JACC: CARDIOVASCULAR IMAGING VOL. 13, NO. 10, 2020

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Lung Ultrasound and Pulmonary Congestion During Stress Echocardiography

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ABSTRACT

OBJECTIVES The purpose of this study was to assess the functional and prognostic correlates of B-lines during stress echocardiography (SE).

BACKGROUND B-profile detected by lung ultrasound (LUS) is a sign of pulmonary congestion during SE.

METHODS The authors prospectively performed transthoracic echocardiography (TTE) and LUS in 2,145 patients referred for exercise (n = 1,012), vasodilator (n = 1,054), or dobutamine (n = 79) SE in 11 certified centers. B-lines were evaluated in a 4-site simplified scan (each site scored from 0: A-lines to 10: white lung for coalescing B-lines). During stress the following were also analyzed: stress-induced new regional wall motion abnormalities in 2 contiguous segments; reduced left ventricular contractile reserve (peak/rest based on force, ≤2.0 for exercise and dobutamine, ≤1.1 for vasodilators); and abnormal coronary flow velocity reserve ≤2.0, assessed by pulsed-wave Doppler sampling in left anterior descending coronary artery and abnormal heart rate reserve (peak/rest heart rate) ≤1.80 for exercise and dobutamine (≤1.22 for vasodilators). All patients completed follow-up.

RESULTS According to B-lines at peak stress patients were divided into 4 different groups: group I, absence of stress B-lines (score: 0 to 1; n = 1,389; 64.7%); group II, mild B-lines (score: 2 to 4; n = 428; 20%); group III, moderate B-lines (score: 5 to 9; n = 209; 9.7%) and group IV, severe B-lines (score: ≥10; n = 119; 5.4%). During median follow-up of 15.2 months (interquartile range: 12 to 20 months) there were 38 deaths and 28 nonfatal myocardial infarctions in 64 patients. At multivariable analysis, severe stress B-lines (hazard ratio [HR]: 3.544; 95% confidence interval [CI]: 1.466 to 8.687; p = 0.006), abnormal heart rate reserve (HR: 2.276; 95% CI: 1.215 to 4.262; p = 0.010), abnormal coronary flow velocity reserve (HR: 2.178; 95% CI: 1.059 to 4.479; p = 0.034), and age (HR: 1.031; 95% CI: 1.002 to 1.062; p = 0.037) were independent predictors of death and nonfatal myocardial infarction.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.04.020

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

EF = ejection fraction

HF = heart failure

LUS = lung ultrasound

LVCR = left ventricular contractile reserve

RWMA = regional wall motion abnormalities

SE = stress echocardiography

TTE = transthoracic echocardiography

WMSI = wall motion score index

CONCLUSIONS Severe stress B-lines predict death and nonfatal myocardial infarction.
(Stress Echo 2020–The International Stress Echo Study [SE2020]; NCT03049995)
(J Am Coll Cardiol Img 2020;13:2085–95) © 2020 by the American College of Cardiology Foundation.

The B-profile of normal lung sliding with B-lines (also known as ultrasound lung comets) by lung ultrasound (LUS) identifies pulmonary congestion at rest (1) associated with a worse outcome in patients with heart failure (HF), acute myocardial infarction, or chronic coronary artery disease (CAD) (2–6). Tailored B-line-driven diuretic treatment of HF is associated with a reduction of acute decompensation events as shown by a randomized trial, with a number needed to treat of 5 (7). B-lines may also appear during physical or pharmacological stress in patients with CAD (8) and/or HF with either reduced (9) or preserved (10) resting left ventricular ejection fraction (EF) (11,12). A "wet lung" with appearance or increasing B-lines is more often found with ischemic regional wall motion abnormalities (RWMA) and/or diastolic dysfunction associated with increase in pulmonary wedge pressure (8–13).

The present study hypothesis is that patients with more B-lines, appearing or increasing during stress, have a greater functional impairment and worse outcome compared to patients without B-lines during stress. To test this hypothesis, a combined transthoracic echocardiography (TTE) and LUS was

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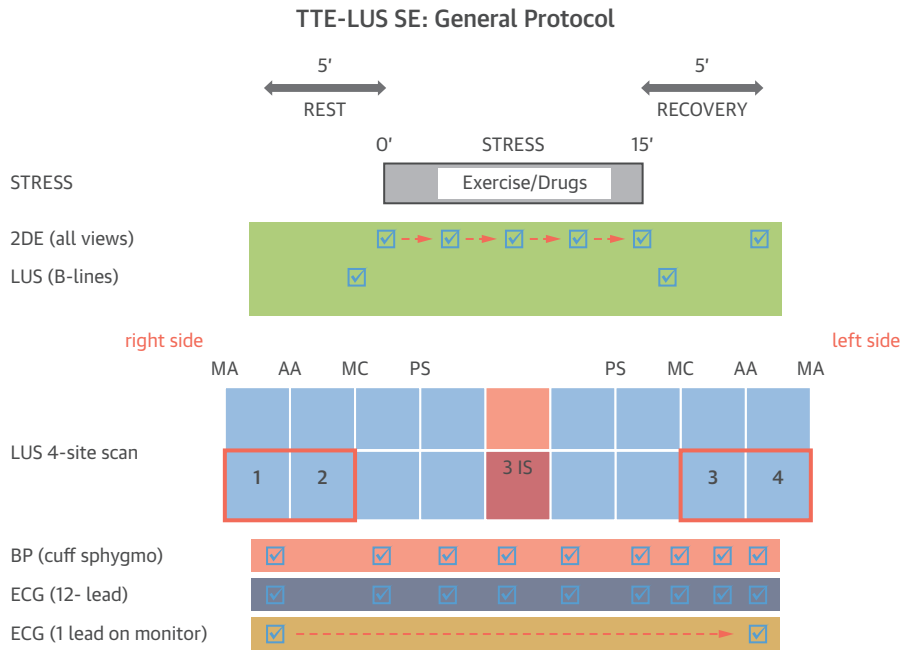
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.
Manuscript received February 26, 2020; revised manuscript received April 22, 2020, accepted April 30, 2020.

