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Background: Pulmonary hypertension (PH) is a frequent and detrimental condition. Right heart catheterization (RHC) is the gold standard to identify PH subtype (precapillary from postcapillary PH) and is key for treatment allocation. In this study, the novel echocardiographic biventricular coupling index (BCI), based on the ratio between right ventricular stroke work index and left ventricular E/E′ ratio, was tested for the discrimination of PH subtype using RHC as the comparator.

Methods: BCI was derived in 334 consecutive patients who underwent transthoracic echocardiography and RHC for all indications. BCI was then tested in a validation cohort of 1,349 patients.

Results: The accuracy of BCI to identify precapillary PH was high in the derivation cohort (area under the curve, 0.82; 95% CI, 0.78-0.88; $P < .001$; optimal cut point, 1.9). BCI identified patients with precapillary PH with high accuracy also in the validation cohort (area under the curve, 0.87 [95% CI, 0.85-0.89; $P < .001$]; subgroup with PH: area under the curve, 0.91 [95% CI, 0.89-0.93; $P < .001$]; cut point, 1.9; sensitivity, 82%; specificity, 89%; positive predictive value, 77%; negative predictive value, 92%). BCI outperformed both the D'Alto score ($Z = 3.56$; difference between areas = 0.05; 95% CI, 0.02-0.07; $P < .001$) and the echocardiographic pulmonary–to–left atrial ratio index ($Z = 2.88$; difference between areas = 0.02; 95% CI, 0.01-0.04; $P = .004$).

Conclusions: BCI is a novel, noninvasive index based on routinely available echocardiographic parameters that identifies with high accuracy patients with precapillary PH. BCI may be of value in the screening workup of patients with PH. (J Am Soc Echocardiogr 2022;35:715-26.)

Keywords: Pulmonary arterial hypertension, Biventricular coupling index, Precapillary, Right ventricular stroke work index, Tissue Doppler imaging, Right heart catheterization

Pulmonary hypertension (PH) is a common condition and is associated with poor prognosis.[1] Pulmonary vasodilators have demonstrated clinical efficacy in precapillary PH (type 1 PH),[2] but they can be detrimental in patients with postcapillary PH.[3] Therefore, the correct diagnosis according to the current classification is mandatory for the choice of the specific therapeutic strategies.[4]

Although right heart catheterization (RHC) remains the gold standard in the diagnostic workup, transthoracic echocardiography is currently part of the screening process and is increasingly used in the longitudinal follow-up of patients with PH.[5-9] Estimated systolic pulmonary artery pressure (sPAP) is recommended to define the probability of PH in symptomatic patients but does not discriminate between pre- and postcapillary PH.[4] Noninvasive echocardiographic

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Conflicts of Interest: None.

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0894-7317/$36.00

https://doi.org/10.1016/j.echo.2022.02.003

Abbreviations

AUC = Area under the curve

BCI = Biventricular coupling index

COMPERA = Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension

cPC-PH = Combined postcapillary and precapillary pulmonary hypertension

ePLAR = Echocardiographic pulmonary–to–left atrial ratio

eRVSWI = Echocardiographic right ventricular stroke work index

iPC-PH = Isolated postcapillary pulmonary hypertension

LR = Likelihood ratio

LV = Left ventricular

mPAP = Mean pulmonary artery pressure

NPV = Negative predictive value

PCWP = Pulmonary capillary wedge pressure

PH = Pulmonary hypertension

PPV = Positive predictive value

RHC = Right heart catheterization

RAP = Right atrial pressure

ROC = Receiver operating characteristic

RV = Right ventricular

RVSP = Right ventricular systolic pressure

RVSWI = Right ventricular stroke work index

sPAP = Systolic pulmonary artery pressure

SV = Stroke volume

SVi = Stroke volume index

indices have been previously proposed for the identification of pre- versus postcapillary PH.[6,10] However, several pitfalls, including small sample size and lack of validation in external populations, have so far limited their application in clinical practice. Notably, measures of right ventricular (RV) systolic function have not been incorporated in previous indices.[5,6]

Patients without isolated postcapillary PH (iPC-PH), and mainly patients with precapillary PH, show a well-known modified physiology of the right ventricle characterized by a change from a preload- to an afterload-dependent condition.[11] RV afterload is characterized by two components, pulmonary vascular resistance and arterial elastance. The latter is an important index of arterial elasticity. RV stroke work index (RVSWI) accounts for both resistance and capacitance and has been used as an index of RV performance.[12] The right ventricle responds to the chronic exposure of increased afterload with an increase in contractility and subsequent progressive dilation.[13,14] The natural history of patients affected by pulmonary arterial hypertension is characterized indeed by a progressive RV decrease in stroke volume (SV) that follows an initial compensatory phase of stable or increased SV.[15] In this scenario it is reasonable to presume that RVSWI is high or normal. Moreover, noninvasive estimation of RVSWI by echocardiography (echocardiographic RVSWI [eRVSWI]) has been previously validated in adult and pediatric populations.[12,16] Conversely, E/E′ ratio as a surrogate marker of left ventricular (LV) filling pressure is generally in the lower range in precapillary PH.[17]

We hypothesized that the ratio between these two measures could make it possible to distinguish between precapillary and postcapillary PH. We named this novel echocardiographic index as "biventricular coupling index" (BCI), calculated as eRVSWI/(E/E′).

To verify its potential applicability in clinical practice for the noninvasive identification of patients with precapillary PH, in the present study we first derived BCI in a derivation cohort undergoing echocardiography and RHC from two referral centers for the management of heart failure and PH, and we then tested it in a large external validation cohort with available echocardiography and RHC.

METHODS

Study Design

The study is the first in an emerging international collaborative network including tertiary care centers (Department of Cardiology of the University of Trieste, Trieste, Italy; Karolinska University Hospital, Stockholm, Sweden; and Cardiology and Cardiovascular Medicine Department, Fondazione G. Monasterio, Pisa, Italy) for the management of heart failure and PH: the European Echo-Net working group. All patients undergoing complete transthoracic echocardiography and RHC for all clinical indications were prospectively and consecutively enrolled between August 2014 until December 2018 at the Department of Cardiology of the University of Trieste and at Karolinska University Hospital[18,19] and were considered eligible for the derivation cohort. Patients with a time interval between echocardiography and RHC of >6 hours or who received infusion of fluids or diuretic administration between the two examinations were excluded. Further exclusion criteria were age < 18 years, uncorrected intra- or extracardiac shunts, and poor echocardiographic image quality.

A wide cohort of patients selected according to the same criteria was obtained from a retrospective registry of the Cardiology and Cardiovascular Medicine Department, Fondazione G. Monasterio,[20] and used as the validation cohort. The validation cohort was also used to compare the performance of the BCI with the previously described indices for the noninvasive discrimination of pre- versus postcapillary PH: the D'Alto score (a multiparameter scoring system considering LV dimension, inferior vena cava collapsibility, and E/E′ ratio)[6] and the echocardiographic pulmonary–to–left atrial ratio (ePLAR) index, defined as the ratio between the peak velocity of tricuspid regurgitation and the E/e′ ratio.[10] Previous studies performed by our echocardiography laboratories provided data on intra- and interobserver variability of each component of BCI and ePLAR, suggesting good reliability of these echocardiographic parameters.[18,20]

The institutional review boards of the participating institutions approved the study, and written informed consent was obtained from each patient. An identifying code was assigned to each patient, in line with anonymization privacy policies.

The aim of the study was to assess the accuracy of BCI to predict the occurrence of precapillary PH.

