

The Added Value of Exercise Stress Echocardiography in Patients With Heart Failure



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Doppler echocardiography can provide reliable and repeatable measures of cardiac index (CI), whereas lung ultrasound (LUS) represents a quantitative approach to assess pulmonary congestion. We tested the hypothesis that simultaneous assessment of CI and LUS during exercise stress echocardiography (ESE) may define heart failure (HF) outpatients with different risk of adverse outcome. Standard transthoracic echocardiography and LUS (B-lines) evaluation were assessed during semisupine ESE. CI and B-lines were measured at baseline and peak exercise. Resting plasma B-type natriuretic peptide levels were also evaluated. We enrolled 105 HF patients (87 males; age 62 ± 11 years; New York Heart Association class I to III) with reduced left ventricular ejection fraction ($30 \pm 7\%$). Patients were classified into 4 profiles: (1) peak CI ≥ 4.0 l/min/m² and peak B-lines < 15 (no evidence of congestion or hypoperfusion, $n = 47$); (2) peak CI ≥ 4.0 l/min/m² and peak B-lines ≥ 15 (congestion with adequate perfusion, $n = 23$); (3) peak CI < 4.0 l/min/m² and peak B-lines < 15 (hypoperfusion without congestion, $n = 13$); and (4) peak CI < 4.0 l/min/m² and peak B-lines ≥ 15 (congestion and hypoperfusion, $n = 22$). There were 21 cardiovascular deaths and 18 hospitalizations for worsening HF during a median follow-up of 29 months. Multivariate predictors of the combined end point were peak hemodynamic profiles (hazard ratio [HR] 1.62, 95% confidence interval [CI] 1.19 to 2.21; $p = 0.002$), B-type natriuretic peptide (HR 1.00, 95% CI 1.00 to 1.01; $p = 0.001$), and rest E/e' (HR 1.09, 95% CI 1.03 to 1.15; $p = 0.002$). Survival analysis showed a worse survival in patients with ESE-derived D profile, followed by patients with C, B, and A profile (log-rank: chi-square = 40.5; $p < 0.0001$). In conclusion, dual evaluation of CI and LUS during ESE is useful for risk stratification of HF patients with reduced ejection fraction. Evidence of pulmonary congestion and low CI at peak ESE identifies a subgroup with a very high risk of adverse outcome. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:1470–1477)

The hemodynamic assessment of patients with heart failure (HF) is a fundamental strength of echocardiography.¹ Echo-directed categorization of HF patients according to hemodynamic profiles can provide information that reflects the patient's fluid status and tissue perfusion. Nevertheless, detection of the early features of decompensation in stabilized chronic HF may be challenging, even for skilled clinicians.

In ambulatory HF patients, exercise stress echocardiography (ESE) may add hemodynamic information that can allow us to classify patients into hemodynamic categories with different risk of adverse outcome. Doppler echocardiography can provide reliable and repeatable measures of cardiac output (CO).² Lung ultrasound (LUS) represents a simple, semiquantitative approach to the assessment of pulmonary congestion in terms of B-lines.^{3,4} As a result, worsening of B-lines and the inability of the heart to increase CO and blood pressure during exercise may be utilized as markers of vulnerability to future episodes of decompensated HF and to assess the risk of death. Our study tested

the hypothesis that simultaneous ESE assessment of cardiac index (CI) and pulmonary congestion by LUS (B-lines) is valuable for risk stratification of HF outpatients.

Methods

We prospectively enrolled 105 consecutive patients between 2014 and 2018. The study was approved by the local institutional review board and was conducted by the revised Declaration of Helsinki. All patients gave written informed consent. The inclusion criteria were: diagnosis of HF (New York Heart Association, NYHA I to III) with reduced left ventricular (LV) function (LV ejection fraction, $EF \leq 40\%$) according to the current guidelines.⁵ The study patients were clinically stable and under oral treatment. Exclusion criteria were: acute coronary syndromes/myocardial revascularization procedures in the previous 3 months, HF secondary to more than moderate degenerative valvular heart disease, peripheral artery disease limiting the capability of performing an exercise stress test, prognosis-limiting concomitant diseases. Of the 116 patients initially selected for the study, 11 were excluded for inability to perform the exercise ($n = 7$) or poor image quality during the exercise ($n = 4$).

All patients underwent a comprehensive echocardiographic and Doppler examination (iE-33, Philips, Medical Systems, Andover, Massachusetts). LV volumes and systo-

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diastolic function parameters were measured according to current recommendations.⁶ Stroke volume (SV) was calculated as LV velocity time integral (cm) times LV outflow tract (LVOT) area and CO as SV times heart rate.⁷ CI was calculated as CO divided by body surface area. All measures were averaged over 3 consecutive cycles or 5 if in atrial fibrillation. Pulmonary capillary wedge pressure (PCWP) was estimated from the ratio of mitral E-peak velocity and averaged e' velocity (E/e'). The degree of mitral regurgitation was semiquantified from absent to severe (score 0 to 3), with an integrated assessment of color flow regurgitant jet, proximal isovelocity surface area (when available), and vena contracta as per recommendations.⁸ Tricuspid annular plane systolic excursion and estimated systolic pulmonary artery pressure were evaluated.⁶

Examinations were performed with patients in the semisupine position, both at rest and peak or immediately after exercise, to assess the presence of B-lines at LUS examination. B-lines were defined as bilateral sonographic reverberation artifacts that originate from water-thickened pulmonary interlobular septa. We analyzed the anterior and lateral hemithoraces, scanning along the parasternal, midclavicular, anterior axillary and midaxillary lines, as previously described.⁹ A total of 28 chest sites were scanned, and the total number of B-lines was recorded as the cumulative B-lines score.

