Eur Respir J 2011; 37: 1096–1103
DOI: 10.1183/09031936.00089610

A noninvasive algorithm to exclude pre-capillary pulmonary hypertension

D. Bonderman*, P. Wexberg*, A.M. Martischnig*, H. Heinzl#, M-B. Lang*, R. Sadushi*, N. Skoro-Sajer* and I.M. Lang*

ABSTRACT: Current guidelines recommend right heart catheterisation (RHC) in symptomatic patients at risk of pre-capillary pulmonary hypertension (PH) with echocardiographic systolic pulmonary artery pressures ⩾36 mmHg. Growing awareness for PH, a high prevalence of post-capillary PH and the inability to distinguish between pre- and post-capillary PH by echocardiography have led to unnecessary RHCs. The aim of our study was to assess whether standard noninvasive diagnostic procedures are able to safely exclude pre-capillary PH.

Data from 251 patients referred for suspicion of pre-capillary PH were used to develop a noninvasive diagnostic decision tree. A prospectively collected data set of 121 consecutive patients was utilised for temporal validation.

According to the decision tree, patients were stratified by the presence or absence of an electrocardiographic right ventricular strain pattern (RVS) and serum N-terminal brain natriuretic peptide (NT-proBNP) levels below and above 80 pg·mL^{-1}. In the absence of RVS and elevated NT-proBNP, none of the patients in the prospective validation cohort were diagnosed with pre-capillary PH by RHC. Combining echocardiography with the diagnostic algorithm increased specificity to 19.3% (p=0.0009), while sensitivity remained at 100%.

Employing ECG and NT-proBNP on top of echocardiography helps recognise one false positive case per five patients referred with dyspnoea and echocardiographic suspicion of PH, while not missing true pre-capillary PH.

KEYWORDS: Diagnostic procedures, pulmonary hypertension

Pre-capillary pulmonary hypertension (PH) is a severe condition leading to right heart failure and death within 2–3 yrs after diagnosis, if left untreated [1]. While idiopathic pulmonary arterial hypertension (PAH) is rare, associated forms of PAH [2] are more common and may be triggered by collagen vascular disease, appetite suppressants [3], HIV-infection [4], increased shear stress and hypoxia [2, 5–7]. A series of medical conditions, including infection, immune disorders, inflammatory bowel disease and permanent venous catheters [8, 9], predispose to chronic thromboembolic pulmonary hypertension (CTEPH) [10].

According to international guidelines [2], which were recently updated [11–13], invasive haemodynamic measurement by right heart catheterisation (RHC) is recommended in patients with clinical suspicion of pre-capillary PH if systolic pulmonary artery pressure ($P_{pa,sys}$) by transthoracic echocardiography (TTE) is ⩾36 mmHg. An invasively measured pulmonary capillary wedge pressure of 15 mmHg has been used to discriminate between pre- and post-capillary pulmonary pressure elevation which mostly occurs as a consequence of left-sided heart disease [14]. The growing awareness for PH, a high prevalence of post-capillary PH [15] and the inability of TTE to distinguish between pre- and post-capillary PH have necessitated invasive haemodynamic measurements for exclusion. Furthermore, Doppler echocardiography is frequently inaccurate in estimating $P_{pa,sys}$ [16]. Given a low specificity of PH symptoms and $P_{pa,sys}$ elevations by TTE, the decision to either proceed with RHC or withhold further invasive testing is a common clinical problem, especially in high-volume PH referral centres [17]. Although rare [18], complications of RHC may be ventricular tachyarrhythmia, vascular or ventricular perforation, bleeding, pneumothorax and even death [19]. However, a restrictive use of RHC may delay a timely diagnosis and treatment [20].

For editorial comments see page 994.

AFFILIATIONS
*Dept of Cardiology, and
#Core Unit for Medical Statistics and Informatics, Medical University of Vienna, Vienna, Austria.

CORRESPONDENCE
D. Bonderman
Dept of Internal Medicine II, Division of Cardiology
Medical University of Vienna
Währinger Gürtel 18-20
1090 Vienna
Austria
E-mail: diana.bonderman@meduniwien.ac.at

Received:
June 10 2010
Accepted after revision:
July 28 2010
First published online:
Aug 06 2010

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

Apart from TTE, 12-lead electrocardiography (ECG), serum N-terminal brain natriuretic peptide (NT-proBNP) and lung function tests with blood gas analysis have been recommended in patients who present with dyspnoea. Typical ECG signs of pre-capillary PH are right ventricular hypertrophy and strain (RVH and RVS, respectively), and signs of right atrial dilation such as P-pulmonale. The role of ECG for the diagnosis of PH has been investigated in a large US registry initiated in the early 1980s. RICH *et al.* [21] reported that electrocardiographic RVH was present in 87% and right axis deviation in 79% of patients with idiopathic PH. Elevated serum NT-proBNP [22] and hypocapnia [23] have been established as independent markers of mortality in PH. However, the combined diagnostic use of these noninvasive tests has not been validated. Therefore, we tested the ability of standard noninvasive diagnostic procedures to correctly identify or exclude pre-capillary PH in patients referred for clinical suspicion of PH and echocardiographic $P_{pa,sys} \geqslant 36$ mmHg. We used a retrospective data set of 251 consecutive individuals and constructed a simple noninvasive diagnostic algorithm. In a prospective temporal validation study enrolling 121 new consecutive patients, the incremental diagnostic value of the combined use of TTE, ECG and NT-proBNP over TTE alone was confirmed.