Standard Echocardiographic Assessment and Hemodynamic Definitions

All patients underwent complete transthoracic echocardiography, including a dedicated protocol for the acquisition of all parameters necessary for hemodynamic evaluation, according to international guidelines.[21,22] Acquisitions were performed mainly by three operators (B. Pinamonti, S.A., and A.D.L.) at Trieste Hospital, by two operators at Karolinska University Hospital (A.V. and A.M.), and by three operators (V.C., C.P., E.M.P.) at Pisa Hospital, at rest in supine position during normal quiet respiration. An average of three cardiac cycles were analyzed (five cycles in patients with atrial fibrillation).

Measurements were obtained both online and offline using dedicated software (Suite Estensa; Esaote, Genoa, Italy), and operators

HIGHLIGHTS

- BCI is a novel index that may correctly identify precapillary PH.
- BCI may reduce unnecessary referrals for RHC.

were blinded to the results of invasive evaluation. No contrast agents were used to increase Doppler signals. At the three centers, the following machines were used: Vivid E9, Vivid E95, Vivid S6, Vivid I, and Vivid Q (GE, Wauwatosa, WI) and iE33 (Philips, Bothell, WA).

eRVSWI was defined in our study as follows:

$$eRVSWI = 0.0136 \times SVi \times (sPAP - RAP) = 0.0136 \times SVi \times [(RVSP + RAP) - RAP] = 0.0136 \times SVi \times RVSP,$$

where SVi is the SV index, and sPAP was calculated as the sum of RV systolic pressure (RVSP), derived from peak tricuspid regurgitation velocity using the modified Bernoulli equation,[23] and estimated right atrial pressure (RAP). We adopted a simplified formula for the calculation of eRVSWI rather than the original hemodynamic formula ($RVSWI = 0.0136 \times SVi \times [mPAP - RAP]$), as echocardiographic estimation of both mean pulmonary artery pressure (mPAP) and RAP is affected by limited reliability.[23] SV was calculated using the integral of pulsed-wave Doppler at the level of the LV outflow tract, as currently recommended.[24] E′ from the medial mitral valve annulus was used for the calculation of E/E′ ratio. BCI was then defined as follows:

$$BCI = \frac{eRVSWI}{E/E'}$$

Hemodynamic classification followed current guidelines.[4] PH was defined as mPAP ≥ 25 mm Hg, precapillary PH as PH with pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg, iPC-PH as

Table 1 Derivation cohort characteristics

	No PH	PH		Pre-capillary PH	iPC-PH	cPC-PH	
	(*n* = 108 [32.3%])	(*n* = 226 [67.7%])	*P*	(*n* = 82 [24.5%])	(*n* = 79 [23.7%])	(*n* = 65 [19.5%])	*P*
Baseline variable							
Age, y	61 ± 15	62 ± 15	.62	63 ± 15	57 ± 16*	65 ± 14‖	.023
Sex, male	50 (47.6)	97 (43.3)	.14	35 (43.2)	58 (73.4)‡	34 (53.1)§	<.001
Body surface area,# m^2	1.9 (0.2)	1.9 (0.2)	.088	1.9 (0.2)	2.0 (0.2)	1.9 (0.3)‖	.005
Current smokers	20 (19.2)	29 (13.5)	.40	10 (13.2)	9 (11.7)	10 (16.1)	.19
Essential hypertension	56 (52.8)	113 (51.6)	.76	35 (44.3)	40 (51.9)	38 (60.3)§	.33
Dyslipidemia	29 (27.4)	57 (26.3)	.74	17 (21.8)	17 (22.4)	23 (36.5)	.24
Diabetes	10 (9.5)	45 (20.5)	.033	10 (12.7)	17 (22.1)	18 (28.6)§	.014
ACE inhibitors/ARBs	51 (47.7)	95 (43.2)	.28	17 (21.8)	48 (60.8)‡	30 (47.6)‡	<.001
β-blockers	59 (74)	118 (80.8)	.24	23 (70)	55 (86)	40 (82)	.18
NYHA functional class							
I	8 (10)	4 (2.8)	.006	2 (6)	1 (2)	1 (2)	.053
II	19 (24)	28 (19.7)		8 (26)	13 (21)	7 (14)	
II	51 (65)	98 (69.0)		19 (61)	45 (73)	34 (69)	
IV	0 (0)	12 (8.5)		2 (6)	3 (5)	7 (14)	
NT-proBNP,# pg/mL	1,812.8 (2,877.6)	2,212.2 (3,202.9)	.37	1,737.6 (3,165.5)	1,864.7 (1,481.6)	2,965.4 (4,507.5)	.22
Echocardiographic data							
LV ejection fraction,# %	49.7 ± 17.6	50.9 ± 18.1	.52	62.3 ± 8.9	42.9 ± 19.4‡	46.5 ± 18.2‡	<.001
LV end-diastolic volume index,# mL/m^2	66.4 (40.7)	68.7 (37.9)	.61	94.8 (37.7)	163.7 (88.2)‡	143.1 (86.5)‡	<.001
SVi,# mL/m^2	35.0 (12.6)	34.6 (12.9)	.79	38.5 (12.4)	31.9 (12.4)‡	33.0 (13.1)*	.007
eRVSWI,# mm Hg/ L × m^2	14.4 (6.1)	24.7 (13.0)	<.001	30.1 (12.5)	19.5 (11.4)‡	24.3 (12.8)†,§	<.001
BIC	1.4 (0.9)	2.1 (1.7)	<.001	3.2 (2.0)	1.4 (1.2)‡	1.5 (1.2)‡	<.001
Tricuspid annular plane systolic excursion,# mm	17.1 (6.1)	16.9 (5.5)	.75	18.0 (5.6)	16.6 (5.7)	15.8 (4.9)*	.14
Septal E/E′ ratio#	11.9 (6.3)	16.0 (9.9)	<.001	11.8 (7.7)	17.5 (9.9)‡	19.4 (10.8)‡	<.001
End-systolic LA volume index,# mL/m^2	41.8 (21.8)	48.2 (24.9)	.025	35.0 (19.8)	57.7 (26.1)‡	54.0 (22.0)‡	<.001
End-systolic RA area,# cm^2	19.0 (8.1)	23.0 (8.4)	<.001	22.3 (8.3)	23.8 (8.6)	22.9 (8.4)	.27

(*Continued*)

Table 1 (*Continued*)