FIGURE 1 **The Combined TTE-LUS Stress and the 4-Region LUS Scanning Protocol**



The lung ultrasound (LUS) acquisition is performed at rest and peak (or immediately after) stress with the 4-site simplified scan on third intercostal space. 3 IS = third intercostal space; AA = anterior axillary; MA = mid-axillary; MC = mid-clavicular; PS = parasternal lines; TTE = transthoracic echocardiography.

performed in patients with known or suspected CAD and/or HF, referred for clinically-driven stress echocardiography (SE) in accredited laboratories of the network of the international, multicenter, prospective SE 2020 (Stress Echo 2020) study (14).

METHODS

STUDY POPULATION. In this prospective study, we considered 2,145 patients recruited by 11 laboratories of 6 countries (Brazil, Bulgaria, Italy, Poland, Russian Federation, and Serbia) with a systematic follow-up program. Patients without available follow-up information (n = 25) or with prognosis-limiting disease or comorbidities known to demonstrate B-lines of extracardiac origin were excluded (e.g., patients with pulmonary fibrosis, lung cancer, pneumonia). The inclusion criteria were: 1) age >18 years; 2) referral for known or suspected CAD (n = 1,927 with history of chest pain, previous myocardial revascularization, and/or previous myocardial infarction, or asymptomatic at risk) or HF (n = 217 with dyspnea as the presenting symptom or asymptomatic with echocardiographic evidence of systolic or diastolic left ventricular dysfunction at rest), with any degree of resting left ventricular systolic function (preserved or reduced); 3) no severe primary valvular or congenital heart disease; 4) wall motion imaging by TTE of acceptable quality at rest; 5) willingness to give their written informed consent allowing scientific use of observational data, respectful of privacy rights; and 6) recruitment in centers with follow-up rate ranging from 95% to 100%.

No patient was discarded due to poor-quality LUS study at rest or during stress.

All patients underwent SE testing as part of a clinically-driven work-up (15) and according to the referring physician's indications. Written informed consent was obtained from all patients before testing. The study protocol was reviewed and approved by the institutional ethics committees as a part of the SE 2020 study (148- Comitato Etico Lazio-1, July 16, 2016; NCT03049995).

REST AND STRESS ECHOCARDIOGRAPHY. We used commercially available ultrasound machines. All patients underwent comprehensive TTE at rest. Left ventricular volumes used to calculate EF were measured by modified biplane Simpson's method