METHODS

Setting and study design

The study was approved by the Ethics Committee of the Medical University of Vienna (Vienna, Austria), and written informed consent was collected from prospectively enrolled patients. The study was performed at the Pulmonary Hypertension Unit of the Medical University of Vienna as a tertiary referral centre for PH.

Retrospective study

Between January 2002 and April 2007, 462 patients were referred for the evaluation of PH. TTE, 12-lead ECG, serum NT-proBNP and lung function tests including arterial carbon dioxide tension (P_{a,CO_2}) were performed upon admission in each patient. Patients with echocardiographic $P_{pa,sys} <36$ mmHg (n=80) were not considered for invasive haemodynamic assessment. Patients carrying pacemakers or implantable cardioverters/defibrillators (n=12) were excluded because of the inapplicability of standard ECG criteria. 71 patients were excluded because of severe valvular disease, congenital malformations and/or severely impaired left ventricular function. Of the 299 patients who were considered appropriate study candidates, 48 were excluded because of incomplete data, leaving 251 patients for analysis. Based on the invasive haemodynamic evaluation by RHC, the diagnosis ''pre-capillary PH'' or ''no pre-capillary PH'' was made.

Prospective study

For temporal validation of the diagnostic algorithm constructed from the retrospective data set, we enrolled consecutive patients referred between June 2007 and October 2008. From a total of 222 individuals, 101 were excluded because of valvular heart disease (n=29), left ventricular dysfunction (n=8), congenital heart disease (n=8), pacemaker (n=17) and an echocardiographic $P_{pa,sys} <36$ mmHg (n=30). In one patient NT-proBNP had not been determined and one patient died prior to a complete assessment. Seven patients refused to participate in the study. In the remaining 121 patients, noninvasive diagnostic procedures were performed in an outpatient setting. Based on the diagnostic algorithm, each patient was categorised as ''pre-capillary PH excluded'' or ''pre-capillary PH likely''. In a next step, all patients underwent invasive haemodynamic assessment by RHC. Based on these results, a diagnosis was made that served as the validation standard.

Transthoracic echocardiography

All TTE studies were performed by board certified physicians in the echo laboratory of the Medical University of Vienna using high-end scanners, such as Acuson Sequoia (Siemens AG, Erlangen, Germany) and Vivid 5 and Vivid 7 (General Electric Medical System, Milwaukee, WI, USA). The current standard in our echo lab is that all readings are performed by two independent observers. TTE studies were based on measurements that are broadly available and routinely used in the evaluation of patients with suspected PH.

Right ventricular dysfunction was diagnosed based on a visual assessment and on a tricuspid annular plane systolic excursion of <18 mm. $P_{pa,sys}$ was calculated by adding estimated right atrial pressure to the tricuspid regurgitation pressure gradient. No contrast agents were used for enhancement of Doppler signals. Right atrial pressure was estimated based on the diameter and respiratory variation of the inferior vena cava [11].

Left ventricular hypertrophy was diagnosed if end-diastolic septal thickness in the apical four-chamber view was $\geqslant$12 mm.

Left ventricular diastolic dysfunction was diagnosed in the presence of a restrictive or pseudo-normal filling pattern and normal or only mildly abnormal left ventricular ejection fraction (>50%). A restrictive filling pattern was defined by an E/A waves ratio >2 and a deceleration time <150 ms. A pseudo-normal filling pattern was diagnosed if E/A waves ratio and deceleration time were normal but changed to abnormal after Valsalva [24].

ECG

Retrospective and prospective study

A 12-lead ECG was recorded according to clinical standards at a paper speed of 25 $mm \cdot s^{-1}$. ECGs were analysed by two cardiologists who were blinded to the clinical and echocardiographic data. ECG rulers and callipers were used. In case of disagreement, consensus was achieved between the two observers in a second reading. The following parameters were obtained: 1) presence or absence of sinus rhythm; 2) heart rate in beats per min; 3) P-wave amplitude in mV in lead II; 4) P-wave axis in degrees; 5) presence or absence of P-pulmonale defined as a P-wave amplitude >0.25 mV; 6) electric heart axis in degrees; 7) right axis deviation defined as a QRS axis >110°; 8) QRS width in ms; 9) presence or absence of bundle branch block defined as a QRS width >100ms, and stratification in right bundle branch block or left bundle branch block; 10) the presence or absence of RVS pattern defined as ST-segment deviation and T-wave inversion in leads V1–V3 [25]; 11) the presence or absence of left ventricular strain pattern defined as ST-segment deviation and T-wave inversions in leads V5 and V6; 12) QT-length in ms and corrected QT-length calculated by the Bazett formula [26]. RVH was defined by a ratio of R and S in lead V1 >1.

Assessments

A detailed medical history including medical conditions known to be associated with PH was obtained [2, 5, 6, 27]. Associated conditions were collagen vascular disease, HIV infection, history of appetite suppressant intake, splenectomy or ventriculo-atrial shunt. In addition, exercise capacity measured by the distance in meters walked in 6 min, and the modified New York Heart Association (NYHA) class [28] at presentation were determined in each patient. Blood gas analysis was performed using a ABL 510 blood gas analyser (Radiometer Medical ApS, Brønshøj, Denmark).