	No PH	PH		Pre-capillary PH	iPC-PH	cPC-PH	
	(*n* = 108 [32.3%])	(*n* = 226 [67.7%])	*P*	(*n* = 82 [24.5%])	(*n* = 79 [23.7%])	(*n* = 65 [19.5%])	*P*
RVSP,[#] mm Hg	37.6 (11.7)	55.6 (18.7)	<.001	61.9 (21.9)	47.6 (12.4)[‡]	64.4 (22.9)[§]	<.001
Moderate or severe mitral regurgitation	2 (1.9)	20 (9.0)	.081	1 (1.2)	15 (19.2)[‡]	4 (6.3)[†]	<.001
Moderate or severe tricuspid regurgitation	8 (7.6)	22 (10.0)	.29	10 (12.5)	7 (9.0)	5 (7.9)	.36
RHC data							
Mean blood pressure,[#] mm Hg	84.1 (14.9)	82.5 (15.6)	.44	85.1 (16.0)	81.3 (13.3)	80.1 (17.3)	.30
SVi,[#] mL/m^2	38.3 (12.1)	37.3 (15.1)	.55	38.5 (12.4)	31.9 (12.4)[‡]	33.0 (13.1)[‖]	<.001
Cardiac index (thermodilution),[#] L/min/m^2	2.5 (0.7)	2.6 (0.9)	.41	2.8 (1.1)	2.6 (0.8)[‡]	2.2 (0.7)[‖]	<.001
Pulmonary vascular resistance,[#] Wood units	1.8 (1.0)	4.1 (3.3)	<.001	5.8 (4.0)	1.8 (0.7)[‡]	4.9 (2.4)[¶]	<.001
PCWP,[#] mm Hg	12.1 (3.8)	18.5 (7.3)	<.001	12.3 (4.2)	23.7 (5.5)[‡]	21.8 (5.6)[‡]	<.001
mPAP,[#] mm Hg	19.5 (3.7)	36.7 (9.9)	<.001	37.5 (11.7)	33.1 (6.5)[†]	40.0 (9.6)[¶]	<.001
DPG,[#] mm Hg	0.4 (3.7)	4.4 (10.2)	<.001	11.2 (11.2)	−2.9 (4.7)[‡]	4.8 (7.3)[‡,¶]	<.001
RAP,[#] mm Hg	5.8 (4.1)	9.5 (5.4)	<.001	6.9 (4.1)	11.3 (5.4)[‡]	10.6 (5.6)[‡]	<.001
RVSWI,[#] mm Hg/L × m^2	7.1 (3.4)	13.6 (6.8)	<.001	16.3 (7.5)	11.3 (5.7)[‡]	12.8 (6.0)[†]	<.001

Data are expressed as mean ± SD or as number (percentage) except as indicated. *P* values refer to global *P* values obtained using analysis of variance.

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blockers; *DPG*, diastolic pulmonary gradient; *LVOT*, LV outflow tract; *NYHA*, New York Heart Association.

*$P < .05$, †$P < .01$, and ‡$P < .001$ (statistical significance for precapillary PH vs iPC-PH [in the column for iPC-PH] or statistical significance for precapillary PH vs cPC-PH [in the column for cPC-PH]).

§$P < .05$, ‖$P < .01$, and ¶$P < .001$ (statistical significance for iPC-PH vs cPC-PH).

#Median (interquartile range).

PH with PCWP > 15 mm Hg and diastolic pressure gradient (diastolic PAP − PCWP) < 7 mm Hg and/or pulmonary vascular resistance ≤ 3 Wood units, and combined postcapillary and precapillary PH (cPC-PH) as PH with PCWP > 15 mm Hg and diastolic pressure gradient (diastolic PAP − PCWP) ≥ 7 mm Hg and/or pulmonary vascular resistance > 3 WU. Further information about echocardiographic assessment and RHC evaluation is available in the Appendix.

Statistical Analysis

All statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, TX), SPSS Statistics version 24.0 (IBM, Armonk, NY), and MedCalc version 19.4.1 (MedCalc Software, Ostend, Belgium).

Descriptive statistics for continuous parameters are reported as mean ± SD or as median (interquartile range) as appropriate, depending on the variable distribution. Absolute and relative frequencies were tabulated for categorical variables. Comparison among groups for continuous parameters were performed by using ANOVA or the Kruskal-Wallis test depending on the variable distribution, with subsequent Bonferroni post hoc correction for multiple comparisons. Comparisons among categorical variables were performed using the χ^2 or Fisher exact test. Correlations between variables were assessed using the parametric Pearson coefficient (*r*) or the nonparametric Spearman ρ coefficient as appropriate.

The accuracy of BCI for the identification of precapillary PH was validated in both the derivation and validation cohorts using receiver operating characteristic (ROC) curve analysis, calculating areas under the curve (AUCs) and their associated 95% CIs. The optimal cut point was established using Youden *J* statistic; moreover, optimal rule-in and rule-out cutoffs were also identified. The DeLong nonparametric test was used to compare the diagnostic performance of the present model with that previous algorithms, as expressed by the *Z* coefficient (the higher the value, the larger the differences between two ROC curves). *P* values < 0.05 were considered to indicate statistical significant for all analyses.

Optimal rule-out and rule-in cutoffs were selected in the derivation cohort considering the highest BCI value with 99% negative predictive value (NPV) and the lowest value with 95% positive predictive value (PPV), respectively. The performance of rule-out and rule-in cutoffs was then assessed in the validation cohort and its subgroups and was evaluated in terms of sensitivity, specificity, NPV, PPV, and negative and positive likelihood ratios (LRs).

RESULTS

Demographic and Clinical Characteristics of the Derivation Cohort and Correlations of BCI: Clinical and Hemodynamic Data

Among 354 patients screened from the Trieste hospital ($n = 105$) and the Karolinska University Hospital ($n = 249$) registries,[18,19] 334 patients (94.3%) had no missing data for the variables of interest and

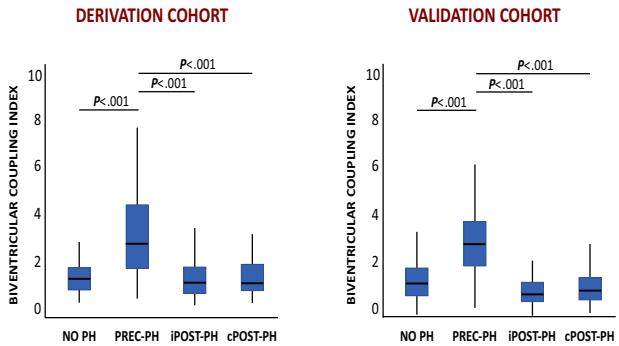


Figure 1 *(Left)* Box plot showing BCI values for no PH (n = 108), precapillary PH (n = 82), iPC-PH (n = 79), and cPC-PH (n = 65) by RHC in the derivation cohort, displayed as medians, quartiles, and ranges graphically and numerically as mean ± SD. Significant P values at 95% confidence level by Student's t test. *(Right)* Box plot showing BCI values for no PH (n = 496), precapillary PH (n = 410), iPC (n = 334), and cPC PH (n = 108) by RHC in the validation cohort displayed as medians, quartiles, and ranges graphically and numerically as mean ± SD. Significant P values at 95% confidence level by Student's t test.

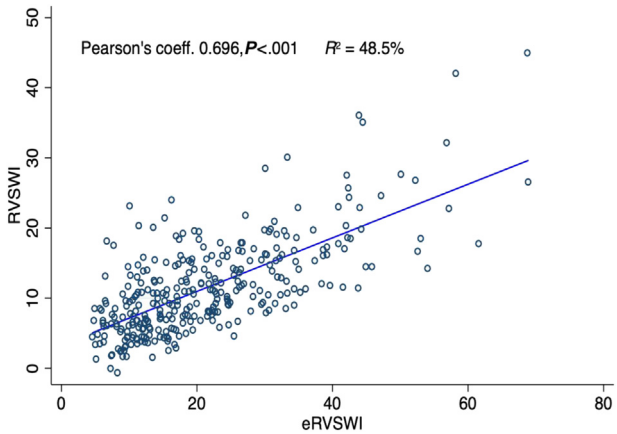


Figure 2 Scatterplot and correlation between invasive RVSWI and eRVSWI showing strong correlation between invasive and noninvasive data.

were thus included in the derivation cohort. Medial E/E′ was not available in 20 patients (5.6%), and RVSP was not available in 19 patients (5.4%). The main demographic and clinical characteristics of the derivation cohort are reported in Table 1.

