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ORIGINAL ARTICLE

Observational Study

Noninvasive model including right ventricular speckle tracking for the evaluation of pulmonary hypertension

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Abstract

AIM

To find parameters from transthorathic echocardiography (TTE) including speckle-tracking (ST) analysis of the right ventricle (RV) to identify precapillary pulmonary hypertension (PH).

METHODS

Forty-four patients with suspected PH undergoing right heart catheterization (RHC) were consecutively included (mean age 63.1 ± 14 years, 61% male gender). All patients underwent standardized TTE including ST analysis of the RV. Based on the subsequent TTE-derived measurements, the presence of PH was assessed: Left ventricular ejection fraction (LVEF) was calculated by Simpsons rule from 4Ch. Systolic pulmonary artery pressure (sPAP) was assessed with continuous wave Doppler of systolic tricuspid regurgitant velocity and regarded raised with values ⩾ 30 mmHg as a surrogate parameter for RA pressure. A concomitantly elevated PCWP was considered a means to discriminate between the precapillary and postcapillary form of PH. PCWP was

considered elevated when the E/e' ratio was > 12 as a surrogate for LV diastolic pressure. E/e' ratio was measured by gauging systolic and diastolic velocities of the lateral and septal mitral valve annulus using TDI mode. The results were then averaged with conventional measurement of mitral valve inflow. Furthermore, functional testing with six minutes walking distance (6MWD), ECG-RV stress signs, NT pro-BNP and other laboratory values were assessed.

RESULTS

PH was confirmed in 34 patients (precapillary PH, *n* = 15, postcapillary PH, *n* = 19). TTE showed significant differences in E/e' ratio (precapillary PH: 12.3 ± 4.4, postcapillary PH: 17.3 ± 10.3, no PH: 12.1 ± 4.5, *P* = 0.02), LV volumes (ESV: 25.0 ± 15.0 mL, 49.9 ± 29.5 mL, 32.2 ± 13.6 mL, *P* = 0.027; EDV: 73.6 ± 24.0 mL, 110.6 ± 31.8 mL, 87.8 ± 33.0 mL, *P* = 0.021) and systolic pulmonary arterial pressure (sPAP: 61.2 ± 22.3 mmHg, 53.6 ± 20.1 mmHg, 31.2 ± 24.6 mmHg, *P* = 0.001). STRV analysis showed significant differences for apical RV longitudinal strain (RVAS: -7.5% ± 5.6%, -13.3% ± 4.3%, -14.3% ± 6.3%, *P* = 0.03). NT pro-BNP was higher in patients with postcapillary PH (4677.0 ± 7764.1 pg/mL, precapillary PH: 1980.3 ± 3432.1 pg/mL, no PH: 367.5 ± 420.4 pg/mL, *P* = 0.03). Patients with precapillary PH presented significantly more often with ECG RV-stress signs (*P* = 0.001). Receiver operating characteristics curve analyses displayed the most significant area under the curve (AUC) for RVAS (cut-off < -6.5%, AUC 0.91, *P* < 0.001), sPAP (cut-off > 33 mmHg, AUC 0.86, *P* < 0.001) and ECG RV stress signs (AUC 0.83, *P* < 0.001). The combination of these parameters had a sensitivity of 82.8% and a specificity of 17.2% to detect precapillary PH.

CONCLUSION

The combination of non-invasive measurements allows feasible assessment of PH and seems beneficial for the differentiation between the pre- and postcapillary form of this disease.

Key words: Echocardiography; Right ventricle function; Pulmonary arterial hypertension