Serum NT-proBNP was measured utilising the Elecsys proBNP kit (Roche, Basel, Switzerland). Haemodynamic assessment by RHC included measurement of cardiac output utilising both the Fick equation and the thermodilution method. Pre-capillary PH was diagnosed if mean pulmonary arterial pressure ($\bar{P}_{pa}$) exceeded 25 mmHg at rest, and pulmonary capillary wedge pressure was <15 mmHg [2].

Statistical analysis

Statistical computations were performed with SPSS (version 15.0; SPSS Inc., Chicago, IL, USA) and SAS (version 9.1; SAS Institute Inc., Cary, NC, USA). Continuous variables were described with mean and SD. Groups were compared using the unpaired t-test. Right-skewed variables were logarithmically transformed before testing. Nominal variables were described with counts and percentages, groups were compared with Chi-squared or Fisher's exact test. Wilson's method was used to compute confidence intervals (CI) for single proportions. McNemar's test was used to compare sensitivities and specificities of diagnostic decision rules. All reported p-values are the result of two-tailed tests, and p-values <0.05 were considered statistically significant.

Univariable logistic regression models were used to assess whether TTE, clinical and ECG variables allowed discrimination between pre-capillary PH and no pre-capillary PH. Stepwise selection (forward search) within the three groups (TTE, clinical and ECG variables) yielded partially independent variable sets. The clinical and the ECG variable sets were used to construct a diagnostic decision tree (Classification and Regression Tree; CART) for pre-capillary PH *versus* no pre-capillary PH employing the CHAID (Chi-Squared Automatic Interaction Detection) method of SPSS and defining diagnostic branch points and terminal nodes. At each branch point a case will either branch to the left or to the right based on a test against a threshold predictor value, and will continue branching in subsequent nodes until a terminal node is reached.

Because of the prognostic implications of a delayed PAH diagnosis and treatment [1], a false negative diagnosis was assumed to have far more serious consequences than a false positive one. Therefore, the class assignment rule was chosen in a way that the percentage of false negative predictions did not exceed 4% (one out of 25) of the true positive cases.

To overcome the problem of overoptimistic results, both an internal and a temporal validation step were added [29]. Internal validation was based on the bootstrap approach [30], reporting an average of 30 bootstrap samples. Temporal validation was based on the prospective sample.

RESULTS

Characteristics of the retrospective patient cohort

Patient characteristics are summarised in table 1. According to RHC results, 187 (74.5%) patients were classified as pre-capillary PH and 64 (25.5%) as no pre-capillary PH.

In the pre-capillary PH group, 49 patients were eventually diagnosed with idiopathic or familial PH, or PH associated with corrected or small (<2 cm) uncorrected atrial septal defects, two patients had a history of anorexigen intake, six were HIV-positive, 10 female patients suffered from collagen vascular disease, two had PH in association with Osler's disease, 13 patients had underlying lung disease [31], 97 patients had CTEPH, 7 had porto-pulmonary hypertension, and one patient suffered from pulmonary veno-occlusive disease.

In the no pre-capillary PH group, 53 patients were diagnosed with post-capillary PH. Of those, 42 patients suffered from PH due to left ventricular diastolic dysfunction (34 with systemic arterial hypertension and 10 with significant coronary artery disease). Nine patients with post-capillary hypertension suffered from PH due to lung disease and/or hypoxaemia [32]. In 11 patients PH was excluded because $\bar{P}_{pa}$ was <25 mmHg. Of those, one patient was diagnosed with pulmonary lymphangioleiomyomatosis, one patient had an isolated pulmonary AV malformation, two patients had manifest hyperthyreoidism, two patients were diagnosed with unilateral pulmonary artery occlusion, two patients had atrial septal defect and three patients had severe isolated tricuspid valve regurgitation.

There were no between-group differences with respect to demographic characteristics, including age and sex. Furthermore, no differences were encountered in the 6-min walking distances or serum creatinine levels. However, statistically significant differences between pre-capillary PH and no pre-capillary PH were found in NYHA class, serum NT-proBNP, P_{a,CO_2}, associated medical conditions, TTE parameters (*e.g.* $P_{pa,sys}$, right ventricular function and diameter, left ventricular wall thickness and diastolic function), haemodynamic parameters, heart rate, and ECG characteristics, *e.g.* P-wave amplitude and axis, QRS axis, RVH, bundle branch block, RVS pattern and the corrected QT interval (table 1).

Characteristics of the prospective patient cohort

Of 64 (52.9%) patients diagnosed with pre-capillary PH (table 2), 26 had CTEPH, 18 idiopathic or familial PH or PH associated with corrected or small uncorrected atrial septal defect, 13 suffered from PH associated with chronic lung disease [31], three had porto-pulmonary hypertension, two suffered from PH in association with collagen vascular disease and two had PH associated with HIV infection.