TABLE 1 Study Patients

	Group I Absent Stress B-Lines (n = 1,388)	Group II Mild Stress B-Lines (n = 428)	Group III Moderate Stress B-Lines (n = 209)	Group III Severe Stress B-lines (n = 119)	Overall (N = 2,144)	p Value
Age, yrs	62.5 ± 11.4	63.6 ± 11.6	63.9 ± 11.4	65.6 ± 11.2*	63.0 ± 11.4	0.012
Male	809 (58.3)	282 (65.9)*	145 (69.4)*†	79 (66.4)	1,315 (61.3)	0.001
BSA, m^2	1.87 ± 0.30	1.89 ± 0.27	1.95 ± 0.28	1.89 ± 0.31	1.88 ± 0.29	0.091
Hypertension	869 (62.6)	333 (77.8)*	164 (78.5)*	93 (78.2)*	1,459 (68.2)	<0.001
Diabetes mellitus	249 (17.9)	83 (19.4)	49 (23.4)	40 (33.6)*†	421 (19.6)	<0.001
History of MI	330 (23.8)	110 (25.7)	71 (30.4)*	40 (33.6)	551 (25.7)	0.003
Previous PCI and/or CABG	225 (16.2)	94 (22.0)	61 (29.2)*	38 (31.9)	418 (19.5)	<0.001
MR ≥ moderate	22 (1.5)	19 (4.4)*	14 (6.7)*	14 (11.8)*†	418 (19.5)	<0.001
Coronary angiography	623	198	100	59	980	
No CAD	325 (52.2)	108 (54.5)	42 (42.0)	27 (45.8)	502 (51.2)	
1 vessel	218 (35.0)	51 (25.8)	28 (28.0)	12 (20.3)	309 (31.5)	
2 or more vessels	80 (12.8)	39 (19.7)	30 (30.0)*	20 (33.9)*	169 (17.2)	<0.001
Type of stress						
Exercise	624 (45.0)	207 (48.4)	113 (54.1)	66 (55.5)	1,010 (47.1)	
Vasodilator	712 (51.3)	209 (48.8)	84 (40.2)	49 (41.2)	1,054 (49.2)	
Dobutamine	51 (3.7)	12 (2.8)	12 (5.7)	4 (3.4)	79 (3.7)	0.074
Rest HR, beats/min	69.9 ± 12.3	68.6 ± 11.0	39.6 ± 11.0	71.7 ± 12.9	69.7 ± 12.0	0.054
Peak HR, beats/min	107.2 ± 26.4	103.9 ± 25.0	107.7 ± 25.3	102.7 ± 23.4	106.4 ± 25.9	0.039
Rest LVEF, %	60.6 ± 9.1	58.9 ± 10.9*	57.1 ± 12.3*	55.9 ± 13.9*†	59.6 ± 10.2	<0.001
Peak LVEF, %	68.9 ± 13.3	64.7 ± 14.1*	62.0 ± 15.6*	58.5 ± 15.3*†	66.8 ± 14.2	<0.001
Rest WMSI	1.09 ± 0.22	1.14 ± 0.30*	1.20 ± 0.35*	1.28 ± 0.47*†	1.12 ± 0.28	<0.001
Peak WMSI	1.13 ± 0.27	1.27 ± 0.39*	1.37 ± 0.42*†	1.52 ± 0.52*†‡	1.20 ± 0.35	<0.001
δWMSI	0.04 ± 0.21	0.13 ± 0.26*	0.17 ± 0.35*†	0.24 ± 0.40*†‡	0.08 ± 0.26	<0.001
NWMA	193 (13.9)	134 (31.3)*	84 (40.2)*†	55 (46.2)*†‡	466 (21.7)	<0.001
Rest SBP, mm Hg	134.4 ± 19.7	132.3 ± 17.6	131.7 ± 17.5	132.2 ± 18.4	133.6 ± 19.1	0.069
Peak SBP, mm Hg	149.2 ± 36.4	153.8 ± 37.0	158.4 ± 36.4*	150.0 ± 34.6	151.1 ± 36.5	0.002
Rest force, mm Hg/ml	4.23 ± 1.88	3.83 ± 1.85*	3.50 ± 1.81*	3.54 ± 2.06*	4.04 ± 1.89	<0.001
Peak force, mm Hg/ml	7.39 ± 4.72	6.29 ± 4.76*	5.87 ± 4.38*†	4.89 ± 4.08*†	6.88 ± 4.72	<0.001
LV CR	1.74 ± 0.86	1.60 ± 0.81*	1.64 ± 0.90	1.33 ± 0.64*†‡	1.68 ± 0.85	<0.001
Abnormal LV CR,	451 (32.6)	185 (43.2)*	100 (47.8)	75 (63.0)*†‡	811 (37.9)	<0.001
Rest B-lines	0 (0-4)	1.5 (0-13)*	3 (0-11)*†	6 (0-35)*†‡	0 (0-35)	<0.001
Peak B-lines	0 (0-1)	3 (2-4)*	6 (5-9)*†	14 (10-40)*†‡	1 (0-40)	<0.001
Drying lung	22 (1.6)	14 (3.3)*	7 (3.3)*	1 (0.8)*†‡	44 (2.1)	<0.001
CFVR (n = 1,806)	2.36 ± 0.55	2.19 ± 0.59*	2.07 ± 0.60*	1.83 ± 0.58*†‡	2.25 ± 0.58	<0.001

Values are mean ± SD or n (%). Drying lung pattern: stress B-lines < rest B-lines for at least 2 points. *p < 0.05 vs. group 1; †p < 0.05 vs. group 2; ‡p < 0.05 vs. group 3.

BSA = body surface area; CAD = coronary artery disease; CFVR = coronary flow velocity reserve; HRR = heart rate reserve; LVCR = left ventricular contractile reserve; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; SBP = systolic blood pressure; WMSI = wall motion score index.

according to the American Society of Echocardiography and European Association of Cardiovascular Imaging (16,17).

All patients underwent exercise or pharmacological SE according to the protocol recommended by the European Association of Cardiovascular Imaging guidelines (16). Exercise protocol was semisupine in these patients (post-treadmill was also allowed). We used dipyridamole dose up to 0.86 mg/kg, dobutamine starting from 5 to 40 μg/kg/min with atropine coadministration up to 1 mg, and adenosine up to 0.14 μg/kg/min over 6 min. Electrocardiogram (ECG) and blood pressure were monitored continuously. ECG leads were positioned so as not to interfere with previously marked acoustic windows. Criteria for interrupting the test were severe chest pain, diagnostic ST-segment shift, excessive blood pressure increase (systolic blood pressure ≥240 mm Hg, diastolic blood pressure ≥120 mm Hg), limiting dyspnea, maximal predicted heart rate, significant arrhythmias. or limiting side effects (17).