At RHC, 226 patients (67.7%) had PH. Among patients with PH, 82 had precapillary PH (36.3%), while 79 had iPC-PH (35.0%) and 65 had cPC-PH (28.8%; Table 1). Overall, patients with PH had worse RV systolic function, worse LV diastolic function on the basis of 2016 American Society of Echocardiography guidelines,[22] and higher brain natriuretic peptide compared with patients without PH ($P < .001$ for all). Patients with precapillary PH had normal left heart functional indices, whereas compared with patients with iPC-PH, those with cPC-PH were older, were more likely women, and had a higher prevalence of cardiovascular risk factors, higher RVSP, a lower rate of significant mitral regurgitation, and smaller LV volumes ($P < .001$ for all). Moreover, patients with precapillary PH had higher RVSWI and lower E/E′ ratios compared with those with iPC-PH and cPC-PH ($P < .001$ all). Accordingly, as shown in Figure 1, BCI was higher in the subgroup of patients with precapillary PH compared with those with iPC-PH or cPC-PH ($P < .001$ for all), but BCI was not able to discriminate between iPC-PH and cPC-PH.

Echocardiographic estimates of sPAP and SVi showed strong to moderate correlations with invasive sPAP and SVi (Supplemental Table 1). eRVSWI demonstrated a good correlation with invasive RVSWI ($r = 0.696$, $P < .001$; Figure 2), while E/E′ ratio was weakly correlated with PCWP ($r = 0.30$, $P < .001$). Finally, BCI showed high diagnostic accuracy in the prediction of precapillary PH in the derivation cohort (AUC, 0.82; 95% CI, 0.78-0.89; $P < .001$), and the optimal cut point for the diagnosis of precapillary PH, according to the best performance on ROC analysis, was set at 1.9, with sensitivity of 73%, specificity of 78%, NPV of 90%, and PPV of 52% in the derivation cohort (Supplemental Figure 1). The optimal rule-out and rule-in cutoffs from the derivation cohort were tested in the validation group. For the rule-out cutoff (0.5), sensitivity and specificity were 99% and 15%. For the rule-in cutoff (5.3), sensitivity and specificity were 11% and 99% in the overall cohort.

Diagnostic Performance of the BCI in the Validation Group

In the validation cohort, among 1,464 patients screened from Fondazione G. Monasterio, 34 individuals (2.4%) <18 years of age were excluded, as well as 15 patients (1.0%) with uncorrected intra- or extracardiac shunts and 67 individuals (4.5%) with poor echocardiographic images. The demographic and clinical characteristics of the validation cohort (1,348 patients; mean age, 67 ± 13 years; 51% men) are reported in Table 2.

At RHC, 852 patients (63.2%) had PH (Table 2). Among patients with PH, 410 had precapillary PH (48.1%), 334 had iPC-PH (39.2%), and 108 had cPC-PH (12.7%; Table 2).

The main characteristics of the validation cohort were consistent with those of the derivation cohort. Specifically, patients with precapillary PH had more impaired right heart functional indices, comparable with those of the derivation cohort (Table 2). Similar to the derivation cohort, BCI was higher in the subgroup of patients with precapillary PH compared with those with iPC-PH and cPC-PH (Table 2, Figure 1).

BCI demonstrated high diagnostic accuracy in detecting precapillary PH in the overall cohort including patients without PH (AUC, 0.88; 95% CI, 0.85-0.90; $P < .001$; Figure 3A). Index performance was even higher when focusing only on patients with PH at RHC (AUC, 0.91; 95% CI, 0.89-0.93; $P < .001$; Figure 3B). Diagnostic accuracy was instead unchanged when selecting patients with suspected PH on echocardiography (AUC, 0.88; 95% CI, 0.86-0.90; Supplemental Figure 2). Similar findings were observed after excluding patients with severe aortic regurgitation (n = 19 [1.4%]) and mitral regurgitation (n = 115 [8.5%]), with BCI still showing high diagnostic accuracy (overall cohort: AUC, 0.87 [95% CI, 0.85-0.89]; patients with PH at RHC: AUC, 0.92 [95% CI, 0.89-0.94]; patients with suspected PH on echocardiography: AUC, 0.87 [95% CI, 0.84-0.89]).

The optimal cutoff of 1.9 for diagnosis of precapillary PH from the derivation cohort showed sensitivity of 82%, specificity of 89%, PPV of 77%, and NPV of 92% in the validation cohort (Figure 3). The optimal rule-out and rule-in cutoffs from the derivation cohort were tested in the validation group. For the rule-out cutoff (0.5), sensitivity and specificity were 99% and 8% in the overall cohort (LR− = 0.08 [95% CI, 0.02-0.34], true-negative n = 54 [96%], false-negative n = 2 [4%]), 99% and 11% in the population with PH at RHC (LR− = 0.06 [95% CI, 0.01-0.23], true-negative n = 39 [95%], false-negative n = 2

Table 2 Clinical, echocardiographic, and RHC characteristics of the validation cohort

	No PH	PH		Precapillary PH	Postcapillary PH	cPC-PH	
	(*n* = 496)	(*n* = 852)	*P*	(*n* = 410 [30.4%])	(*n* = 334 [24.8%])	(*n* = 108 [8.0%])	*P*
Baseline variables							
Age, y	67 ± 12	67 ± 14	.43	64 ± 16	69 ± 11‡	73 ± 9‡,§	<.001
Sex, male	256 (52)	431 (51)	.76	242 (59)	124 (37)‡	55 (51)‡	<.001
Body mass index, kg/m^2	26.7 ± 12.1	27.1 ± 7.1	.66	26.5 ± 8.4	27.9 ± 5.6	26.8 ± 5.0	.30
Body surface area, m^2	1.83 ± 0.23	1.86 ± 0.24	.03	1.8 ± 0.22	2.0 ± 0.25‡	1.8 ± 0.22¶	<.001
Systolic blood pressure, mm Hg	117.5 ± 24.4	118.3 ± 18.5	.87	116.1 ± 18.8	117.9 ± 18.2	124.8 ± 18.2	.26
Diastolic blood pressure, mm Hg	65.9 ± 12.2	70.9 ± 13.5	.09	68.9 ± 10.8	70.9 ± 14.4	79.3 ± 16.6	.46
Heart rate, beats/min	70.4 ± 13.6	75.2 ± 14.6	<.001	74.3 ± 12.8	75.8 ± 16.5	76.4 ± 15.3	.69
Smokers/past smokers	72 (14)/141 (28)	111 (13)/292 (34)	.13	57 (14)/153 (37)	41 (12)/110 (32)	13 (12)/29 (27)	.32
Essential hypertension	209 (42)	513 (60)	<.001	296 (72)	165 (49)‡	52 (48)‡	<.001
Dyslipidemia	165 (33)	230 (27)	.015	87 (21)	105 (31)†	38 (35)†	.001
Diabetes	93 (19)	263 (31)	<.001	110 (27)	9 (34)	15 (37)*	.04
ACE inhibitors/ARBs	323 (65)	472 (55)	<.001	139 (34)	262 (78)‡	71 (66)‡,§	<.001
β-blockers	414 (63)	516 (61)	.32	137 (33)	293 (88)‡	86 (83)‡	<.001
MRAs	262 (53)	474 (55)	.31	163 (40)	238 (71)‡	73 (68)‡	<.001
Calcium channel blockers	73 (14)	95 (11)	.056	56 (14)	30 (9)	9 (8)	.08
Amiodarone	11 (2)	31 (4)	.148	6 (1.5)	20 (6)‡	5 (5)	.004
Digoxin	42 (9)	107 (13)	.021	46 (11)	44 (13)	17 (16)	.41
Furosemide	310 (63)	707 (83)	<.001	322 (79)	287 (86)‡	98 (90)‡	<.001
Oral anticoagulant therapy	146 (29)	347 (41)	<.001	149 (36)	150 (45)	48 (44)	.054
NYHA functional class							
I	51 (10)	85 (10)	.003	51 (13)	27 (8)	8 (7)	<.001
II	142 (29)	215 (25)		48 (12)	137 (41)‡	30 (28)	
III	94 (19)	208 (24)		98 (23)	82 (25)	28 (26)	
IV	17 (3)	62 (7)		33 (8)	18 (5)	11 (10)	
Undetermined	192 (38)	281 (33)		180 (44)	70 (21)‡	31 (29)	
NT-proBNP,# pg/mL	543 (182-1,576)	1,366 (382-3,497)	<.001	467 (138-1,698)	1,870 (972-4,243)‡	3,541 (1,415- 6,971)‡,¶	<.001
Echocardiographic data							
LV ejection fraction, %	51.3 ± 16.4	52.2 ± 18.2	.35	63.8 ± 9.2	40.5 ± 17.6‡	44.6 ± 18.7‡	<.001
LV end-diastolic volume index,# mL/m^2	69 (55-95)	62 (49-85)	<.001	52 (43-61)	85 (66-111)‡	74 (54-97)‡	<.001
SV, mL	75.0 ± 11.2	70.9 ± 10.9	<.001	73 (67-79)#	68 (62-77)‡,#	65 (58-71)‡,¶,#	<.001
eRVSWI, mm Hg/L × m^2	18.2 (13.6-23.8)#	25.5 (18.4-35.7)#	<.001	31.3 ± 12.9	20.0 ± 8.0‡	26.0 ± 9.7‡,¶	<.001
BIC#	1.46 (0.99-2.09)#	1.67 (0.93-3.13)#	<.001	3.2 ± 1.4	1.1 ± 0.6‡	1.4 ± 0.9‡,‖	<.001
Cardiac output, L/min	5.3 ± 0.7	5.1 ± 0.7	.001	5.3 ± 0.6	5.0 ± 0.8‡	4.7 ± 0.7‡	<.001
Cardiac index, L/min/m^2	2.9 ± 0.5	2.8 ± 0.4	<.001	3.0 ± 0.4	2.6 ± 0.4‡	2.6 ± 0.4‡	<.001