Of the 57 (47.1%) patients diagnosed with no pre-capillary PH, 32 suffered from post-capillary PH associated with either chronic lung disease [32] or diastolic left ventricular dysfunction, and 25 had normal pulmonary pressures [16]. Patients with normal pulmonary pressures suffered from parenchymal or bronchial pulmonary diseases (n=9), collagen vascular disease (n=3), coronary artery disease (n=2), unilateral occlusion of the pulmonary artery (n=1), isolated tricuspid regurgitation (n=1), patent arterial duct (n=1) or abnormal pulmonary vein drainage (n=1), and seven patients suffered from isolated systemic hypertension.

TABLE 1 Retrospective clinical, echocardiographic, haemodynamic and electrocardiographic characteristics of patients with pre-capillary pulmonary hypertension (PH) and no pre-capillary PH

	Pre-capillary PH	No pre-capillary PH	p-value
Subjects n	187	64	
Clinical parameter			
Age yrs	56.3±15.8	60.9±15.5	0.045
Male	71 (38.0)	26 (40.6)	0.77
6MWD m	336±139	367±117	0.15
NYHA classes III+IV	123 (65.8)	29 (45.3)	0.005
Serum NT-proBNP pg·mL^{-1}	1348±1693	478±1055	<0.001
Serum creatinine mg·dL^{-1}	1.1±0.3	1.1±0.3	0.77
P_{a,CO_2} mmHg	34.5±5.3	37.5±4.3	<0.001
Associated medical condition	52 (27.8)	5 (7.8)	<0.001
Transthoracic echocardiography parameter			
$P_{pa,sys}$ mmHg	82.2±27.2	50.0±13.4	<0.001
Right atrial diameter mm	58.0±9.5	54.6±8.0	0.012
Right atrial pressure mmHg	10.0±4.0	6.8±2.4	<0.001
TR severity: moderate + severe	81 (43.3)	17 (26.6)	0.017
Right ventricular dysfunction	108 (61.4)	2 (3.2)	<0.001
Right ventricular diameter mm	43.8±8.3	35.0±5.9	<0.001
Left ventricular hypertrophy	48 (28.9)	31 (50.0)	0.005
Left ventricular diastolic dysfunction	79 (47.6)	43 (69.4)	0.004
Haemodynamic parameter			
Cardiac output L·min$^{1\#}$	4.5±1.3	6.0±1.8	<0.001
$\bar{P}_{pa}$ mmHg	49.3±14.0	23.5±7.5	<0.001
PVR dyn·s·cm^{-5}	751.4±365.3	158.2±86.2	<0.001
P_{pcw} mmHg	10.4±5.6	12.6±5.2	0.007
ECG parameter			
Heart rate beats·min^{-1}	81.6±15.3	73.2±14.9	<0.001
P-wave amplitude mV¶	0.21±0.08	0.15±0.05	<0.001
P-wave axis° ¶	64.3±18.0	56.1±22.9	0.019
QRS axis°	67.3±64.5	40.5±43.3	<0.001
QRS duration ms	102±20	97±19	0.14
Right ventricular hypertrophy^{+}	92 (49.2)	7 (10.9)	<0.001
Right bundle branch block	66 (35.3)	4 (6.3)	<0.001
Left bundle branch block	2 (1.1)	8 (12.5)	<0.001
Right ventricular strain	147 (78.6)	5 (7.8)	<0.001
Left ventricular strain	16 (8.6)	7 (10.9)	0.62
QT interval ms	384±38	390±45	0.32
Corrected QT interval	434±34	424±31	0.041

Data are presented as mean±SD or n (%), unless otherwise stated. 6MWD: 6-min walk distance; NYHA: New York Heart Association; NT-proBNP: N-terminal brain natriuretic peptide; P_{a,CO_2}: arterial carbon dioxide tension; $P_{pa,sys}$: systolic pulmonary artery pressure; TR: tricuspid valve regurgitation; $\bar{P}_{pa}$: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; P_{pcw}; pulmonary capillary wedge pressure. #: derived from measurements based on the thermodilution method; ¶: 19 patients were excluded from p-wave analysis because of atrial fibrillation; +: diagnosed when the ratio of R and S in lead V1 was >1.

Predictors of diagnosis

Based on retrospective patient data, univariable (table 3) and three separate multivariable logistic regression models (table 4) were constructed for TTE, clinical parameters and ECG variables. $P_{pa,sys}$ (OR 1.06, 95% CI 1.03–1.09; p<0.001), right ventricular dysfunction (OR 10.28, 95% CI 2.18–48.44; p=0.003) and the absence of left ventricular hypertrophy (OR 0.34, 95% CI 0.15–0.75; p=0.008) were identified as independent predictors of pre-capillary PH. Of the clinical variables tested, serum NT-proBNP (OR 2.01, 95% CI; p=0.007), P_{a,CO_2} (OR 0.86, 95% CI 0.79–0.93; p<0.001) and associated medical conditions (OR 3.37, 95%CI 1.04–10.90; p=0.043) remained independent discriminative factors. ECG variables with the strongest diagnostic accuracy were heart rate (OR 1.05, 95% CI 1.02–1.08; p<0.001) and RVS (OR 52.93, 95% CI 17.27–162.18; p<0.001).