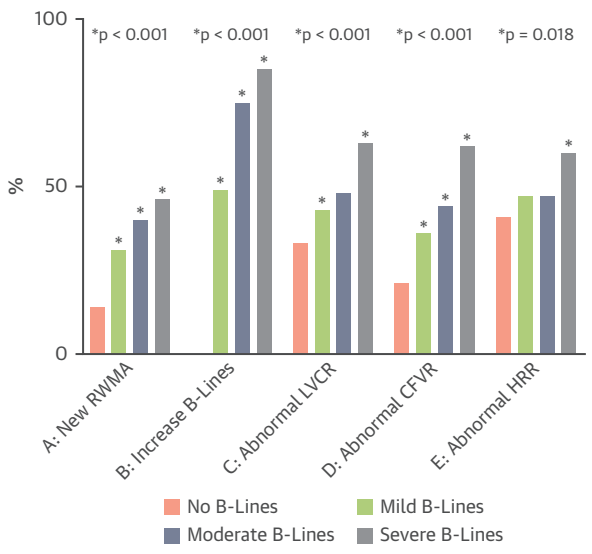
QUADRUPLE IMAGING IN ABCDE PROTOCOL. The ABCDE SE protocol was used. Step A for Asynergy and regional wall motion abnormalities, step B for B-lines, step C for left ventricular Contractile reserve, step D for Doppler-based coronary flow velocity reserve (CFVR) and step E for heart rate reserve based on ECG. Each laboratory completed the upstream

quality control process (18). Echocardiographic imaging was performed from the parasternal long-axis view; short-axis view; and apical 4-, 3-, and 2-chamber view, using conventional 2-dimensional echocardiography. Step A included assessment of wall motion abnormalities and was performed in all patients. Wall motion score index (WMSI) was calculated in each patient at baseline and peak stress, in a 4-point score ranging from 1 (normal) to 4 (dyskinetic) in a 17-segment model of the left ventricle (19). The A criterion was considered positive in presence of stress-induced RWMA (WMSI stress > rest) when at least 2 adjacent segments of the same vascular territory of the left ventricle showed an increment of at least 1 point of segmental score during SE (19). Step B of protocol included the assessment of B-lines with lung ultrasound (20). The B criterion was considered positive in the presence of stress or rest B-lines ≥2 U (12). Step C of protocol included the force-based assessment of left ventricular contractile reserve (LVCR) as the stress/rest ratio of force, calculated as systolic blood pressure/end-systolic volume (21). Stress-specific abnormal cutoff values for force-based LVCR were: ≤2.0 for exercise and dobutamine, and ≤1.1 for dipyridamole and adenosine (13). CFVR (step D) was assessed during the standard SE examination using intermittent imaging of wall motion and LAD (2). Coronary flow in the mid-distal portion of the LAD was imaged from the low parasternal long-axis view and/or modified apical 2-, 3-, or 4-chamber view under the guidance of color Doppler flow mapping (13). At each timepoint, 3 optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. CFVR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities. A CFVR value ≤2.0 was considered abnormal based on previously defined diagnostic and prognostic cutoff values (13).

The last imaging-independent step of the ABCDE protocol was the "E" step, based on ECG. Heart rate reserve (step E) was calculated as the peak/rest heart rate from 12-lead ECG (22). A blunted heart rate reserve (HRR) is a prognostically relevant index of reduced sympathetic reserve and abnormal cardiac autonomic function (22). The "E" criterion was considered positive in the presence of HRR <1.80 for exercise and dobutamine, and ≤1.22 for vasodilators (23). Beta-blockers reduce resting and peak heart rate but do not affect HRR and its cutoff value for outcome prediction (22,23).

All doctors and nurses involved were trained in Basic Life Support and Advanced Cardiac Life Support. The procedure for acquisition between centers was standardized through a web-based learning module before starting data collection. All readers (1 for each center) underwent a quality control as previously described (13,19,24).

FIGURE 2 ABCDE-Stress Echo Results

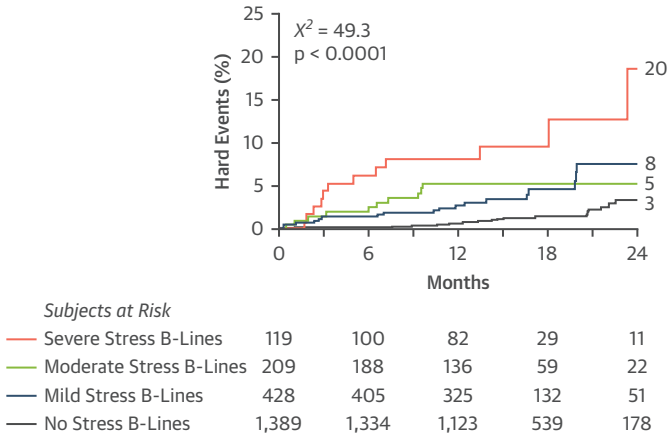


Abnormal results for each step are more frequent in patients with greater number of peak B-lines: group I (absent); group II (mild); group III (moderate); group IV (severe). *Intergroup significance. CFVR = coronary flow velocity reserve; HRR = heart rate reserve; LVCR = left ventricular contractile reserve.

LUNG ULTRASOUND ("B" STEP OF ABCDE IMAGING PROTOCOL). The general TTE-LUS SE protocol is shown in **Figure 1**. The same cardiac transducer was used for TTE and LUS. The depth was adjusted according to the body habitus of the patient to visualize the pleural line. A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artifact that arises from the pleural line extending to the bottom of the screen without fading and moving synchronously with lung sliding. We adopted the 4-site simplified scan (20). We analyzed the anterior and lateral hemithoraces, scanning from midaxillary to midclavicular lines on the third intercostal space. Detailed description of the scanning procedure and scanning sites is also available in a 4-min movie from our laboratory on YouTube (25). The sequence of scanning sites is shown in **Figure 1**. All readers passed the quality control for B-lines reading upstream to starting data collection (24).