(*Continued*)

Table 2 (*Continued*)

	No PH	PH		Precapillary PH	Postcapillary PH	cPC-PH	
	(*n* = 496)	(*n* = 852)	*P*	(*n* = 410 [30.4%])	(*n* = 334 [24.8%])	(*n* = 108 [8.0%])	*P*
Tricuspid annular plane systolic excursion, mm	20.5 ± 5.2	18.6 ± 5.4	<.001	19.8 ± 5.6	18.1 ± 5.0‡	16.1 ± 4.8‡,¶	<.001
RV fractional area change, %	40.1 ± 8.2	33.1 ± 8.9	<.001	31.1 ± 7.9	37.2 ± 8.9‡	30.7 ± 9.6¶	<.001
Septal E/E′ ratio	12.4 (9.9-15.9)#	14.5 (10.4-21.3)#	<.001	12.4 ± 5.9	22.6 ± 16.2‡	23.6 ± 14.0‡	<.001
End-systolic LA volume index, mL/m^2	37.7 ± 15.1	40.5 ± 15.7	.001	46 (24-35)#	47 (40-56)‡,#	46 (40-56)‡,#	<.001
Estimated RAP,# mm Hg	6 (4-7)	8 (5-11)	<.001	5 (4-7)	10 (8-12)‡	11 (9-13)‡	<.001
Estimated sPAP, mm Hg	38.9 ± 9.2	60.8 ± 17.5	<.001	61.0 ± 17.1	50.7 ± 10.7‡	66.1 ± 15.1‡	<.001
Moderate or severe aortic regurgitation	59 (12)	105 (12)	.98	24 (6)	64 (19)‡	17 (15)	<.001
Moderate or severe mitral regurgitation	183 (37)	378 (44)	.005	48 (12)	254 (76)‡	77 (71)‡	<.001
Moderate or severe tricuspid regurgitation	234 (47)	576 (64)	<.001	240 (59)	250 (75)‡	89 (82)‡	<.001
Pericardial effusion	65 (13)	202 (24)	<.001	110 (27)	68 (20)‡	24 (22)‡	<.001
RHC data							
SVi,# mL/m^2	42 (35-51)	37 (30-45)	<.001	40.2 (32.5-49.2)	35.6 (28.7-43.7)‡	29.5 (24.4-36.7)‡,¶	<.001
Cardiac output, L/min	5.4 ± 1.5	5.0 ± 1.5	<.001	5.3 ± 1.4	5.1 ± 1.6‡	4.0 ± 1.0‡,¶	<.001
Cardiac index, (thermodilution), L/min/m^2	3.0 ± 0.8	2.8 ± 0.8	<.001	3.0 ± 0.8	2.7 ± 0.7‡	2.3 ± 0.6‡,¶	<.001
Pulmonary vascular resistance,# Wood units	1.3 (0.8-1.9)	3.2 (1.9-5.6)	<.001	5.2 (3.6-7.5)	1.8 (1.3-2.3)‡	4.5 (3.5-5.6)‡,‖	<.001
PCWP, mm Hg	10.8 ± 4.6	16.3 ± 8.5	<.001	8.8 ± 3.2	23.6 ± 5.0‡	23.0 ± 5.3‡	<.001
sPAP, mm Hg	30.5 ± 6.9	57.3 ± 15.4	<.001	61.0 ± 17.1	50.3 ± 10.0‡	64.8 ± 13.4†,¶	<.001
Diastolic pulmonary artery pressure, mm Hg	12.1 ± 3.7	24.1 ± 6.7	<.001	24.2 ± 7.3	22.4 ± 4.8*	28.8 ± 7.7‡,¶	<.001
mPAP, mm Hg	18.2 ± 4.1	35.5 ± 9.1	<.001	36.8 ± 9.6	32.0 ± 5.5‡	41.5 ± 8.2‡,¶	<.001
DPG, mm Hg	2 (0-5)#	7 (1-15)#	<.001	15.5 ± 8.0	−1.5 ± 4.1‡,¶	6.1 ± 6.3‡,¶	<.001
RAP, mm Hg	5 (3-7)#	7 (4-12)#	<.001	5.4 ± 3.5	10.8 ± 5.1‡	11.6 ± 5.2‡	<.001
RVSWI,# mm Hg/L × m^2	7.7 (3.5)	14.4 (7.1)	<.001	17.7 (7.4)	12.5 (6.9)‡	10.8 (5.1)‡,§	<.001

Data are expressed as mean ± SD or as number (percentage) except as indicated. *P* values refer to global *P* values obtained using analysis of variance.

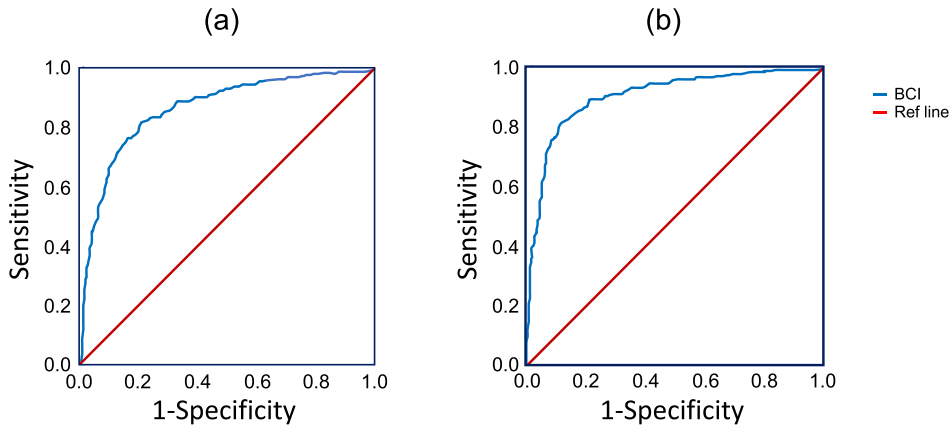
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *DPG*, diastolic pulmonary gradient; *LVOT*, LV outflow tract; MRA, mineral-corticoid receptor antagonist; *NYHA*, New York Heart Association.