According to Forrester classification, patients were classified into 4 profiles: (1) CI ≥ 2.2 l/min/m² and B lines <15 (no evidence of congestion or hypoperfusion); (2), CI ≥ 2.2 l/min/m² and B lines ≥ 15 (congestion with adequate perfusion); (3), CI <2.2 l/min/m² and B lines <15 (hypoperfusion without congestion); and (4), CI <2.2 l/min/m² and B lines ≥ 15 (congestion and hypoperfusion).¹⁰

All patients underwent semisupine bicycle ESE according to International Recommendations.¹¹ The graded bicycle was performed starting at an initial workload of 20 Watts (W) and lasting for 2 minutes; the workload increased stepwise by 10 W at 2-minute intervals. ECG and blood pressure were continuously monitored. The maximum rate-pressure product (heart rate times systolic blood pressure) and exercise time (in minutes) were also evaluated. Echocardiographic imaging was performed using conventional 2-D echocardiography. At the end of the exercise test, peak CO and peak CI were derived. Echocardiographic images were analyzed by 2 cardiologists (NRP, IF), unaware of the identity of the patient. Again, we identified 4 hemodynamic profiles at peak exercise, after running a receiver operating characteristic (ROC) analysis to identify optimal cutoff of peak CI and peak B-lines for predicting composite end point. For all patients included in the study, we had reproducible and repeatable measures of CI and LUS baseline and at peak exercise.

Venous blood samples were collected before ESE. B-type natriuretic peptide (BNP) concentrations were processed by Alere Triage BNP Test for Beckman Coulter Immunoassay Systems (Alere San Diego Inc., San Diego, California).

For survival analysis, observation began on the date of the index exercise stress echocardiogram. Follow-up data were obtained by the review of the patient's hospital records, by personal communications with the patient's

physician or telephone interviews. Death certificates were obtained in case of need. We considered a combined end point of cardiovascular death and hospitalization for worsening HF.

Continuous variables were expressed as mean \pm standard deviation or median and interquartile ranges, when appropriate. Categorical variables are shown as frequency. Continuous variables were compared using parametric and nonparametric tests where necessary. Nonparametric tests compared categorical variables. Cox proportional hazard regression analysis was used to identify predictors of outcome in the time-dependent analysis. Demographic, clinical, and echo variables were evaluated for the prediction of end point in a univariate Cox proportional hazard model (95% confidence intervals). ROC curves were generated to define the best cut-off values for outcome prediction, including sensitivity, specificity, and area under the curve (AUC). The cumulative survival probability was explored using the Kaplan-Meier method, followed by the chi-squared log-rank test.

We evaluated the intra- and interobserver (IF and NRP in a blinded manner) reproducibility for CI and LUS at rest and peak exercise in 20 randomly selected patients by the intraclass correlation coefficient (ICC) with its 95% CIs. Concordance between 2 raters was assessed using the Kappa statistic. The probability level was set at $p < 0.05$ for all the data examined. Data were analyzed using SPSS software (version 23.0; SPSS, Inc., Chicago, Illinois).

Results

Mean age of the study population was 61.6 ± 11.4 years (82.9% males). Most patients were in NYHA class I to II (76.2%), with a mean LV EF of $30.3 \pm 7\%$. Patient characteristics of the overall population at rest and peak exercise are summarised in [Table 1](#).

As far as reproducibilities of echo-derived hemodynamic measures are concerned, we obtained good intraobserver (all ICCs > 0.9) and interobserver variabilities (all ICCs > 0.9) of either CI or LUS assessment of pulmonary congestion. Concordance between 2 raters for LUS assessment using the Kappa statistic was 0.97.

Applying Forrester classification at rest, 75 patients (71.4%) were classified as profile A, 11 (10.5%) as profile B, 12 (11.4%) as profile C, and 7 (6.7%) as profile D. Then, we determined the best value for outcome prediction at ROC analysis of peak CI (cutoff: 4 l/min/m², 69% sensitivity, 83% specificity, and AUC 0.794; $p < 0.0001$) and peak B-lines at LUS examination (cutoff: 15, 72% sensitivity, 74% specificity, and AUC 0.746; $p < 0.0001$). Then, patients were divided into 4 groups according to peak hemodynamic profiles ([Figure 1](#)): (1) peak CI >4.0 l/min/m² and peak B-lines <15 (no congestion or hypoperfusion, $n = 47$); (2) peak CI >4.0 l/min/m² and peak B-lines ≥ 15 (congestion with normal perfusion, $n = 23$); (3) peak CI ≤ 4.0 l/min/m² and peak B-lines <15 (hypoperfusion without congestion, $n = 13$); and (4) peak CI ≤ 4.0 l/min/m² and peak ESE-B lines ≥ 15 (congestion and hypoperfusion, $n = 22$). Patient characteristics according to peak hemodynamic profiles are displayed in [Table 2](#). Peak profile D represented the most compromised hemodynamic scenario and