The LUS study started at the end of exercise and beginning of recovery within 1 to 2 min after termination of stress, or just at the moment of antidote administration in pharmacological stress. B-lines recover slowly after test interruption, and still persist at 5 min of recovery after termination of exercise (10).

FIGURE 3 Hard Event-Free Survival Curves Based on Peak B-Line Value



Event rate in patients categorized according to the peak stress B-line value: absent-trivial (0 to 1); mild (2 to 4); moderate (5 to 9); and severe (≥10) pulmonary congestion.

A total of 4 chest sites was scanned, and each site had a score from 0 to 10 (20). The B-lines score was the sum of the score in each of the 4 chest sites (each site with possible score from 0 to 10), generating a total score of all 4 chest zones from 0 (all 4 sites with individual site score of 0) to 40 (all 4 sites with individual site score of 10). B-line response was evaluated as the number of B-lines (rest, peak, and their change from rest to peak). The number of stress B-lines was categorized as: absent (score points 0 to 1), mild (2 to 4), moderate (5 to 9), and severe (≥10 points), adapting to the 4-site scan score previously prognostically validated with the 28-site scan (3,26).

DATA STORAGE AND ANALYSIS. The results for each test were entered in the databank at the time of testing by each recruiting center and sent monthly to the core laboratory with the electronic case report form with clinical data. After checking for internal consistency by trained technical staff, and double-checking with the center for data verification on possibly inconsistent input, the data were added to the data bank and frozen.

CORONARY ANGIOGRAPHY. Invasive coronary angiography (n = 201) or noninvasive multidetector coronary angiography showing no CAD (n = 17) were available in 218 patients. Obstructive significant CAD was defined by a quantitatively assessed coronary diameter reduction ≥50% in the view showing the most severe stenosis. Images were read by experienced invasive cardiologists unaware of the results of SE.

OUTCOME DATA ANALYSIS. This is the interim analysis of the pre-specified evaluation of long-term outcomes to be completed by the end of 2023 (13,14). Deaths were identified from the National Health Service Database. To avoid misclassification of the cause of death, overall death was considered. Assessors were blinded to clinical, TTE, and LUS results (13,14).

STATISTICAL ANALYSIS. Categorical data are expressed in terms of number of subjects and percentage, and continuous data are expressed as mean ± SD or median (minimum, maximum) depending on the variables' distribution. For continuous variables, intergroup differences were tested with 1-way analysis of variance and intergroup comparison by Bonferroni or Kruskal-Wallis followed by Mann-Whitney test as appropriate. The chi-square or Fisher exact test was used to compare the distribution of categorical variables among groups. B-line response was evaluated as the number of B-lines (rest, peak, and their change from rest to peak). According to B-lines at peak stress, patients were divided into 4 different groups, with absent, mild, moderate, and severe B-lines. A pulmonary decongestion pattern ("drying lung") was defined as stress B-lines < rest B-lines for at least 2 points.

Event-free survival related to the endpoints of interest was estimated using the Kaplan-Meier method, and survival curves were compared with the log-rank test. Univariate Cox proportional hazards model were used to identify candidate predictors for selected endpoints. All variables with $p < 0.10$ at univariate analysis were considered for the inclusion in multivariate Cox proportional hazards model. The final multivariable models were obtained excluding just those variables causing collinearity evaluated using the variance inflation factor. None of the variables considered in the analysis violated the non-proportionality of hazard assumption according to the Schoenfeld test. The incremental value of stress B-lines was evaluated comparing multivariable models with and without stress B-lines using global chi-square value to evaluate improvement of goodness-of-fit as well as continuous net reclassification index to assess improvement in risk stratification. Statistical significance was set at $p < 0.05$. All analyses were performed using Stata statistical software version 14 (StataCorp, College Station, Texas) and R version 3.6 (R Foundation, Vienna, Austria).

RESULTS

The main clinical characteristics of the 2,145 study patients are described in Table 1. The employed stress

was exercise (n = 1,010, 47.1%; with semi-supine bike, n = 799, 79.1%; or post-treadmill, n = 211, 20.9%), vasodilator (n = 1,054, 49.2%; dipyridamole, n = 1,034; adenosine, n = 20), or dobutamine (n = 79; 3.7%).

TTE AND LUS RESULTS. Interpretable TTE and LUS images were obtained in all patients at peak stress, with an overall feasibility of 100%.

According to B-lines at peak stress, patients were divided into 4 different groups: group I, absence of stress B-line (score: 0 to 1; n = 1,388; 64.7%); group II, mild B-line (score: 2 to 4; n = 428; 20.0%); group III, moderate B-line (score: 5 to 9; n = 209; 9.7%) and group IV, severe B-line (score: ≥10; n = 119; 5.4%). The main clinical, echocardiographic characteristics of the 4 groups are described in Table 1.

All functional and coronary anatomic indexes of disease severity were more advanced in group IV compared with the other 3 groups, including extent of angiographically assessed CAD, history of myocardial infarction, and severity of mitral regurgitation (Table 1).

Stress-induced RWMA (step A positivity), increase in number of peak B-lines ≥2 compared with rest (step B positivity), abnormal LVCR (step C positivity), abnormal CFVR (step D positivity), and abnormal HRR (step E positivity of ABCDE protocol) showed a gradient being least frequent in group I and most frequent in group IV (Figure 2).