Core tip: We investigated the value of speckle-tracking (ST) analysis of the right ventricle (RV) in patients with suspected pulmonary hypertension. It focuses on a non-invasive model including parameters derived from standard transthorathic echocardiography (TTE) and ST, as well as electrocardiogram (ECG), six minutes walking distance and NT-pro BNP in order to distinguish the precapillary and postcapillary forms of PH. ST-derived apical RV longitudinal strain (RVAS < -6.5%), TTE-derived systolic pulmonary artery pressure (sPAP > 33 mmHg) and ECG RV stress signs were associated with precapillary PH, their combination had a sensitivity of 82.8% and a specificity of 17.2% for the detection of precapillary PH.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a precapillary form of pulmonary hypertension (PH). This severe disease is characterized by raised intrapulmonary pressures and changes in pulmonary haemodynamics that lead to high right ventricular (RV) afterload and chronic RV load[1]. The natural course of PAH is fatal within two to three years if missed and left untreated. Since heterogenous pathophysiological mechanisms[2] lead to elevated intrapulmonary pressures, it is crucial to distinguish the precapillary forms from the postcapillary forms of PH in order to initiate adequate therapy. According to current guidelines, the standard procedure for definite diagnosis is right heart catheterization (RHC)[3]. This invasive diagnostic mean is not widely available and inapplicable for routine follow-up (FU), due to its invasive nature and entails the risk of rare but serious complications. Therefore, a non-invasive diagnostic scheme that is reliable in: (1) diagnosing PAH; and (2) discriminating between the precapillary and postcapillary forms of PH would be of significant clinical benefit.

Recent research has aimed to detect different non-invasive diagnostic means that meet these requirements when combined. Thus, the design of our study was based on several considerations: A combination of electrocardiographic (ECG) criteria and N-terminal pro-Brain Natriuretic Peptide (NT pro-BNP) has been reported sufficient to rule out precapillary PH[4]. Transthorathic echocardiography (TTE) is a widespread, non-invasive and cost-effective instrument routinely used to assess left and right ventricular function. Speckle tracking (ST) analysis is a novel quantitative ultrasound technique that allows an angle-independent estimation of myocardial deformation[5] and function. We added ST analysis to our approach in order to level out the most important limitation of TTE, its angle- and observer-dependence.

The utility of echocardiography and ST analysis of the RV as an implement to assess presence and severity of PH has been the focus of current studies[6-8]. Due to its variable clinical presentation and difficult treatment, PH presents a clininal picture that needs functional assessment in its course, most commonly evaluated by six minutes walking distance (6MWD).

The aim of this study was to investigate the predictive significance of a non-invasive algorithm including parameters derived from ECG, echocardiography including RV strain analysis, functional testing with determination of 6MWD, lung function test and spirometry as well as NT pro-BNP and blood count for the diagnosis and

discrimination of pre- and postcapillary PH in a patient cohort with known RHC results, which were unknown to the assessor of the non-invasive measurements.

MATERIALS AND METHODS

Patients

Between April 2013 and April 2014 50 patients with suspected PH were prospectively included after undergoing RHC. All patients underwent informed consent and the study was approved by the Ethics Committee of the University Hospital of Bonn.

Right heart catheterization and definition of PH

Invasive hemodynamic parameters were evaluated during RHC according to current guidelines[9], defining precapillary PH as mean pulmonary arterial pressure (mPAP) $\geqslant$ 25 mmHg and pulmonary capillary wedge pressure (PCWP) of $\leqslant$ 15 mmHg and postcapillary PH as mPAP $\geqslant$ 25 mmHg and PCWP > 15 mmHg.

Non-invasive measurements

Non-invasive measurements consisting of TTE with special focus on the RV function and hemodynamics including speckle tracking analysis of the RV. Functional testing includes lung function test and 6MWD, as well as laboratory testing with the assessment of blood count, bilirubin, uric acid, serum creatinine, creatinine clearance and NT pro-BNP.

TTE and right ventricular speckle tracking

All participants underwent a complete echocardiographic examination including two-dimensional (2D) and Doppler echocardiography performed with commercially available ultrasound scanner with a 2,5-MHz phased array transducer (Vivid 7, General Electric Medical Health, Waukesha, Wisconsin, United States; iE 33 Philips Medical Systems, Koninklijke N.V.) according to the standard echocardiography protocol used at our clinic. The echocardiographic views were obtained in 2D and color tissue Doppler imaging (TDI) modes. In addition to parasternal long- and short-axis and apical two- and four-chamber (4CV) views, RV-focused views were obtained. The following measurements derived from TTE were utilized to assess the presence of PH considering a concomitantly elevated PCWP as a means to discriminate between the pre- and postcapillary forms of PH.

