CTD patients had higher PASP at rest (Table 2, Figure 2). Total fibrosis score and the number of B-lines were correlated with resting PASP, but total GGO score was not (r=0.41, p=0.005, r=0.46, p=0.0002, and r=0.26, p=0.08, respectively).

Exercise Pulmonary Hemodynamics and their Association with Resting Lung Ultrasound and CT Findings

As compared to controls, peak exercise workload was impaired and exercise duration was shorter in CTD patients (75 [60, 80] vs 50 [40, 68] watts, p=0.008 and 668 [538, 856] vs 560 [477, 687] sec. p=0.04). The number of B-lines unchanged with exercise in both CTD patients (2 [0, 9] at rest vs 2 [0, 8] during peak exercise, p=0.30) and controls (0 [0, 0] at rest vs 0 [0, 0] during exercise, p=0.27).

During peak exercise, heart rate, and LV systolic and diastolic function remained similar between groups (Table 3). Compared to control subjects, CTD patients displayed a marked reduction in oxygen saturation with exercise (-2±3 vs -6±5%, p=0.001). The difference in PASP between groups increased further and CO was a trend toward lower in the patients than controls (Table 3, Figure 2). Exercise-induced PH was occurred in 4 (17%) controls and in 18 (44%) patients with CTD (p=0.02). In simple correlation analyses, resting oxygen saturation levels, pulmonary function data, and GGO score were unrelated to peak PASP (all |r| <0.3). In contrast, total fibrosis score and resting B-lines were directly correlated with peak PASP (Figures 3). The number of total B-lines at rest was also correlated with peak TAPSE/PASP (r=-0.31, p=0.01) and change in PASP from baseline to peak exercise (r=0.35, p=0.005).

Ultrasound B-lines and Exercise-Induced PH

The number of ultrasound B-lines displayed a good predictive ability for exercise-induced PH, with an AUC of 0.79 (p=0.0003). An increase in B-line at rest was associated with a 123% increased risk of exercise-induced PH (Odds ratio [OR]: 1.23 per 1 B-line increment, 95% confidence interval [CI]: 1.08 to 1.40, p=0.0003). The number of B-lines remained significantly associated with exercise-induced PH after adjusting for fibrosis score in the right upper lung (OR 1.21 per 1 increment, 95%CI 1.04-1.41, p=0.006), but not after adjusting for total fibrosis score (OR 1.15 per 1 increment, 95%CI 0.99-1.34, p=0.07).

DISCUSSION

Identification of exercise-induced PH may have important clinical implications.[10,11] In this preliminary study, we examined the association between resting ultrasound B-lines and the development of PH during exercise in patients with CTD. There are three key findings that have clinical implications: (1) ultrasound B-lines associated with ILD were detected at right upper chest zones where GGO and fibrosis scores were relatively low; (2) the total number of B-lines obtained in 4 lung sites at rest was highly correlated with PASP during peak exercise; and (3) resting B-lines displayed a reasonable ability for predicting exercise-induced PH (AUC 0.79). These data may demonstrate the potential value of a simple resting assessment of lung ultrasound as a tool for predicting exercise-induced PH in CTD patients (Figure 4).

Identification of Early Interstitial Lung Disease by Lung Ultrasound

An emerging body of evidence has shown that interstitial lung syndrome can be reliably demonstrated by lung ultrasound.[17,27] The presence of ultrasound B-lines in patients with CTD reflects interstitial pulmonary involvement. Increases in B-lines are associated with the severity of radiological signs of interstitial disease as well as the progression of ILD.[18,19,33] Consistent with the previous studies, we observed that the number of B-lines at rest was higher in patients with CTD than control subjects and was correlated with the radiological fibrosis score. Intriguingly, there was a dissociation between sonographic and radiological severity of interstitial disease in the right upper regions (Table 1). These data along with slightly abnormal pulmonary function test findings in the current study may suggest that lung ultrasound could identify an early phase of interstitial lung involvement. Further prospective studies are required to examine if baseline B-lines could predict the incidence of ILD on follow-up CT scans.

Development of Pulmonary Hypertension During Exercise and its Association with Ultrasound B-lines

PH is associated with increased morbidity and mortality in patients with CTD.[1,2] Abnormal pulmonary response to exercise is associated with the development of resting PH, reduced aerobic capacity, worse RV-PA coupling, and poor clinical outcomes, making identification of exercise-induced PH high priority.[3,6–9] Exercise stress echocardiography plays a central role in this purpose.[14] Not all patients are uniformly at risk for EIPH and it may be necessary to assess pre-test probability to determine which patients have priority in undergoing exercise testing. Previous studies reported that low DLCO and high FVC%/DLCO% ratio were associated with exercise-induced PH in patients with SSc.[34,35] In the current study, we performed a simplified resting lung ultrasound with four-site scanning in the right hemithorax in CTD patients and demonstrated that the number of total B-lines was highly correlated with PASP during peak exercise. We also found that the number of B-lines displayed a good predictive value for exercise-induced PH, with an AUC of 0.79. The current preliminary data may suggest the utility of the simple resting lung ultrasound as a potential test for assessing risks to develop exercise-induced PH in CTD patients. Further study is needed to better understand potential mechanisms between ultrasound B-lines and the development of exercise-induced PH.