OUTCOME DATA RESULTS. During a median follow-up of 15.2 months (interquartile range: 12 to 20 months) there were 38 deaths and 28 nonfatal myocardial infarctions in 64 patients. Event rate was lowest in patients with absent peak B-lines (Group I). Increasing values of peak B-lines were associated with progressively worse event-free survival in the patients with severe peak B-lines (Figure 3).

At multivariable analysis, severe stress B-lines (hazard ratio [HR]: 3.544; 95% confidence interval [CI]: 1.466 to 8.687; p = 0.006), abnormal HRR (HR: 2.276; 95% CI: 1.215 to 4.262; p = 0.010), abnormal CFVR (HR: 2.178; 95% CI: 1.059 to 4.479; p = 0.034), and age (HR: 1.031; 95% CI: 1.002 to 1.062; p = 0.037) were independent predictors of death and nonfatal myocardial infarction (Table 2). Revascularization was nonsignificant even when considered as a time-varying covariate (p = 0.147). At incremental analysis, global chi-square of clinical model for the prediction of hard events increased from 38.79 (p < 0.001) to 51.86 (p < 0.001) with the addition of stress B-lines, and risk reclassification was also significantly improved with net reclassification index: 0.21 (95% CI: 0.01 to 0.42; p = 0.049).

TABLE 2 Univariate and Multivariate Predictors of Death and Nonfatal Myocardial Infarction

	Univariate Analysis	
	HR (95% CI)	**p Value**
Age, yrs	1.038 (1.014–1.063)	**0.002**
Male	0.689 (0.402–1.185)	**0.179**
LV ejection fraction at rest, %	1.037 (1.017–1.056)	**<0.001**
Previous PCI or CABG	1.681 (0.964–2.932)	**0.067**
Stress-induced RWMA	2.344 (1.367–4.022)	**0.002**
Severe stress B-lines	8.271 (4.171–16.398)	**<0.001**
Abnormal LVCR	1.651 (1.004–2.716)	**0.048**
Abnormal CFVR	3.697 (2.073–6.592)	**<0.001**
Abnormal HRR	2.960 (1.750–5.005)	**<0.001**

	Multivariate Analysis			
	Model 1		**Model 2**	
	HR (95% CI)	**p Value**	**HR (95% CI)**	**p Value**
Age, yrs	1.036 (1.007–1.065)	**0.015**	1.031 (1.002–1.062)	**0.037**
Severe stress B-lines			3.544 (1.466–8.687)	**0.006**
Abnormal CFVR	2.726 (1.501–4.951)	**0.001**	2.178 (1.059–4.479)	**0.034**
Abnormal HRR	2.331 (1.258–4.318)	**0.007**	2.276 (1.215–4.262)	**0.010**
			Continuous NRI (95% CI): 0.21 (0.01–0.42); p = 0.049	

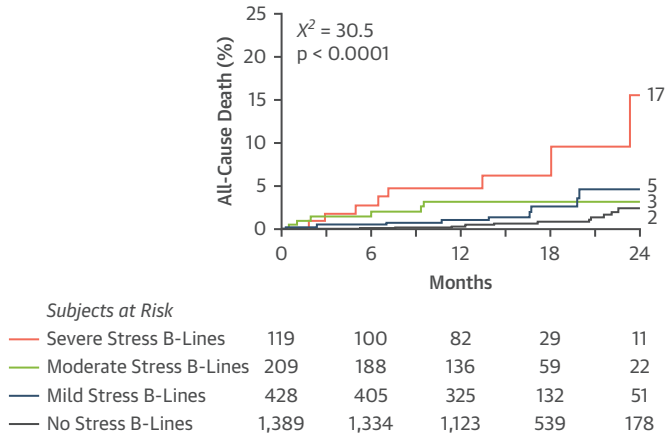
Multivariate analysis model 1, without B-lines; model 2, with B-lines. **Bold** p values indicate statistical significance.
Abbreviations as in Table 1.

When only all-cause mortality was considered, the 2-year survival was 2% in patients of group 1, 2-fold higher in patients of groups II and III, and 8-fold higher in patients of group IV (Figure 4).

DISCUSSION

Dual imaging TTE-LUS during SE is feasible and simple, with 100% success rate for B-lines and only a minimal increase in imaging time. A greater number of peak stress B-lines indicate a less benign functional profile, consisting of a worse regional left ventricular function, weaker global force-based LVCR, blunted CFVR during stress, and more frequently abnormal cardiac autonomic function mirrored by blunted heart rate reserve. Outcome is worse in patients with higher number of peak stress B-lines (Central Illustration). The likely underlying pathophysiological mechanism is the stress-induced change of pulmonary capillary wedge pressure, which is the driving force for fluid filtration and correlates with B-line number at rest (26) and during stress (9,12). In a healthy cardiovascular response, left ventricular end-diastolic pressure decreases, the pulmonary capillary wedge pressure similarly decreases, and B-lines are absent. In an unhealthy cardiovascular condition, left ventricular end-diastolic pressure increases, the pulmonary capillary

FIGURE 4 Survival Curves Based on Peak B-Line Value



Subjects at Risk					
Severe Stress B-Lines	119	100	82	29	11
Moderate Stress B-Lines	209	188	136	59	22
Mild Stress B-Lines	428	405	325	132	51
No Stress B-Lines	1,389	1,334	1,123	539	178

Survival is worse in patients with severe B-lines, and best in patients with absent B-lines at peak stress.

wedge pressure similarly increases, and B-lines may appear or worsen during exercise stress (8,9,11,12,27,28) or vasodilator stress (29). We and others have previously repeatedly shown that the presence and number of stress B-lines is related to stress E/e' during exercise SE (8-12), with an R value of 0.71 observed by Scali et al. (9) in 103 patients with HF and depressed EF.