*$P < .05$, †$P < .01$, and ‡$P < .001$ (statistical significance for precapillary PH vs iPC-PH [in the column of iPC-PH] or statistical significance for precapillary PH vs cPC-PH [in the column of cPC-PH]).

§$P < .05$, ‖$P < .01$, ¶$P < .001$ (statistical significance for iPC-PH vs cPC-PH).

#Median (interquartile range).

[5%]), and 99% and 7% in the population with suspected PH on echocardiography (LR− = 0.04 [95% CI, 0.01-0.28], true-negative *n* = 47 [98%], false-negative *n* = 1 [2%]). For the rule-in cutoff (5.3), sensitivity and specificity were 9% and 99% in the overall cohort (LR+ = 15.57 [95% CI, 6.66-36.38], true-positive *n* = 41 [87%], false-positive *n* = 6 [13%]), 8% and 100% in the population



ROC AUC: 0.87 (95% IC 0.85-0.89), *P*<.001
Youden Index 0.61 associated criterion >1.9
Sensitivity 82%, Specificity 80%

ROC AUC: 0.91 (95% IC 0.89-0.93), *P*<.001
Youden Index 0.71 associated criterion >1.9
Sensitivity 82%, Specificity 89%

Figure 3 ROC curves showing the accuracy of BCI to predict precapillary PH in the validation cohort including patients without PH **(A)** and excluding patients without PH **(B)**. BCI with a cutoff value of 1.9 has high accuracy to predict precapillary PH.

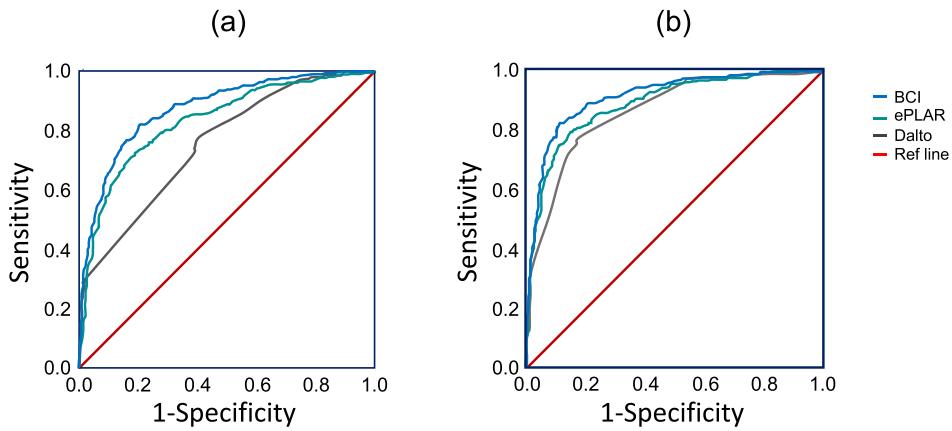
with PH at RHC (LR+ = 22.00 [95% CI, 5.36-90.37], true-positive $n = 41$ [95%], false-positive $n = 2$ [5%]), and 9% and 99% in the population with suspected PH on echocardiography (LR+ = 14.85 [95% CI, 5.92-37.28], true-positive $n = 41$ [89%], false-positive $n = 5$ [11%]).

BCI demonstrated superior performance compared with previously proposed echocardiographic indices in the discrimination of precapillary PH, both in the overall study cohort (BCI vs D'Alto score: $Z = 8.04$, difference between areas = 0.12 [95% CI, 0.09-0.14; $P < .001$]; BCI vs ePLAR: $Z = 4.56$, difference between areas = 0.04 [95% CI, 0.02-0.05; $P < .001$]; Figure 4) and after excluding patients without PH (BCI vs D'Alto score: $Z = 3.56$, difference between areas = 0.05 [95% CI, 0.02-0.07; $P < .001$]; BCI vs ePLAR: $Z = 2.88$, difference between areas = 0.02 [95% CI, 0.01-0.04; $P = .004$]; Figure 4).[6,10]

As shown in Figure 5, BCI was superior to the D'Alto and ePLAR scores in the discrimination between precapillary PH and iPC-PH, but not in the discrimination between precapillary PH and cPC-PH. All three indices had low accuracy in discriminating between iPC-PH and cPC-PH.

DISCUSSION

In the present study we (1) demonstrated the ability of BCI to discriminate pre- versus postcapillary PH in a multicenter cohort



BCI vs Dalto: Z statistic 8.04, Diff betw areas 0.12 (95% IC 0.09-0.14), *P*<.001*
BCI vs ePLAR: Z statistic 4.56, Diff betw areas 0.04 (95% IC 0.02-0.05), *P*<.001*
ePLAR vs Dalto: Z statistic 5.6, Diff betw areas 0.08 (95% IC 0.05-0.11), *P*<.001*

BCI vs Dalto: Z statistic 3.56, Diff betw areas 0.05 (95% IC 0.02-0.07), *P*<.001*
BCI vs ePLAR: Z statistic 2.88, Diff betw areas 0.02 (95% IC 0.01-0.04), *P*=.004*
ePLAR vs Dalto: Z statistic 1.86, Diff betw areas 0.02 (95% IC 0.001-0.04), *P*=.006*

* DeLong statistics for comparison

Figure 4 ROC curves showing the accuracy of BCI to predict precapillary PH, including patients without PH **(A)** and excluding patients without PH **(B)**. BCI was superior to the previously validated D'Alto score and ePLAR in the prediction of precapillary PH.[6,10]