Table 1
Characteristics of the study population

Variable	Overall population (n = 105)
Age (y)	61.6 ± 11.4
Gender male	87 (83%)
Body mass index (kg/m ²)	25.2 (20.2–34.8)
Body surface area (m ²)	1.9 ± 0.2
Ischemic heart disease	46 (44%)
Diabetes mellitus	20 (19%)
Arterial hypertension	54 (51%)
History of heart failure	59 (56%)
Estimated glomerular filtration rate (ml/min/1.73m ²)	74.3 (62.5–84.3)
Chronic kidney disease*	28 (27%)
New York Heart Association I	38 (36%)
New York Heart Association II	42 (40%)
New York Heart Association III	25 (24%)
Brain natriuretic peptide (pg/ml)	175.5 (53–464)
Implantable cardioverter defibrillator	46 (44%)
Cardiac resynchronization therapy	30 (29%)
Exercise time, min	6.2 ± 2.8
Rest systolic arterial pressure (mm Hg)	120 (107–132)
Rest Diastolic Arterial Pressure (mm Hg)	78 (70–80.7)
Rest Heart Rate (beats per minute)	79.1 ± 13.3
Peak Systolic Arterial Pressure (mm Hg)	155 (140–183.5)
Peak Diastolic Arterial Pressure (mm Hg)	90 (80–100)
Peak heart rate (beats per min)	126.5 ± 20.2
Rest left ventricular end-diastolic volume index (ml/m ²)	100 (85–119)
Rest left ventricular end-systolic volume index (ml/m ²)	68.6 (58–88)
Rest cardiac output (l/min)	4.3 (3.6–5)
Rest cardiac index (l/min/m ²)	2.3 ± 0.5
Rest left ventricular ejection fraction (%)	30.3 ± 7
Rest tricuspid annular plane systolic excursion (mm)	17.5 ± 3.3
Rest systolic pulmonary artery pressure (mm Hg)	42 ± 11
Peak left ventricular end-diastolic volume index (ml/m ²)	88.7 (75–107.6)
Peak left ventricular end-systolic volume index (ml/m ²)	51.6 (34–75.7)
Peak cardiac output (l/min)	8.3 (6.6–10.4)
Peak cardiac index (l/min/m ²)	4.5 ± 1.5
Peak left ventricular ejection fraction (%)	42 ± 19.1
Delta left ventricular ejection fraction (%)	7.1 (1–21)
Peak tricuspid annular plane systolic excursion (mm)	23 ± 4
Peak systolic pulmonary artery pressure (mm Hg)	48 ± 13
Rest mitral regurgitation	31 (29.5%)
Peak mitral regurgitation	35 (33%)
Rest mitral regurgitation vena contracta (mm)	3 (2-4)
Peak mitral regurgitation vena contracta (mm)	4 (2-5)
Rest E/e'	12 (9–14.7)
Rest left atrial volume indexed for body surface area (ml/m ²)	38.1 (31.2–43.3)
Rest B-lines	0 (0–26)
Peak B-lines	10 (0–28.5)
Digoxin	28 (27%)
Beta-blockers	76 (72%)
ACE-inhibitors	93 (89%)
Diuretics	82 (78%)
Mineral-corticoid receptor antagonist	63 (60%)

Values are mean ± SD, median (5 to 95 percentiles) and n (%).

* Chronic kidney disease is defined as eGFR < 60 ml/min/1.73 m².

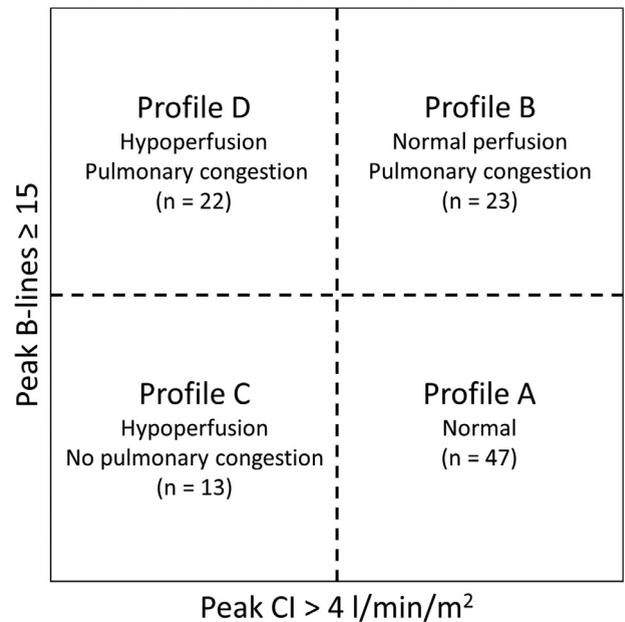


Figure 1. Four-square diagram for hemodynamic assessment of patients with heart failure using echocardiography-derived variables measured at peak exercise (modified Forrester classification). CI = cardiac index.

was significantly associated with worse NYHA class, renal dysfunction, higher BNP circulating levels, and presented the more advanced impairment of baseline echocardiographic measures, that is, greater LV volumes, lower EF, and higher E/e', compared with the other profiles recorded at peak exercise.