COMPARISON WITH PREVIOUS STUDIES. The 100% feasibility is consistent with reports from our group and others (9,10,11,12,22). It has been previously shown that B-lines can appear or increment during exercise or pharmacological stress in patients with known or suspected CAD and/or HF (12). In patients with HF and reduced EF, the number of peak stress B-lines is tightly correlated with indexes of functional severity such as peak oxygen consumption ($R = -0.90$) or resting cardiac natriuretic peptide values ($R = 0.88$) (9). The present study corroborates previous findings and shows that the presence and severity of peak stress B-lines elicited with any form of physical or pharmacological stress is associated with greater functional impairment and worse outcome in patients with CAD and/or HF.

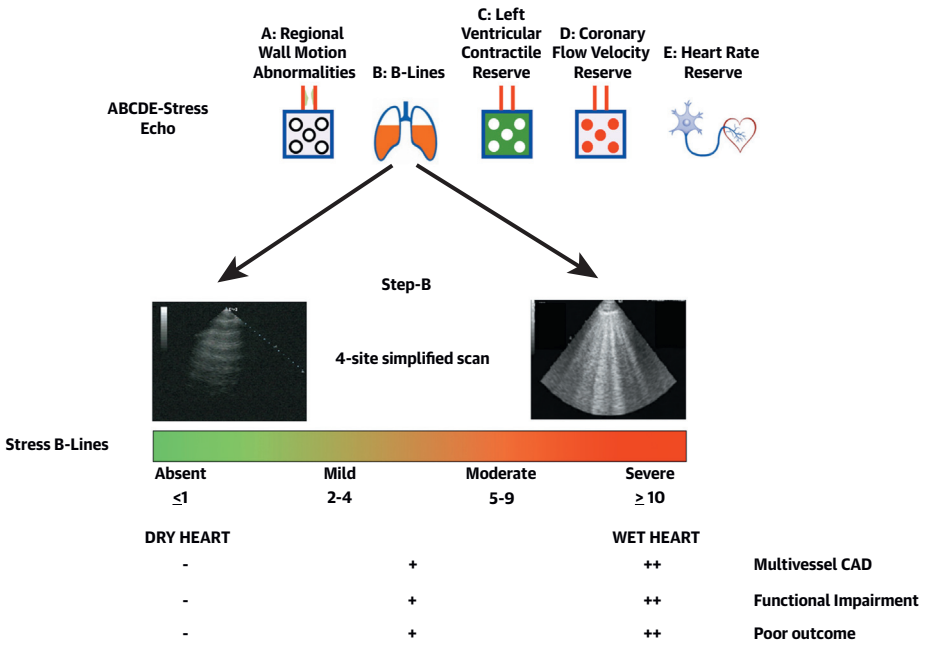
CLINICAL IMPLICATIONS. The present study underlines the importance of identifying and quantifying B-lines by LUS, both at rest and during stress. The same resting pattern is associated with a wide spectrum of stress responses, with heterogeneous functional and coronary anatomic correlates. The combination of TTE and LUS with identification of different dynamic LUS patterns expands the spectrum of prognostic stratification achieved by rest B-lines and SE without B-lines. In addition, stress B-lines might have a role in refining therapy in heart failure. A rest B-line–driven therapy of diuretic therapy has been shown to be highly effective in reducing hospital readmissions in patients with heart failure (7). This personalized approach with targeted therapy might be further refined with dynamic assessment of B-lines during stress, because patients without resting B-lines may develop pulmonary congestion during stress, and patients with resting B-lines may improve during stress.

LUS focused on B-lines is now incorporated in the standard ABCDE protocol, with step A for Asynergy and regional wall motion abnormalities, step B for B-lines, step C for left ventricular Contractile reserve and step D for Doppler-based CFVR (14,18). Step E is imaging-independent, and provides useful information on cardiac autonomic dysfunction independent and complementary to the other steps (22). SE can take the most from its unsurpassed versatility (30) overcoming the limitations on an approach based only on RWMA, and in the ABCDE format, provide a comprehensive view of different pathophysiological and prognostic vulnerabilities of the patient with CAD and/or HF (31).

STUDY LIMITATIONS. We selected a consecutive population of patients arriving to the SE laboratory with known or suspected CAD and/or HF, and with the whole spectrum of underlying resting left ventricular function, from normal to severely reduced. The substantial heterogeneity of enrolled patients is likely to reflect the variety of patients met in real-world conditions. SE is safe and indicated not only in chest pain, but also in patients with dyspnea as chief complaint and in patients with systolic or diastolic left ventricular dysfunction at rest with any degree of resting left ventricular function (preserved or reduced) (15,16,17,29).