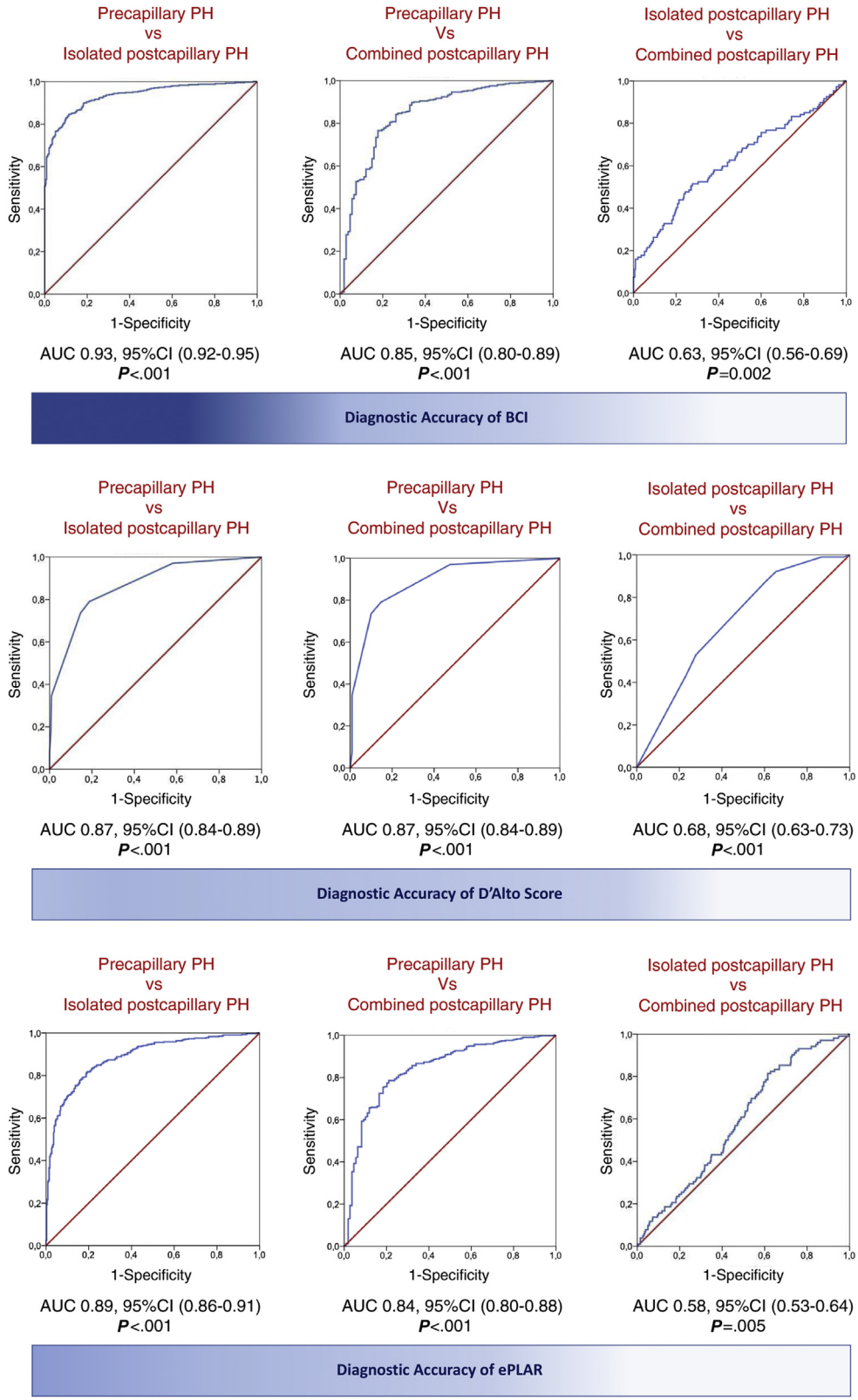


Figure 5 ROC curves showing the performance of BCI and the D'Alto and ePLAR scores (*top*, *middle*, and *bottom*, respectively) in the discrimination between precapillary PH and iPC-PH *(left column)*, precapillary PH and cPC-PH *(middle column)*, and iPC-PH and cPC-PH *(right column)*. See text for further explanation.

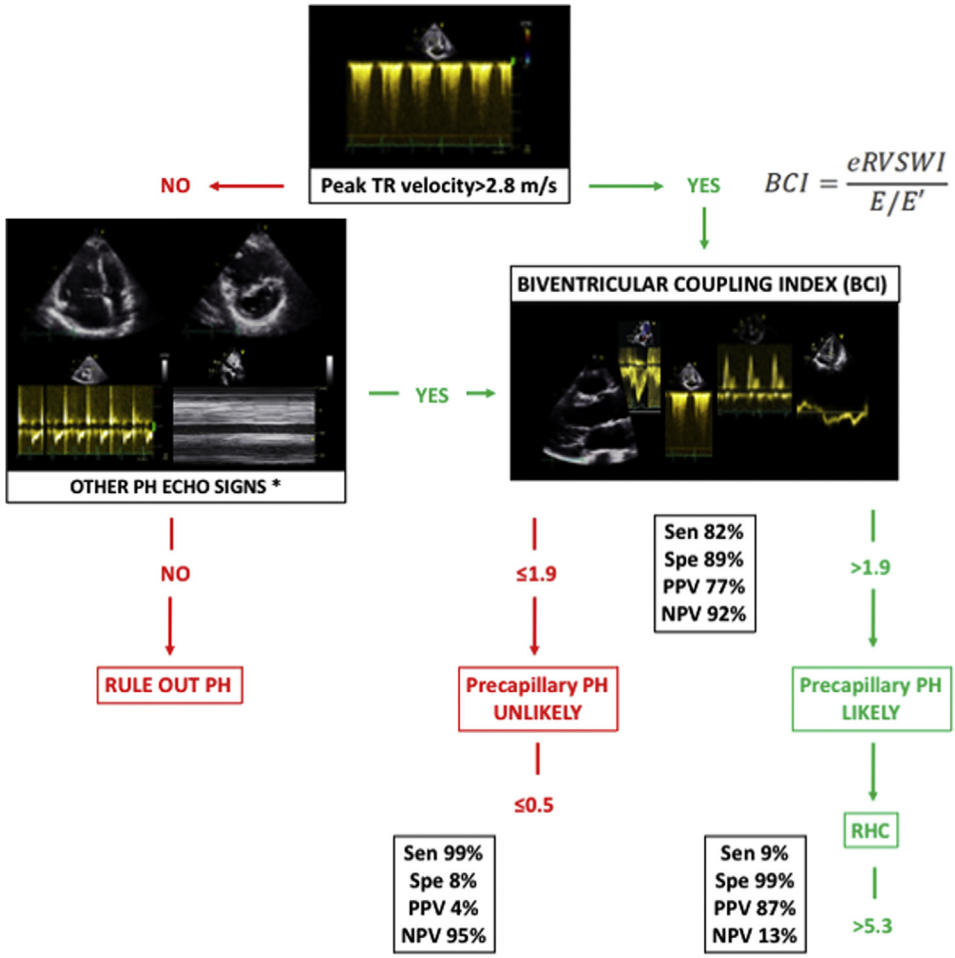


Figure 6 In patients with high peak tricuspid regurgitation velocity (>2.8 m/sec) or indirect echocardiographic signs of PH BCI (BCI = eRVSWI/[E/E']) should be assessed to discriminate pre- versus postcapillary PH. A BCI value > 1.9 is associated with high probability of precapillary PH (sensitivity, 82%; specificity, 89%; PPV, 77%; NPV, 92%), and the patient should be referred for RHC for diagnostic confirmation and risk stratification.[4] *Echocardiographic signs associated with PH. *(Top left)* Apical four-chamber view showing that right heart chambers are wider than left heart chambers. *(Top right)* Short-axis view showing typical septal shape associated with right chambers overload. *(Bottom left)* Pulsed-wave Doppler at the level of the RV outflow tract showing the typical notch sign associated with PH. *(Bottom right)* Dilated inferior vena cava with reduced collapsibility using M-mode echocardiography; this aspect is frequently associated with PH.[4]

of patients with concomitant transthoracic echocardiography and RHC, (2) validated the accuracy of BCI to predict the subtype of PH in a large cohort of all comers undergoing echocardiographic assessment and RHC at a tertiary care center for heart failure and PH management, (3) demonstrated the superiority of BCI compared with previously proposed noninvasive algorithms for the identification of precapillary PH, and (4) demonstrated the non-superiority of the BCI compared with previously proposed noninvasive algorithms to differentiate iPC-PH from cPC-PH. To our knowledge this is the first study assessing the new BCI as a novel index for the discrimination of PH subtype and, with a total of 1,683 patients with available RHC and echocardiography, the largest study to date assessing a noninvasive method against RHC for the identification of precapillary PH.