Over a mean follow-up of 29 ± 17 months, a total of 39 events occurred: 21 cardiovascular deaths and 18 hospitalizations for worsening HF. Table 3 shows the results of the Cox regression univariate analysis for predicting combined end point. At multivariate analysis, BNP (HR: 1.00, 95% CI 1.00 to 1.01; p = 0.0001), resting E/e' (HR 1.09, 95% CI 1.03 to 1.15; p = 0.002), and peak hemodynamic profiles (HR 1.62, 95% CI 1.19 to 2.21; p = 0.002) emerged as powerful predictors of the composite end point (Table 3).

We performed the Kaplan-Meier event-free survival analysis to stratify patients according to peak CI (Figure 2A) and peak B-lines (Figure 2B) using previously ROC-validated cutoffs. Peak hypoperfusion and peak pulmonary congestion were associated with the adverse outcome (chi-squared: 36.4, p < 0.0001 and chi-squared log-rank 15.6, p = 0.0001, respectively). Considering resting and peak hemodynamic profiles, survival curves demonstrated a significantly worse prognosis from profile A to profile D, with higher statistical significance using peak profiles (chi-square log-rank: 35.4, p < 0.0001 and chi-square log-rank: 40.5, p < 0.0001, Figure 3, respectively). Finally, a logistic regression analysis was carried out to assess whether patients' stratification by peak hemodynamic profiles was additive upon demographic, clinical, and instrumental findings, including resting hemodynamic profiles, for predicting the combined end point. The base model included older age (>65 years old), male gender, diabetes mellitus, advanced chronic kidney disease (stage ≥ 3), coronary artery disease, history of HF and NYHA class III.

Table 2
Characteristics of stress hemodynamic profiles

Variable	Profile A (n = 47)	Profile B (n = 23)	Profile C (n = 13)	Profile D (n = 22)	p Value
Age (y)	60.2 ± 10.7	65.5 ± 13	62.7 ± 11.7	59.4 ± 10.3	ns
Gender male	39 (83%)	17 (74%)	12 (92%)	19 (86%)	ns
Body mass index (kg/m ²)	25.1 (24.2–28)	25.3 (24.5–27.9)	24.7 (22.1–27.2)	23.4 (22.1–26.5)	ns
Body surface area (m ²)	1.9 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	ns
Ischemic heart disease	19 (40%)	8 (35%)	6 (46%)	13 (59%)	ns
Diabetes mellitus	6 (13%)	7 (30%)	3 (23%)	4 (18%)	ns
Arterial hypertension	28 (59%)	13 (56%)	7 (54%)	6 (27%)	ns
History of heart failure	25 (53%)	10 (44%)	10 (77%)	14 (64%)	ns
Estimated glomerular filtration rate (ml/min/1.73m ²)	85.7 (74–90)	75.2 (52.5–85)	70.3 (49–80)	54.3 (42.5–79)*	0.03
Chronic kidney disease*	7 (15%)	7 (30%)	4 (31%)	10 (45.5%)	0.007
New York Heart Association I	28 (60%)	7 (30%)	2 (15%)	1 (4.5%)	<0.0001
New York Heart Association II	14 (29%)	9 (39%)	8 (61%)	11 (50%)	ns
New York Heart Association III	5 (11%)	7 (30%)	3 (23%)	10 (45.5%)	ns
Brain natriuretic peptide (pg/mL)	101 (35–199)	120 (51–277)	403 (204–742)	762 (322–1344)*#	<0.0001
Implantable cardioverter defibrillator	12 (25.5%)	10 (43.5%)	9 (69%)	15 (68%)	0.002
Cardiac resynchronization therapy	7 (15%)	9 (39%)	5 (38.5%)	9 (41%)	0.01
Rest systolic arterial pressure (mm Hg)	124 (110–138)	125 (114–140)	120 (97–132)	110 (100–120)*#	0.003
Rest diastolic arterial pressure (mm Hg)	80 (70–88)	78 (70–83.7)	70 (64–81)	71 (60–80)*	0.01
Rest heart rate (beats per minute)	78 ± 13	78.5 ± 14	78.4 ± 12	82.3 ± 14	ns
Peak systolic arterial pressure (mm Hg)	170 (155–190)	155 (140–190)	133 (117–155)*#	140 (130–150)*#	<0.0001
Peak diastolic arterial pressure (mm Hg)	92 (80–100)	90 (80–101)	80 (70–96)	85 (75–90)	ns
Peak heart rate (beats per minute)	133 ± 18	124 ± 16	121 ± 25	118 ± 22*	0.001
Rest left ventricular end-diastolic volume index (ml/m ²)	92 (80.7–107)	105 (87–121)	111 (85–134)*	110 (100–136)*	0.01
Rest left ventricular end-systolic ventricular index (ml/m ²)	61 (56–74)	68 (61–89)	80 (58–100)*	75 (71–95)*	0.006
Rest cardiac output (l/min)	4.5 (4–5.3)	4.6 (4.1–5.6)	3.3 (3.1–4.1)*#	3.6 (3.1–4.8)*#	<0.0001
Rest cardiac index (l/min/m ²)	2.4 ± 0.2	2.5 ± 0.4	1.9 ± 0.4*#	2.0 ± 0.7*#	<0.0001
Rest left ventricular ejection fraction (%)	34 ± 5.6	30.4 ± 6.1	26.3 ± 7.4*	24.9 ± 5.9*#	<0.0001
Rest tricuspid annular plane systolic excursion (mm)	19 ± 3	18.6 ± 2.5	18.2 ± 2.7	18 ± 2.4	ns
Rest systolic pulmonary artery pressure (mm Hg)	36 ± 9	46 ± 8	39 ± 10	48 ± 9	0.03
Peak left ventricular end-diastolic volume index (ml/m ²)	82 (72–96)	89 (75–111)	110 (84–128)*	102 (82–116)*	0.004
Peak left ventricular end-systolic volume index (ml/m ²)	40 (30–54)	51 (33–76)*	84 (51–104)*#	76 (57–95)*#	<0.0001
Peak cardiac output (l/min)	10.4 (8.5–12)	8.9 (7.9–9.3)*	6.1 (4.8–6.8)*#	5.3 (4.4–6.5)*#	<0.0001
Peak cardiac index (l/min/m ²)	5.4 ± 0.4	4.8 ± 0.3	3.1 ± 0.5*#	2.9 ± 0.6*#	<0.0001
Peak left ventricular ejection fraction (%)	50 ± 14	45.6 ± 15	25 ± 12*#	24.3 ± 9.2*#	<0.0001
Delta left ventricular ejection fraction (%)	18 (6–29)	13 (5–24)	1.5 (–1.4–3.8)*#	–1 (–6.3–3.9)*#	<0.0001
Peak tricuspid annular plane systolic excursion (mm)	23 ± 2.2	22 ± 3.1	22 ± 3.9	21 ± 3.5	ns
Mitral regurgitation†	12 (25.5%)	5 (22%)	3 (23%)	11 (50%)	ns
Rest E/e'	11 (8–12)	12 (7.6–14.7)	14 (9.7–17.5)*	13.5 (12–18)*#	0.003
Rest left atrial volume indexed (ml/m ²)	36.3 (31.1–37.2)	36.8 (32.2–38.1)	38.2 (34.1–40.8)	40.1 (37.1–43.2)	0.06
Rest B-lines	0 (0–0)	8 (5–15)*	0 (0–0)#	11 (5–20)*§	<0.0001
Peak B-lines	0 (0–3.7)	25 (15–55)*	0 (0–5)#	39 (25–70)*§	<0.0001