For B-line assessment, we used a 4-site simplified scan instead of the 28-region approach adopted in previous studies (9). In fact, adding points does not proportionally increase the sensitivity and accuracy, because lung water accumulation during stress follows a predictable spatial pattern with wet spots preferentially aligned with the third intercostal space. There is an excellent linear correlation between 28- and 4-site scan results during stress ($R^2 = 0.916$), and the sensitivity of 100% of 28-site scan decreases only marginally to 93.5% with 4-site scan (20). This finding has 2 key implications for lung SE. First, the 4-site scan during exercise is the best trade-off for SE, when there is little time available (13). Second, there is no significant loss

CENTRAL ILLUSTRATION **ABCDE Stress Echo: Focus on B Step**



Scali, M.C. et al. J Am Coll Cardiol Img. 2020;13(10):2085–95.

(Top) The 5 pathophysiological targets of ABCDE-SE: epicardial coronary artery stenosis (step A, with regional wall motion abnormalities); lung water (step B, with B-lines); myocardial function (step C, with left ventricular end-systolic volume); small vessels (step D, with coronary flow velocity reserve); and cardiac autonomic balance (step E, with heart rate reserve). **(Bottom)** Zoom on B-step. Stress B-lines can range from absent to mild, moderate, or severe. More stress B-lines correspond to more advanced coronary anatomic disease, more profound left ventricular functional impairment, and worse prognostic outcome. CAD = coronary artery disease.

in sensitivity and the response can be efficiently titrated, as it happened with 28-site scan (3), with adjusted cutoff values of cumulative B-line score (20).

We used a semiquantitative B-line scoring system that was previously validated versus physiological and prognostic standards (1,3,9), although the original version based on 28-site scan was here adapted to the simplified 4-site scan (20). The B-line score integrates the horizontal (number of sites with B-lines) and vertical (number of B-lines per site) dimensions of pulmonary congestion. This approach is conceptually similar to the assessment of inducible ischemia with WMSI, which integrates horizontal extent (number of involved segments) and vertical severity (hypokinesia, akinesia, or dyskinesia) of RWMA to generate a prognostically powerful peak stress score.

We pooled the data of different physical or pharmacological stress modalities. They have different mechanisms of action, but similar accuracy and prognostic value, and are used interchangeably in most laboratories to provide a flexible and versatile approach to all patients (16). The final common hemodynamic pathway for all stresses increasing B-lines is the increase in left ventricular end-diastolic pressure and the increase in pulmonary wedge pressure, due for instance to ischemia or diastolic dysfunction, mitral insufficiency, or afterload mismatch (12). As data mature with larger sample sizes and longer follow-up, it will be possible to make a separate analysis for different conditions (CAD vs. HF) and different stresses (exercise vs. pharmacological). Different stressors showed similar patterns of stress B-lines, with severe peak stress B-lines detectable in 6% of patients during exercise, 5% with dobutamine, and 4% with vasodilators (Table 1).

Coronary angiography was performed in a subgroup of 980 patients, and showed that stress severe B-lines pattern was associated with more extensive disease compared with absent, mild, or moderate B-line patterns (Table 1). This is an additional biomarker of a more advanced disease associated with peak B-lines, but certainly lung water estimate is a poor predictor of CAD. B-lines at rest or after stress are not—and cannot be conceptually—a diagnostic

marker of coronary anatomy, but rather a useful parameter for risk stratification and functional characterization of the patient.

Images were interpreted in real time at bedside or soon after the study on stored video-clips. There was no temporal blinding to the time point. This is the only feasible modality in a real-world setting, with the operator interpreting and reporting an exam with 4 variables (wall motion, B-lines, CFVR and LVCR) and a very limited time slot in clinically oriented environments.

Images were interpreted in real time at bedside or soon after the study on stored video clips by certified readers from recruiting center who had passed the quality control procedures (22). The peripheral reading of recruiting centers was entered in the databank, as required for an effectiveness study evaluating the technique when deployed in the clinical arena.

Results were accessible to the referring physician, but B-line results are unlikely to have affected subsequent decision-making because no evidence is available to date to support a B-line-driven change in management.

CONCLUSIONS

TTE can be easily complemented with LUS at rest and during stress to assess dynamic changes in interstitial pulmonary congestion through B-lines, associated with greater functional impairment. Severe stress B-lines portend a worse outcome.

ACKNOWLEDGMENT Dr. Maurizio Galderisi passed away on March 27, 2020, from COVID-19. For all of us, he was an inspiring colleague and an enthusiastic leader. For anyone who knew him personally, he was a real and rare gentleman with a unique kind touch. For Eugenio, Quirino, Eduardo, Paolo, Giovanni, Rodolfo, Fausto, Tonino, Maria Chiara and many others, he was a personal friend always available in good and bad times. Thank you, Maurizio, our gentle giant. We will miss you.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The use of ABCDE stress echocardiography protocol is feasible with high success rate and allows simultaneous insight into ischemia (step A), pulmonary congestion (step B), contractile reserve (step C), coronary microvascular function (step D) and cardiac autonomic reserve (step E). In particular, step B (the number of B-lines at lung ultrasound) proved robust and able to stratify outcome independently and incrementally from wall motion during SE.

TRANSLATIONAL OUTLOOK: B-lines are in principle amenable to quantification and easy to incorporate in ABCDE-artificial intelligence stress echo, so that rest and stress echocardiography + lung ultrasound + ECG can be established as the quantitative, unsupervised, and objective stress test assessing the many vulnerabilities of the patient that extend well beyond and above epicardial coronary artery stenosis.

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KEY WORDS coronary artery disease, heart failure, lung ultrasound, stress echocardiography