Accuracy of CART

Because all patients with $P_{pa,sys}$ ⩾36 mmHg and a suspicion of PH were referred for RHC, the sensitivity of TTE was 100%

TABLE 2 Prospective clinical, echocardiographic, haemodynamic and electrocardiographic characteristics of patients with pre-capillary pulmonary hypertension (PH) and no pre-capillary PH

	Pre-capillary PH	No pre-capillary PH	p-value
Subjects n	64	57	
Clinical parameter			
Age yrs	59.8±15.6	63.7±11.9	0.13
Male	27 (42.2)	23 (40.4)	0.84
6MWD m	325±126	330±126	0.83
NYHA classes III+IV	49 (76.6)	29 (45.3)	0.004
Serum NT-proBNP pg·mL^{-1}	3648±6541	1489±3518	<0.001
Serum creatinine mg·dL^{-1}	1.2±0.6	1.1±0.2	0.23
P_{a,CO_2} mmHg	36.1±7.2	38.4±5.3	0.049
Associated medical condition	20 (31.3)	3 (5.3)	<0.001
Transthoracic echocardiography parameter			
$P_{pa,sys}$ mmHg	82.6±24.3	55.2±16.3	<0.001
Right atrial diameter mm	58.7±10.9	59.1±11.5	0.870
Right atrial pressure mmHg	9.5±3.2	8.4±3.5	0.074
TR severity: moderate + severe	36 (56.3)	22 (38.6)	0.016
Right ventricular dysfunction	42 (65.6)	2 (3.5)	<0.001
Right ventricular diameter mm	44.0±9.2	38.2±6.9	<0.001
Left ventricular hypertrophy	24 (37.5)	30 (52.6)	0.39
Left ventricular diastolic dysfunction	31 (48.4)	42 (73.7)	0.001
Haemodynamic parameter			
Cardiac output L·min^{-1} #	4.2±1.1	5.0±1.4	0.001
$\bar{P}_{pa}$ mmHg	46.8±13.4	28.4±11.0	<0.001
PVR dyn·s·cm^{-5}	736.8±332.0	107.2±121.6	<0.001
P_{pcw} mmHg	10.9±5.1	16.5±8.4	<0.001
ECG parameter			
Heart rate beats·min^{-1}	85.7±14.6	77.3±18.6	0.007
P-wave amplitude mV¶	0.19±0.07	0.15±0.06	0.004
P-wave axis° ¶	61.0±29.7	65.3±15.2	0.43
QRS axis°	75.3±66.7	48.3±49.5	0.02
QRS duration ms	103±20	99±21	0.36
Right ventricular hypertrophy+	37 (57.8)	9 (15.8)	<0.001
Right bundle branch block	12 (18.8)	8 (14.0)	0.49
Left bundle branch block	0 (0.0)	1 (1.8)	0.47
Right ventricular strain	41 (64.1)	10 (17.5)	<0.001
Left ventricular strain	12 (18.8)	8 (14.0)	0.49
QT interval ms	380±39	384±41	0.29
Corrected QT interval	433±31	426±32	0.053

Data are presented as mean±standard deviation or n (%), unless otherwise stated. 6MWD: 6-min walk distance; NYHA: New York Heart Association; NT-proBNP: N-terminal brain natriuretic peptide; P_{a,CO_2}: arterial carbon dioxide tension; $P_{pa,sys}$: systolic pulmonary artery pressure; TR: tricuspid valve regurgitation; $\bar{P}_{pa}$: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; P_{pcw}; pulmonary capillary wedge pressure. #: derived from measurements based on the thermodilution method; ¶: 27 patients were excluded from p-wave analysis because of atrial fibrillation; +: diagnosed when the ratio of R and S in lead V1 was >1.

and the specificity was 0.0%. For a more specific noninvasive diagnostic decision tree, all independent clinical and ECG parameters that had been identified in the multivariable logistic regression models (table 4) were fed into the CART algorithm. The model automatically selected RVS and NT-proBNP for primary decision tree construction (fig. 1).

CART had a sensitivity of 99.4% and a specificity of 40.7%. Because these figures may be too optimistic as they are computed from data the tree had been derived from, two validation steps were added. Internal validation by the bootstrap technique was performed on the original data set resulting in a sensitivity of 97.9% (95% CI 94.5–99.2%) and a specificity of 17.3% (95% CI 9.5–29.5%). Temporal validation was performed on data from 121 prospectively recruited patients and yielded a sensitivity of 100% (95% CI 94.3–100%) and a specificity of 19.3% (95%CI: 11.1–31.3%) (table 5). While sensitivity was unchanged (100% *versus* 100%; p=1.0), specificity had improved from 0.0% according to current clinical practice to 19.3% (p=0.0009).

TABLE 3 Clinical, echocardiographic and ECG parameters to predict pre-capillary pulmonary hypertension in the retrospective cohort (univariable logistic regression)