Values are mean ± SD, median (25 to 75 percentiles) and n (%).

* p < 0.01 vs Profile A; # p < 0.01 vs Profile B; § p < 0.01 vs Profile C.

Chronic kidney disease is defined as eGFR < 60 ml/min/1.73 m².

† at least moderate MR.

The stepwise inclusion of BNP, echocardiographic parameters, resting and peak hemodynamic profiles provided additive and significant contributions to the final model: BNP > 150 pg/ml (p < 0.001), peak LV EF < 35% and resting E/e' ≥ 13; p = 0.005), resting hemodynamic profiles (p = 0.002) and peak hemodynamic profiles (chi-square: 71.3, p = 0.003; Figure 4).

Discussion

In outpatients with HF and reduced LV EF, dual evaluation of CI and B-lines at peak exercise is useful to stratify high-risk patients. The increase in B-lines and the inability

of the heart to propel adequate CI during ESE are markers of vulnerability to worsening HF and cardiovascular death. Assessment of hemodynamic exercise profiles proved to be complementary and incremental to clinical findings and other established prognostic predictors.

The evaluation of the hemodynamic profiles can take place either invasively or noninvasively.^{12,13} Catheterization identifies 4 hemodynamic profiles that are useful to recognize whether patients are “wet or dry” based on evidence for pulmonary congestion (if PCWP > 18 mm Hg), and whether their perfusion is likely to be adequate (“warm”) or critically reduced (“cold”, if CI ≤ 2.2 l/min/m²).¹⁴ Indeed, both invasive and noninvasive evaluation of

Table 3
Univariate and multivariate predictors of the combined end point

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.00 (0.98–1.03)	ns		
Male gender	1.54 (0.65–3.68)	ns		
Diabetes mellitus	2.34 (1.19–4.61)	0.01		
Estimated glomerular filtration rate (ml/min/1.73 m ²)	1.75 (0.92–3.36)	ns		
Coronary artery disease	1.09 (0.58–2.08)	ns		
Hypertension	0.57 (0.30–1.10)	ns		
Previous HF hospitalization	1.43 (0.76–2.70)	ns		
New York Heart Association Class	2.01 (1.32–3.06)	0.001		
Brain natriuretic peptide (pg/ml)	1.00 (1.00–1.01)	<0.0001	1.00 (1.00–1.01)	0.001
Implantable cardioverter defibrillator	3.43 (1.78–6.60)	0.0003		
Cardiac resynchronization therapy	2.87(1.52–5.41)	0.001		
Rest left ventricular ejection fraction (%)	0.86 (0.81–0.91)	<0.0001		
Stress left ventricular ejection fraction (%)	0.94 (0.91–0.96)	<0.0001	0.99 (0.91–1.07)	ns
Δ Left ventricular ejection fraction (%)	0.95 (0.93–0.98)	0.0006		
Rest tricuspid annular plane systolic excursion (mm)	0.97 (1.23–0.07)	ns		
Peak tricuspid annular plane systolic excursion (mm)	1.01 (0.99–1.21)	ns		
Rest systolic pulmonary arterial pressure (mm Hg)	1.23 (0.92–1.39)	ns		
Mitral regurgitation	1.13 (0.58–2.19)	ns		
Rest E/e'	1.11 (1.06–1.16)	<0.001	1.09 (1.03–1.15)	0.002
Rest cardiac index (L/min/m ²)	0.50 (0.30–0.82)	0.007		
Stress cardiac index (L/min/m ²)	0.45 (0.33–0.61)	<0.0001		
Rest B-lines	1.02 (1.01–1.07)	0.006		
Stress B-lines	1.04 (1.01–1.03)	0.005		
Rest hemodynamic profiles	2.08 (1.60–2.70)	<0.0001		
Stress hemodynamic profiles	2.13 (1.63–2.76)	<0.0001	1.62 (1.19–2.21)	0.002