According to current guidelines, echocardiography is the first-line approach for patients at risk for PH and estimates pulmonary artery pressures and the likelihood of PH.[4] However, after complete diagnostic workup, the final diagnosis and categorization of PH necessarily require RHC to determine the correct treatment. Indeed, pulmonary vasodilators are indicated only for precapillary type 1 PH and may be detrimental in patients with postcapillary PH and left heart disease.[4]

RHC is an invasive test associated with potential discomfort and risk to patients, is not systematically available in all centers, and requires adequate expertise for the correct interpretation of data. For these reasons, patients with suspected pulmonary arterial hypertension require referral to highly specialized centers. On the other hand, PH is an extremely frequent condition, with an estimated prevalence of 20% in older (>72 years) Americans.[25] The most common causes of PH are secondary to left heart disease and thus characterized by high PCWP.[26] This subset is not eligible for specific therapy with pulmonary vasodilators and is usually treated according to the underlying left heart disease. Whether all these patients should be referred to tertiary care centers for the invasive assessment of pulmonary pressures is a matter of debate, as invasive procedures expose patients to potential complications, and specialized centers might not have the resources to perform large-scale RHC.[27] The alternative is to improve the appropriateness of RHC by limiting it to patients with higher likelihood of precapillary PH. Multiparametric scores

and noninvasive imaging indices have been previously proposed to define the probability of precapillary PH in patients with echocardiographically estimated high pulmonary pressures.[6,8,10]

D'Alto *et al.*[6] proposed a multiparametric scoring system (eight parameters) to predict precapillary PH. The score was derived in a relatively small population and validated internally. The AUC was 0.75. Scalia *et al.*[10] decided to focus on a simpler index, the ePLAR index, which corrected peak tricuspid regurgitation velocity for the E/E′ ratio. The performance of ePLAR was good (AUC, 0.87), but it was tested in a cohort of only 133 patients, all with PH, while the normal ranges were derived from a large normal reference population without invasive assessment. In contrast to ePLAR index, in which no parameters included in the formula are directly related to RV function, in the BCI, SVi is a parameter of RV contractility. This aspect could in part explain the better performance of BCI compared with ePLAR, because, as discussed above, in patients with precapillary PH the increasing contractility of the right ventricle is a response to increased afterload.

In this study we introduce BCI as an alternative method for the identification of precapillary PH. In contrast to the ePLAR index, BCI is not based on a simple ratio between sPAP and a surrogate of LV filling pressures but also on the response of the right ventricle to increased afterload. Changes in SVi may be secondary to reduced LV systolic function, and in this case eRVSWI could theoretically not be properly representative of RV performance. However, the good correlation between eRVSWI and invasive RVSWI observed in our study supports the use of eRVSWI as an indirect measure of intrinsic RV performance.

In patients without iPC-PH, and mainly in patients with precapillary PH, the increase in pressure afterload leads the right ventricle to low contractility and reduced SV, with an increase in pulmonary pressure.[14] RVSWI is thus relatively high and, if corrected for the low E/E′ ratio, yields higher BCI values. On the other hand, in postcapillary PH due to left heart disease, there is a combination of pressure and volume overload, the second generally produced by systemic congestion. In addition, the cardiomyopathic process may involve the RV myocardium.[14,28,29] The increase in RAP, RV overdistension, worsening of tricuspid regurgitation, and ventricular interdependence are direct consequences of the congestive status.[30] Congestive status along with the intrinsically impaired RV contractility lead to low RVSWI values that generate low BCI values after correction for the high E/E′ ratio typical of left heart disease. Accordingly, in our study we observed higher BCI values in patients with precapillary PH, intermediate values in those without PH, and lower values in those with postcapillary PH, with a slight difference in this last subgroup between iPC-PH and cPC-PH, which might deserve further focused investigations. Indeed, the performance of BCI in the discrimination between iPC-PH and cPC-PH seems suboptimal, looking at the quite large overlap of the index between these subgroups of patients and the related ROC curves (Figures 1 and 5). However, this diagnostic weakness is shared both by the D'Alto and ePLAR scores. Nonetheless, the validation of our index in a very large unselected cohort of patients referred for RHC allowed us to demonstrate the validity of BCI in both all comers and patients with PH (either suspected on echocardiography or diagnosed on RHC), supporting the feasibility (on the basis of conventional Doppler metrics) and the potential utility of BCI in discriminating precapillary versus postcapillary PH. The validation cohort was rather representative of real-world PH epidemiology, as suggested by the evidence from the COMPERA (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry.[28] In fact, right heart chambers were commonly involved, in terms of reduced RV function, even in the COMPERA registry, and the ePLAR index,[10] based on peak tricuspid regurgitation velocity, may have lower performance in this setting.

The accuracy of BCI in the large validation cohort ($n = 1,348$) was high, in particular among patients with PH (AUC, 0.91), and it outperformed previously proposed methods.[6,10] The identified cutoff value of 1.9 showed relatively high sensitivity, specificity, NPV, and PPV in the discrimination of pre- versus postcapillary PH in this cohort. Moreover, we have provided optimal rule-out and rule-in cutoffs from the derivation cohort tested in the validation group (Figure 6, *bottom right*) to reach the highest NPV and PPV, respectively. However, the cutoff of 1.9 was maintained as the best balance between sensitivity and specificity. The validation of the cutoff in other external cohorts would further strengthen the potentiality of BCI in screening for precapillary PH, supporting its inclusion in the algorithm for the assessment of patients with suspected PH (Figure 6). Nonetheless, it must be specified that RHC remains necessary to confirm the diagnosis and to stratify the risk of patients with high probability of precapillary PH.[4]

Study Limitations

The study population was enrolled at tertiary care centers for heart failure and PH management, which might introduce selection bias. As with most previously published studies on noninvasive hemodynamic assessment, RHC and echocardiographic evaluation were not exactly simultaneous, although they were performed with a short time delay (<6 hours).[23] With regard to the BCI formula, we decided to use the medial E/E′ ratio rather than average E/E′ to preserve the feasibility and general applicability of BCI as a screening parameter for the identification of precapillary PH. Moreover, the simplified formula for estimation of eRVSWI similarly aimed to use standard echocardiographic metrics routinely collected during a conventional transthoracic echocardiography. In this view, echocardiographic estimation of mPAP and RAP, which suffers from known limitations, was removed from the formula. Our decision was supported by the good correlation between RVSWI and eRVSWI (Figure 2, Supplemental Table 1).

Advanced echocardiography was previously proposed for the assessment of left atrial function as an alternative to the E/E′ ratio.[19] In our study, deformation imaging was not systematically available. Moreover, one of our major aims was to provide a feasible and largely applicable index useful during the screening process of patients with suspected PH.

CONCLUSION

BCI is a novel echocardiographic index that demonstrated high accuracy in the discrimination of precapillary PH and was superior to previously proposed methods for the noninvasive estimation of PH subtype. Routine use of BCI might be included in the diagnostic algorithm for suspected PH to support clinicians in the optimal selection of patient candidates for invasive hemodynamic assessment.

ACKNOWLEDGMENTS

We thank Dr. De Scordilli for his help in the collection of echocardiographic data and Dr. Pinamonti for his valuable suggestions during the revision phase. We acknowledge the work of two sonographers, Claudia Taddei and Elisa Poggianti, for their help in the acquisition of echocardiographic cases at Fondazione Toscana G. Monasterio. We thank Fondazione CRTrieste, Fondazione CariGO, Fincantieri,

and all the health care professionals for their continuous support in the clinical management of patients affected by heart failure and PH, followed in the Heart Failure Outpatient Clinic of Trieste, and their families.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2022.02.003.

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