	OR (95%CI)	p-value
Clinical parameter		
Age yrs	0.98 (0.96–1.00)	0.047
Male	0.89 (0.50–1.600	0.71
6MWD km#	0.17 (0.02–1.93)	0.15
NYHA classes III+IV	2.32 (1.30–4.13)	0.004
Serum NT-proBNP ng·mL^{-1}#	2.05 (1.31–3.22)	0.002
P_{a,CO_2} mmHg	0.89 (0.84–0.95)	<0.001
Associated medical condition	4.55 (1.73–11.96)	0.002
TTE parameter		
$P_{pa,sys}$ mmHg	1.08 (1.05–1.10)	<0.001
Right atrial diameter mm	1.04 (1.01–1.08)	0.0113
Right atrial pressure mmHg	1.32 (1.19–1.47)	<0.001
TR severity moderate + severe	2.36 (1.26–4.42)	0.008
Right ventricular dysfunction	48.44 (11.47–204.61)	<0.001
Right ventricular diameter mm	1.18 (1.12–1.24)	<0.001
Left ventricular hypertrophy	0.41 (0.22–0.74)	0.003
Left ventricular diastolic dysfunction	0.40 (0.22–0.75)	0.004
ECG parameter		
Heart rate beats·min^{-1}	1.04 (1.02–1.06)	<0.001
P-wave amplitude μV#	1.01 (1.01–1.02)	<0.001
P-wave axis°	1.02 (1.01–1.04)	0.009
QRS axis°	1.01 (1.00–1.01)	0.003
QRS duration ms	1.01 (1.00–1.03)	0.14
Right ventricular hypertrophy	7.89 (3.42–18.19)	<0.001
Right bundle branch block	8.18 (2.85–23.51)	<0.001
Left bundle branch block	0.08 (0.02–0.37)	0.001
Right ventricular strain	43.37 (16.32–115.26)	<0.001
Left ventricular strain	0.76 (0.30–1.95)	0.57
Corrected QT interval	1.01 (1.00–1.02)	0.043

6MWD: 6-min walk distance; NYHA: New York Heart Association; NT-proBNP: N-terminal brain natriuretic peptide; P_{a,CO_2}: arterial carbon dioxide tension; TTE: transthoracic echocardiography; $P_{pa,sys}$: systolic pulmonary artery pressure; TR: tricuspid valve regurgitation. #: units of measurement were adjusted for better readability of confidence intervals.

TABLE 4 Clinical, echocardiographic and ECG parameters to predict pre-capillary pulmonary hypertension in the retrospective cohort (multivariable logistic regression)

	OR (95% CI)	p-value
Clinical parameter		
Serum NT-proBNP ng·mL^{-1}#	2.01 (1.21–3.33)	0.007
P_{a,CO_2} mmHg	0.86 (0.79–0.93)	<0.001
Associated medical condition	3.37 (1.04–10.90)	0.043
TTE parameter		
$P_{pa,sys}$ mmHg	1.06 (1.03–1.09)	<0.001
Right ventricular dysfunction	10.28 (2.18–48.44)	0.003
Left ventricular hypertrophy	0.34 (0.15–0.75)	0.008
ECG parameter		
Heart rate beats·min^{-1}	1.05 (1.02–1.08)	<0.001
Right ventricular strain	52.93 (17.27–162.18)	<0.001

NT-proBNP: N-terminal brain natriuretic peptide; P_{a,CO_2}: arterial carbon dioxide tension; TTE: transthoracic echocardiography; $P_{pa,sys}$: systolic pulmonary artery pressure. #: units of measurement were adjusted for better readability of confidence intervals.

DISCUSSION

According to current guidelines [2], a significant proportion of patients referred for unexplained dyspnoea are undergoing invasive pressure measurements. To test the accuracy of standard noninvasive diagnostic tools, we analysed data sets from 251 retrospective and 121 prospective patients who underwent RHC for evaluation of PH. The main finding of our study was that ECG and NT-proBNP in addition to TTE suffice to predict significant pre-capillary pulmonary vascular disease at a level of sensitivity of 100% and specificity of 19.3%. In practice, based on the CART algorithm, RHC can be safely withheld in 9% of patients with elevated echo $P_{pa,sys}$ and clinical PH suspicion without overlooking true PH cases.

PAH, which is one of the major causes of pre-capillary PH, is a severe condition with serious prognosis [33]. The availability of potent vasodilator therapies that positively impact on morbidity and mortality [2, 34] has supported early recognition and treatment [20, 35]. Moreover, screening of asymptomatic individuals at increased risk for PH has been recommended. While invasive haemodynamic assessment has been considered the diagnostic gold standard in PH, TTE is the recommended screening tool [20, 34]. TTE is noninvasive, broadly available and most studies report a high correlation of 0.57–0.93 between TTE and invasive measurements of pulmonary arterial systolic pressures [2]. However, elevated $P_{pa,sys}$ may result from either pre-capillary PH or post-capillary PH, which cannot be safely distinguished by TTE alone. In contrast to post-capillary PH

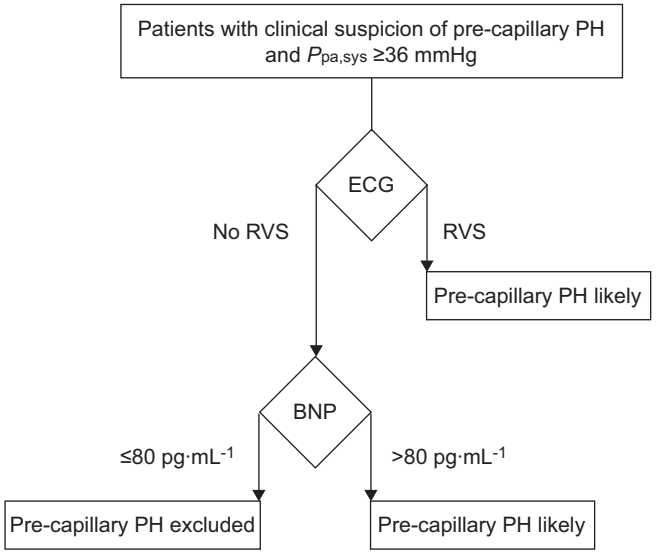

FIGURE 1. Pulmonary hypertension (PH) diagnosis tree based on the Classification and Regression Tree algorithm. $P_{pa,sys}$: systolic pulmonary artery pressure; BNP: brain natriuretic peptide; RVS: right ventricular strain.