hemodynamic profiles can predict survival, with increased mortality in the event of pulmonary congestion and an even worse outcome when hypoperfusion coexists.^{11,15} HF exacerbations are frequently related to a progressive rise in PCWP that precipitates pulmonary congestion. Nevertheless, most patients with chronic HF are clinically stable at rest, with no signs of extravascular lung water accumulation. In many of them, however, the exercise may increase PCWP, and the rise of the filling pressure during exertion can be the driver toward lung congestion. Exercise stress testing may trigger

abnormalities that are not present at rest or worsen any resting abnormality, such as mitral regurgitation severity.¹⁶ An elevation of PCWP over 25 mm Hg induces the water filtration from the vascular to the extravascular compartment, exceeding the attractive force of the oncotic pressure and resulting in a net increase of extravascular lung water.¹⁷ Assessment of peak exercise stroke indexes can be useful to provide insights into the course of the disease, the pathophysiology of the transition from stable HF to decompensated HF and the outcome.^{18,19} In chronic stable HF, resting blood

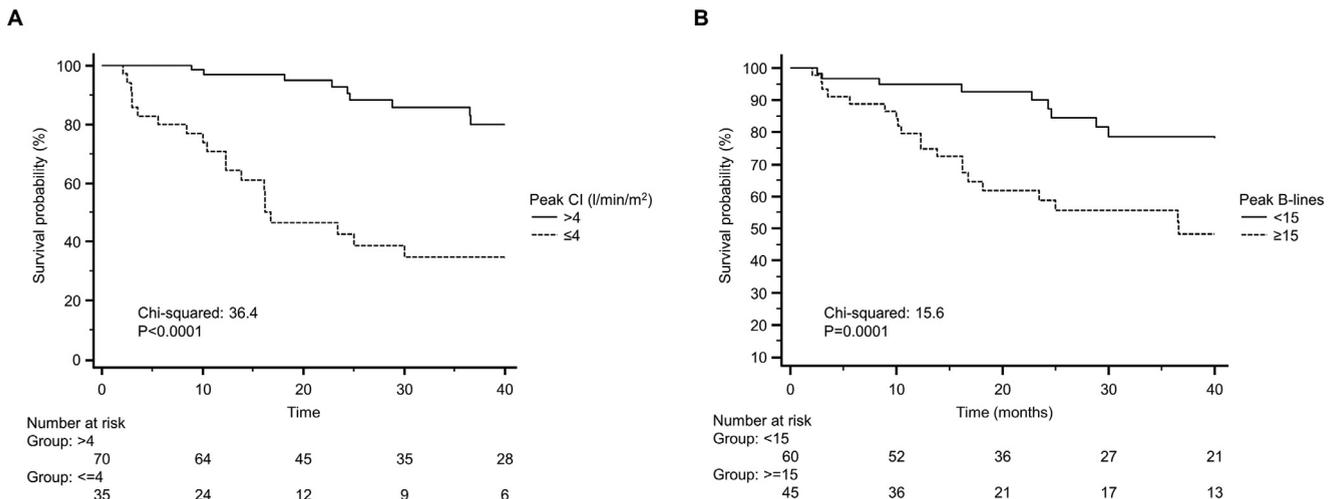


Figure 2. Kaplan-Meier survival curves for the composite end point (cardiovascular death and hospitalization for worsening heart failure) according to the presence of hypoperfusion at peak exercise (Peak CI ≤ 4 l/min/m², Panel A) and pulmonary congestion (Peak B-lines ≥ 15, Panel B). CI=cardiac index.