Limitations

All participants were referred for exercise stress echocardiography, introducing selection bias. The sample size was relatively small, which could bias the results. The control group was not normal as they were referred for exercise stress echocardiography in the evaluation of exertional dyspnea and had comorbidities, which could also bias the results. However, the fact that the control population was more diseased than a truly normal healthy control population only biases our data toward the null. The primary limitation of the current study is the limited lung ultrasound scanning points for the detection of B-lines.[27] In this study, lung ultrasound was performed in four chest regions on the right hemithorax because of the time constraints for imaging during exercise. Because B-lines may also be caused by lung congestion related to left-sided heart failure (wet B-lines), it was necessary to examine changes in B-lines with exercise in the current study.[30] Scali et al. recently demonstrated that a simplified four-site lung scan provided equivalent information on lung congestion to the full 28-region assessments.[31,32] However, the simplified scanning might reduce the total number of B-lines compared to the 28-site approach, and it is possible that some of the patients might have B-lines if more regions of the chest, especially those in lower lobes, were scanned. The limited lung ultrasound sampling may also preclude the possibility to determine cutoff points of B-lines to identify exercise-induced PH.

Conclusions

In this preliminary analysis, the number of B-lines at rest was associated with the development of PH during exercise in patients with CTD. These data suggest the value of a simple resting assessment of lung ultrasound B-lines as a potential tool for assessing risk of exercise-induced PH in CTD patients.

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Author contributions

Concept/design, MO; Data analysis/interpretation, KK, TH, KY, SK, TI, MO; Drafting article, KK; Critical revision of article, all authors; Approval of article, all authors; Statistics, KK, MO; Funding secured by, MO; Data collection, KK, TH, MO.

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Table 1: Baseline Characteristics

	Controls (n=24)	CTD (n=41)	P value
Age (years)	64±14	65±10	0.70
Female, n (%)	15 (63)	31 (76)	0.26
Body mass index (kg/m^2)	24.8±3.8	22.2±3.9	0.01
Comorbidities			
Coronary disease, n (%)	2 (8)	2 (5)	0.57
Diabetes mellitus, n (%)	1 (4)	6 (15)	
Hypertension, n (%)	18 (75)	25 (61)	0.25
Interstitial lung disease, n (%)	1 (4)	27 (66)	<0.0001
Connective tissue disease*			
Systemic sclerosis, n (%)		32 (78)	
Sjogren's syndrome, n (%)		7 (17)	
Rheumatoid arthritis, n (%)		5 (12)	
Others, n (%)		8 (20)	
Medications			
ACEI or ARB, n (%)	8 (33)	10 (24)	0.43
Beta-blocker, n (%)	4 (17)	5 (12)	0.61
Calcium channel blocker, n (%)	10 (42)	12 (29)	0.31
Loop diuretic, n (%)	8 (33)	2 (5)	0.002
Laboratories			
Hemoglobin (g/dl)	13.1±1.7	12.8±1.2	0.54
BNP (pg/ml)	35 (8, 83)	40 (20,53)	0.69
Pulmonary function test[†]			
VC %predicted (%)	107±12	87±17	0.03
FEV1.0%(G) (%)	93±6	99±8	0.07
DLCO % predicted (%)	94 (84,101)	68 (57,79)	0.03
DLCO/VA %predicted (%)	91±5	81±25	0.06
CT score[#]			
Right upper GGO	0 (0, 0)	0 (0, 1)	0.09
Total GGO	0 (0, 1)	2 (0, 8)	0.009
Right upper fibrosis score	0 (0, 0)	0 (0, 1)	0.009
Total fibrosis score	0 (0, 0)	3 (0, 9)	0.0008
LV structure and function			
LV diastolic dimension (mm)	44±5	43±4	0.12
LV mass index (gm/m^2)	80±16	82±18	0.77

LV ejection fraction (%)	66±9	65±7	0.58
LA volume index (ml/m^2)	26 (20, 29)	22 (17, 34)	0.51
RV function			
TAPSE (mm)	17.6±5.2	18.4±3.3	0.52
TV s’ (cm/sec)	12.1±3.2	13.1±2.7	0.16

Data are mean ± SD, median (interquartile range), or n (%). *Some patients had multiple connective tissue diseases. [†]Data were available in 34 participants. [#]Data were available in 47 participants. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BNP, B-type natriuretic peptide; CT, computed tomography; CTD, connective tissue disease; DLCO, diffusing capacity of the lung for carbon monoxide; E/e’ ratio, the ratio of early diastolic mitral inflow to mitral annular tissue velocities; GGO, ground-glass opacity; LA, left atrial; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion; TVs’, systolic tissue velocities at the lateral tricuspid annulus; VA, volume of alveolar;VC, vital capacity; and FEV1, forced expiratory volume in 1.0 second.