TABLE 5 Prospective validation of the Classification and Regression Tree algorithm

Pre-capillary PH diagnosed by RHC	RVS	No RVS and NT-proBNP >80 pg·mL^{-1}	No RVS and NT-proBNP ⩽80 pg·mL^{-1}	Total
Yes	41	23	0	64
No	11	35	11	57
Total	52	58	11	121

Data are presented as n and results reflect the true predictive power of the decision tree because the prospectively recruited patients did not contribute to decision tree construction. A total of 121 patients were studied. Right ventricular strain (RVS) pattern was present in 52 patients, 41 of whom were diagnosed with pre-capillary pulmonary hypertension (PH) by right heart catheter (RHC). Patients without RVS pattern on ECG (n=69) were further dichotomised according to serum N-terminal brain natriuretic peptide (NT-proBNP) levels. 58 patients displayed serum NT-proBNP levels >80 pg·mL^{-1}; of these 23 were diagnosed with pre-capillary PH. In contrast, none of the 11 patients with serum NT-proBNP ⩽80 pg·mL^{-1} were diagnosed with pre-capillary PH.

[15], pre-capillary vascular disease is a rare condition [7]. These circumstances have recently led to numerous invasive procedures for exclusion. To narrow the grey zone that is blurring the distinction between pre- and post-capillary disease by echocardiography, current recommendations propose an invasive diagnostic work-up in patients with echocardiographic $P_{pa,sys}$ values >50 mmHg [36]. According to our assessments, this diagnostic approach would have substantially increased specificity to 42.1%; however, at the cost of overlooking 6.2% of true pre-capillary PH cases.

Although of limited value, standard ECG has diagnostic [37] and prognostic [38] potential in PH. Despite the fact that post-capillary PH may cause an RVS pattern on ECG [39], RVS remained the strongest predictor of pre-capillary PH in our study. RVS depicts right ventricular electric repolarisation, and appears to be a sensitive and immediate marker of right ventricular strain. The presence of RVS correctly identified 78.8% of pre-capillary PH cases. In addition, several non-invasive prognostic parameters have been established over the years, *e.g.* the 6-min walk distance [40], NYHA functional class [1], P_{a,CO_2} [23], associated medical conditions [27, 41–43], and serum NT-proBNP levels [44]. NT-proBNP is released from both cardiac ventricles in response to increased wall tension and is elevated in PH correlating well with pulmonary vascular resistance [45]. Its discriminative accuracy with respect to cardiac *versus* noncardiac causes of dyspnoea has been described previously [46], and is primarily based upon its excellent negative predictive value of 96% [47]. The combination of RVS and NT-proBNP, one being a strong positive, the other a strong negative predictor, confers clinical usefulness.

A main limitation of our study is its single centre design. A centre-specific bias with respect to diagnostic procedures, in particular TTE, cannot be excluded. Different referral patterns may influence proportions of PH *versus* non-PH cases. However, in contrast to positive and negative predictive values, sensitivities and specificities for the detection of PH are independent of the prevalence of healthy individuals in a given cohort.

Taken together, we would like to emphasise that RHC remains the gold standard for the evaluation of PH [11–13]. However, it is widely accepted that a diagnostic procedure that is primarily undertaken to rule out a disease is ideally noninvasive. In a selected patient population referred for dyspnoea and echocardiographic suspicion of PH, integration of the decision tree subsequent to TTE helps to avoid unnecessary RHCs in 9% of cases while not missing a single true PH case.

SUPPORT STATEMENT

This study received financial support from by the European Commission under the 6th Framework Programme (Contract No LSHM-CT-2005-018725, PULMOTENSION to I.M. Lang). This publication reflects only the author's views and the European Community is in no way liable for any use that may be made of the information contained therein. The research was supported by the Austrian fellowship grant FWFL 513-B11 to D. Bonderman and the Hans und Blanca Moser Stiftung to A.M. Martischnig.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.
2 Galie N, Torbicki A, Barst R, *et al.* Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243–2278.
3 Abenhaim L, Moride Y, Brenot F, *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 335: 609–616.
4 Petitpretz P, Brenot F, Azarian R, *et al.* Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. *Circulation* 1994; 89: 2722–2727.
5 Bonderman D, Jakowitsch J, Adlbrecht C, *et al.* Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. *Thromb Haemost* 2005; 93: 512–516.
6 Bonderman D, Wilkens H, Wakounig S, *et al.* Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2009; 33: 325–331.
7 Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998; 352: 719–725.
8 Bonderman D, Jakowitsch J, Redwan B, *et al.* Role for staphylococci in misguided thrombus resolution of chronic thromboembolic pulmonary hypertension. *Arterioscler Thromb Vasc Biol* 2008; 28: 678–684.