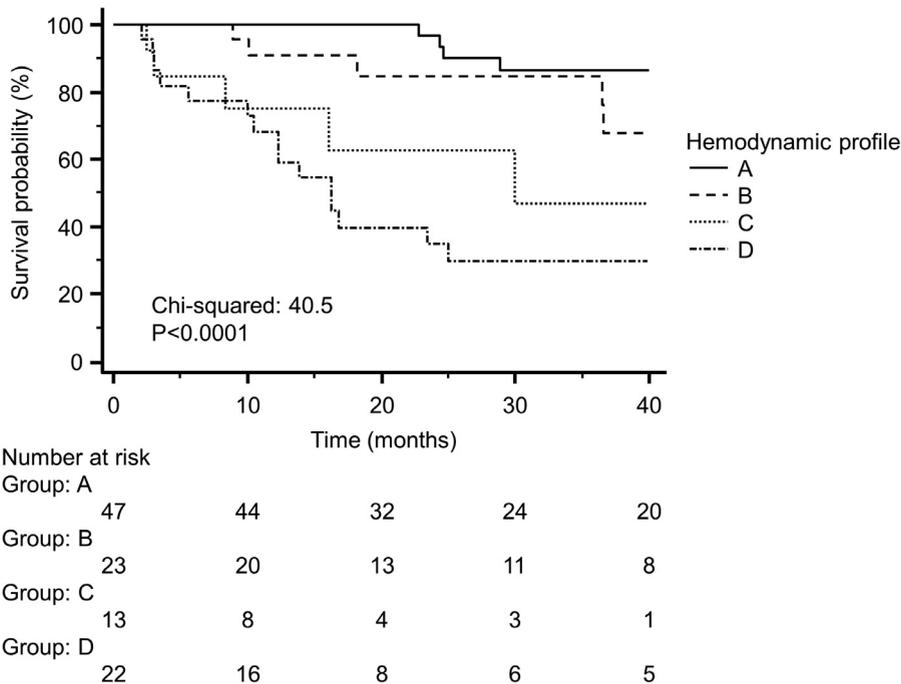


Figure 3. Kaplan-Meier survival curves (composite end point: cardiovascular death and hospitalization for worsening heart failure): patients were categorized into 4 hemodynamic profiles according to echocardiography-derived variables measured at peak exercise (cardiac index and B-lines).

flow is still within the normal range while exhibiting limited increases during the effort.

Echocardiography allows the estimation of several important hemodynamic variables at rest and throughout the exercise, including SV, CO, and LV filling pressures. Therefore, ESE has the potential to provide a comprehensive and noninvasive evaluation of the hemodynamic response to exercise. B-lines are a reliable and inexpensive

tools for the assessment of extravascular lung water in patients with HF.^{20–22} Moreover, detection of B-lines during ESE can provide a reliable, noninvasive tool for the evaluation of incipient pulmonary congestion, demonstrating a much higher prognostic significance than the presence of B-lines at rest.^{23,24}

In our study, we observed that the presence of exercise-induced B-lines >15 was associated with an increased event

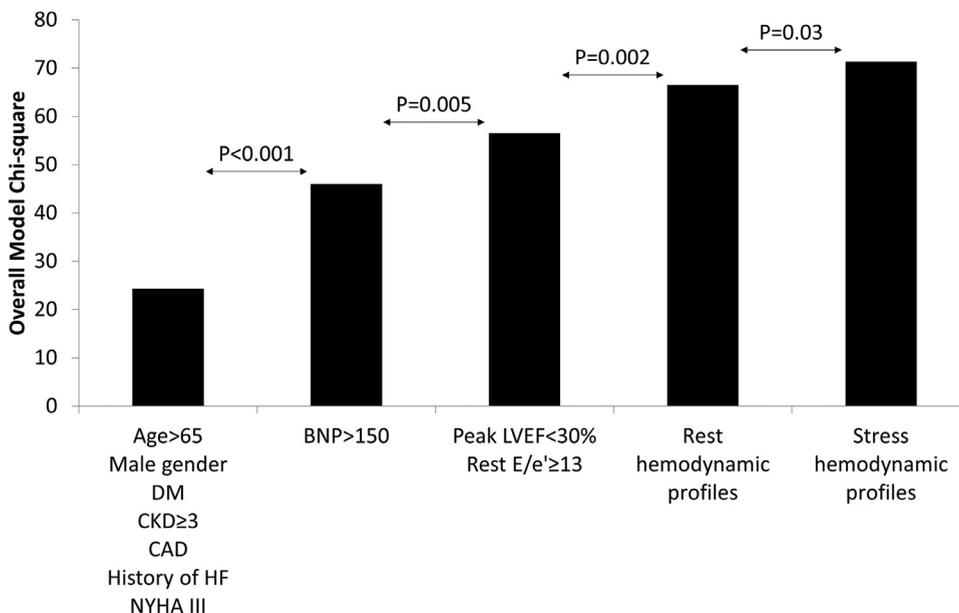


Figure 4. Incremental prognostic value of peak hemodynamic profiles for predicting the composite end point (cardiovascular death and hospitalization for worsening heart failure) over demographic and clinical parameters (step 1), brain natriuretic peptide (BNP) >150 pg/ml (step 2), echocardiographic variables (step 3), and resting hemodynamic profiles (step 4). CAD = coronary artery disease; CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; LVEF = left ventricle ejection fraction.

rate. Interestingly, the prognosis was worsened further by the coexistence of hypoperfusion and pulmonary congestion during exercise, as indicated by peak profile D (wet and cold). By contrast, peak profile A (dry and warm) described a group of well-compensated patients with an excellent overall prognosis. From these findings, it is apparent that hemodynamic profiling by dual assessment of CI and LUS during ESE can be utilized for the early identification of higher risk patients, with a latent adverse hemodynamic profile reflecting the evolution toward overt congestion and low perfusion. In particular, assessment of the ESE-derived hemodynamic profiles seems helpful to guide the management of HF patients in an outpatient setting.