Table 2: Baseline Vital Signs and Echocardiographic Measures

	Controls (n=24)	CTD (n=41)	P value
Heart rate (bpm)	75±14	76±13	0.77
Systolic BP (mmHg)	129±16	129±19	0.92
Saturation (%)	96±3	97±2	0.03
LV ejection fraction (%)	66±9	65±7	0.58
E-wave (cm/sec)	64±21	63±19	0.77
A-wave (cm/sec)	73±21	77±21	0.47
Mitral e’ (cm/sec)	7.0±2.6	6.5±2.1	0.45
Mitral s’ (cm/sec)	8.4±2.1	8.2±1.8	0.77
E/e’ ratio	9.7±3.1	10.3±3.8	0.50
Cardiac output (L/min)	4.4±1.2	4.1±1.3	0.28
TR velocity (m/sec)	1.9±0.4	2.2±0.4	0.0008
PASP (mmHg)	18±6	23±6	0.001
mPAP (mmHg)	13±4	16±4	0.001
RAP (mmHg)	3 (3, 3)	3 (3, 3)	0.46
Total B-lines (n)	0 (0, 0)	2 (0, 9)	<0.0001

Data are mean ± SD or median (interquartile range). BP indicates blood pressure; Mitral e’ and s’, mitral early diastolic and systolic annular velocity; TR, tricuspid regurgitation; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure.

Table 3: Vital Signs and Echocardiographic Measures during Peak Exercise

	Controls (n=24)	CTD (n=41)	P value
Borg dyspnea score	7 (4, 8)	7 (6, 8)	0.66
Borg fatigue score	16 (13, 18)	14 (12, 16)	0.50
Heart rate (bpm)	115±17	117±21	0.78
Systolic BP (mmHg)	166±25	178±31	0.12
Saturation (%)	94±4	91±6	0.06
LV ejection fraction (%)	73±9	74±7	0.73
E-wave (cm/sec)	112±23	113±26	0.85
A-wave (cm/sec)	108±29	106±30	0.87
Mitral e’ (cm/sec)	10.0±3.0	10.1±2.9	0.89
Mitral s’ (cm/sec)	9.4±2.0	9.5±2.2	0.87
E/e’ ratio	12.0±3.3	11.6±2.9	0.78
Cardiac output (L/min)	8.2±2.5	7.1±1.9	0.05
TR velocity (m/sec)	2.7±0.6	3.2±0.5	0.0005
PASP (mmHg)	35±13	48±14	0.0006
mPAP (mmHg)	24±8	31±8	0.001
RAP (mmHg)	3 (3, 8)	3 (3, 8)	0.19
Total B-lines (n)	0 (0, 0)	2 (0, 8)	0.0004

Data are mean ± SD, median (interquartile range). Abbreviations as in table 2.

Figure legends

Figure 1. The total number of B-lines in the 4 lung sites at rest was higher in patients with connective tissue disease (CTD) than in control subjects.

Figure 2. At rest, pulmonary artery systolic pressure (PASP) was higher in CTD patients than in controls (p=0.001). During peak exercise, PASP was increased to a greater extent in CTD patients than in controls (p=0.02). *p=0.001 vs controls; **p=0.0006 vs controls. Abbreviations as in Figure 1.

Figure 3. (A) Total fibrosis score was directly correlated with PASP during exercise. **(B)** The total number of B-lines at rest was also correlated with exercise PASP. Abbreviations as in Figure 2.

Figure 4. Lung ultrasound, computed tomography (CT), and exercise stress echocardiographic images in a patient with CTD. Multiple B-lines are observed in the right third intercostal space at rest. Chest CT demonstrates interstitial lung involvement in the left lower lobe (GGO [ground-glass opacity] score 0 and fibrosis score 5). Note that no interstitial abnormality was observed in the upper lobes. Echocardiography reveals normal PASP at rest (30 mmHg), but it increased to 58mmHg during exercise. Abbreviations as in Figures 1 and 2. Yellow arrows indicate ultrasound B-lines.