9 Jais X, Ioos V, Jardim C, *et al.* Splenectomy and chronic thromboembolic pulmonary hypertension. *Thorax* 2005; 60: 1031–1034.
10 Lang IM. Chronic thromboembolic pulmonary hypertension: not so rare after all. *N Engl J Med* 2004; 350: 2236–2238.
11 Badesch DB, Champion HC, Sanchez MA, *et al.* Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S55–S66.
12 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.
13 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493–2537.
14 Hoeper MM, Barbera JA, Channick RN, *et al.* Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S85–S96.
15 Paulus WJ, Tschope C, Sanderson JE, *et al.* How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; 28: 2539–2550.
16 Fisher MR, Forfia PR, Chamera E, *et al.* Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179: 615–621.
17 Michelakis ED. Soluble guanylate cyclase stimulators as a potential therapy for PAH: enthusiasm, pragmatism and concern. *Eur Respir J* 2009; 33: 717–721.
18 Hoeper MM, Lee SH, Voswinckel R, *et al.* Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *J Am Coll Cardiol* 2006; 48: 2546–2552.
19 Schenk P, Stiebellehner L, Burghuber OC, *et al.* [Examination of pulmonary circulation using right heart catheterization. Position paper of the Cardiopulmonary Task Force of the Austrian Society for Pneumology and the Austrian Society for Cardiology]. *Wien Klin Wochenschr* 2005; 117: 651–662.
20 McGoon M, Gutterman D, Steen V, *et al.* Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: Suppl. 1, 14S–34S.
21 Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987; 107: 216–223.
22 Fijalkowska A, Kurzyna M, Torbicki A, *et al.* Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest* 2006; 129: 1313–1321.
23 Hoeper MM, Pletz MW, Golpon H, *et al.* Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2007; 29: 944–950.
24 Dickstein K, Cohen-Solal A, Filippatos G, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; 29: 2388–2442.
25 Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 5th Edn. Philadelphia, Elsevier Health, 2004.
26 Burchell HB. The QT interval historically treated. *Pediatr Cardiol* 1983; 4: 139–148.
27 Bonderman D, Skoro-Sajer N, Jakowitsch J, *et al.* Predictors of outcome in chronic thromboembolic pulmonary hypertension. *Circulation* 2007; 115: 2153–2158.
28 Hoeper MM, Oudiz RJ, Peacock A, *et al.* End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol* 2004; 43: Suppl. 12, 48S–55S.
29 Koenig IR, Malley JD, Weimar C, *et al.* Practical experiences on the necessity of external validation. *Statist Med* 2007; 26: 5499–5511.
30 Efron B, Tibshirani RJ. An Introduction to the Bootstrap. New York, Chapman and Hall, 1993.
31 Weitzenblum E, Chaouat A, Canuet M, *et al.* Pulmonary hypertension in chronic obstructive pulmonary disease and interstitial lung diseases. *Semin Respir Crit Care Med* 2009; 30: 458–470.
32 Funk GC, Lang I, Schenk P, *et al.* Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. *Chest* 2008; 133: 1354–1359.
33 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
34 Grunig E, Weissmann S, Ehlken N, *et al.* Stress Doppler echocardiography in relatives of patients with idiopathic and familial pulmonary arterial hypertension. results of a multicenter European analysis of pulmonary artery pressure response to exercise and hypoxia. *Circulation* 2009; 119: 1747–1757.
35 Galie N, Rubin L, Hoeper M, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093–2100.
36 Olschewski H, Hoeper MM, Borst MM, *et al.* [Diagnosis and therapy of chronic pulmonary hypertension]. *Pneumologie* 2006; 60: 749–771.
37 Ahearn GS, Tapson VF, Rebeiz A, *et al.* Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. *Chest* 2002; 122: 524–527.
38 Bossone E, Paciocco G, Iarussi D, *et al.* The prognostic role of the ECG in primary pulmonary hypertension. *Chest* 2002; 121: 513–518.
39 Enomoto H. Clinical studies on the ventricular strain pattern electrocardioogram (I) : clinical statistical studies. *Jap Circ J* 1961; 25: 1277–1286.
40 Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.
41 Kawut SM, Taichman DB, Archer-Chicko CL, *et al.* Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003; 123: 344–350.
42 Kawut SM, Taichman DB, Ahya VN, *et al.* Hemodynamics and survival of patients with portopulmonary hypertension. *Liver Transpl* 2005; 11: 1107–1111.
43 Rich S, Shillington A, McLaughlin V. Comparison of survival in patients with pulmonary hypertension associated with fenfluramine to patients with primary pulmonary hypertension. *Am J Cardiol* 2003; 92: 1366–1368.
44 Nagaya N, Nishikimi T, Uematsu M, *et al.* Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; 102: 865–870.
45 Pruszczyk P. N-terminal pro-brain natriuretic peptide as an indicator of right ventricular dysfunction. *J Card Fail* 2005; 11: Suppl. 5, S65–S69.
46 Tabbibizar R, Maisel A. The impact of B-type natriuretic peptide levels on the diagnoses and management of congestive heart failure. *Curr Opin Cardiol* 2002; 17: 340–345.
47 Maisel AS, Krishnaswamy P, Nowak RM, *et al.* Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347: 161–167.