Some study limitations should be acknowledged. The echocardiographic estimation of SV depends on accurate assessment of LVOT, errors of which are squared during cross-sectional area calculations, luckily, dimensions of the LVOT are highly correlated with body surface area, and this may enable us to achieve better results in LVOT measurements.⁷ Other limitations include that detection of B-lines does not necessarily imply their cardiogenic origin²⁵ and that sometimes the appearance of B-lines depends on other factors which prevent fluid accumulation, like oncotic plasma pressure, lymphatic drainage, and perivascular fibrotic changes of pulmonary vasculature.²⁶ Finally, peak systolic pulmonary artery pressure and peak E/e' were available only in a subset of patients, thus precluding our ability to relate them to hemodynamic profiling and clinical outcome, however, the latter are only surrogate estimates of pulmonary congestion, while B-lines more likely reflect the "wet" status, that is, the transfer of fluid into the lung tissue.

In conclusion, ESE evaluation is well suited for dual assessment of CI and LUS and the acquisition of exercise hemodynamic profiles that portend a prognostic significance and may be useful for the early recognition of impending decompensation that is crucial to guide management since prompt initiation of evidence-based treatment can prevent or slow down further progression.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2019.02.008>.

- Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, Ha JW, Kane GC, Kreger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Hear J Cardiovasc Imaging* 2016;17:1191–1229.
- Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler Quantification Task Force of the N, Standards Committee of the American Society of E. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167–184.
- Agricola E, Picano E, Oppizzi M, Pisani M, Meris A, Fragasso G, Margonato A. Assessment of stress-induced pulmonary interstitial edema by chest ultrasound during exercise echocardiography and its correlation with left ventricular function. *J Am Soc Echocardiogr* 2006;19:457–463.
- Picano E, Pellikka PA. Ultrasound of extravascular lung water: a new standard for pulmonary congestion. *Eur Heart J* 2016;37:2097–2104.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meier P van der. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129–2200.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for Cardiac Chamber Quantification by echocardiography in adults (2015). *Eur Heart J Cardiovasc Imaging* 2015;28:1–39.
- Dimi FL, Mele D, Conti U, Ballo P, Citro R, Menichetti F, Marzilli M. Peak power output to left ventricular mass: an index to predict ventricular pumping performance and morbidity in advanced heart failure. *J Am Soc Echocardiogr* 2010;23:1259–1265.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd 3rd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314.
- Scali MC, Zagatina A, Simova I, Zhuravskaya N, Ciampi Q, Paterni M, Marzilli M, Carpeggiani C, Picano E. on behalf of the Stress Echo 2020 study group of the Italian Society of Cardiovascular Echography. B-lines with lung ultrasound: the optimal scan technique at rest and during stress. *Ultrasound Med Biol* 2017;43:2558–2566.
- Forrester JS, Diamond G, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 1976;295:1356–1362.
- Morley D, Brozena SC. Assessing risk by hemodynamic profile in patients awaiting cardiac transplantation. *Am J Cardiol* 1994;73:379–383.
- Fonarow GC, Stevenson LW, Walden JA, Livingston NA, Steimle AE, Hamilton MA, Moriguchi J, Tillisch JH, Woo MA. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol* 1997;30:725–732.
- Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;41:1797–1804.
- Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;261:884–888.
- Shah MR, Hasselblad V, Stinnett SS, Gheorghide M, Swedberg K, Califf RM, O'Connor CM. Hemodynamic profiles of advanced heart failure: association with clinical characteristics and long-term outcomes. *J Card Fail* 2001;7:105–113.
- Chomsky DB, Lang CC, Rayos GH, Shyr Y, Yeoh TK, Pierson RN 3rd, Davis SF, Wilson JR. Hemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. *Circulation* 1996;94:3176–3183.
- Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065–1072.
- Griffin BP, Shah PK, Ferguson J, Rubin SA. Incremental prognostic value of exercise hemodynamic variables in chronic congestive heart failure secondary to coronary artery disease or to dilated cardiomyopathy. *Am J Cardiol* 1991;67:848–853.
- Metra M, Faggiano P, D'Aloia A, Nodari S, Gualeni A, Raccagni D, Dei Cas L. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. *J Am Coll Cardiol* 1999;33:943–950.
- Gheorghide M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, Veldhuisen DJ van, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure

- Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;12:423–433.
21. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, Tritto I, Zannad F, Girerd N. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail* 2015;17:1172–1181.
 22. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. *Eur J Heart Fail* 2017;19:1154–1163.
 23. Picano E, Gargani L, Gheorghiade M. Why, when, and how to assess pulmonary congestion in heart failure: pathophysiological, clinical, and methodological implications. *Heart Fail Rev* 2009;15:63–72.
 24. Scali MC, Cortigiani L, Simionuc A, Gregori D, Marzilli M, Picano E. Exercise-induced B-lines identify worse functional and prognostic stage in heart failure patients with depressed left ventricular ejection fraction. *Eur J Heart Fail* 2017;19:1468–1478.
 25. Aras MA, Teerlink JR. Lung ultrasound: a “B-line” to the prediction of decompensated heart failure. *Eur Heart J* 2016;37:1252–1254.
 26. Gargani L. Lung ultrasound: a new tool for the cardiologist. *Cardiovasc Ultrasound* 2011;9:6.