Left ventricular ejection fraction (LVEF) was calculated using Simpson's formula. Systolic pulmonary artery pressure (sPAP) was measured with continuous wave Doppler of systolic tricuspid regurgitant velocity and regarded raised with values $\geqslant$ 30 mmHg. PCWP was considered elevated when the E/e' ratio was > 12 as a surrogate for LV diastolic pressure. E/e‘ ratio was measured according to recommendations of the American Society of Echocardiography by gauging systolic and diastolic velocities of the lateral and septal mitral valve annulus using TDI mode. These measurements were then averaged with conventional measurement of mitral valve inflow[10].

The combination of sPAP > 30 mmHg and E/e‘ <12 was deemed to reflect precapillary PH, while sPAP > 30 mmHg and E/e‘ ratio >12 indicated postcapillary PH. Tricuspid annular plane systolic excursion (TAPSE) was obtained using M-Mode in the apical 4-Ch- view of the longitudinal excursion of the lateral tricuspid annulus towards the RV apex[11]. Additionally, diastolic interventricular septal thickness (IVSd), endsystolic (ESV) and enddiastolic volume (EDV) were measured. TTE derived parameters of our study population are shown in Table 1.

2DST analysis of the RV was performed using a routine grayscale apical 4-Ch view and a commercially available software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). As the region of interest, the RV endocardial border was manually delineated and was tracked by the 2D strain software. In order to ensure precise tracking of segments, visual assessment during cine loop playback was applied. The RV was divided visually in a basal, midventricular and apical segment and six corresponding time-strain curves were generated. Following the approach of Dambrauskaite[12] and Lopez-Candales[13] longitudinal lateral apical RV (RVAS) strain and global longitudinal RV strain (RVGS) entered further analysis. The longitudinal strain of the RV free wall, was calculated as the average of each of the three regional peak systolic strains along the entire right ventricle. An example for RV speckle tracking analysis is depicted in Figure 1.

Functional testing and assessment of clinical impairment

All our patients underwent a set of non-invasive testing in order to estimate the extent of their physical impairment due to PH. Shortness of breath was classified according to the World Health Organization (WHO) functional class score and gauged by 6MWD, using walking aids or portable oxygen if necessary. Standard 12-channel-ECG was screened for signs of RV strain such as RV hypertrophy, right axis deviation, right bundle block or signs of right atrial dilation[14]. Furthermore, pulmonary function was measured with spirometry and bodyplethysmography including total lung capacity, residual volume, vital capacity, forced expiratory volume and tiffeneau index. Blood count, bilirubin, uric acid, serum creatinine, creatinine clearance and NT pro-BNP were registered one to six weeks after RHC.

Statistical analysis

Data analysis was exploratory, variables underwent no adjustments. Normal distribution of continuous variables was examined employing the Kolmogorov-Smirnov test. Continuous data was expressed as mean values ± standard deviation. Two-tailed *P*-values were computed and regarded significant if ranging below 0.05 (95%CI). Two group comparisons were done using student's-*T*

Table 1 Echocardiographic and invasive measurements

	All patients (n = 44)	No PH (n = 10)	Precapillary PH (n = 15)	Postcapillary PH (n = 19)	P
TTE					
EF, %	61.3 ± 13.8	62 ± 9.5	67 ± 10.3	56.5 ± 16.7	0.28
EDV, mL	92.8 ± 36.1	87.8 ± 33.1	73.6 ± 34	110.6 ± 31.8	0.04
ESV, mL	37.4 ± 24.6	32.2 ± 13.6	25 ± 15	49.9 ± 29.6	0.04
IVSd, cm	1.2 ± 0.4	1.1 ± 0.2	1.1 ± 0.6	1.3 ± 0.4	0.12
LAV, mL	84.0 ± 52.7	82.4 ± 55.2	79.9 ± 64.9	85.2 ± 48.7	0.6
sPAP, mmHg	51.1 ± 24.4	31.2 ± 24.6	61.2 ± 22.3	53.6 ± 20.4	0.003
RVDs, cm	2.4 ± 1.1	2.2 ± 1.0	2.4 ± 1.1	2.3 ± 1.1	0.8
RVDd, cm	3.3 ± 1.4	3.0 ± 1.2	3.4 ± 1.6	3.3 ± 1.3	0.36
TAPSE, cm	1.8 ± 0.6	2.1 ± 0.6	1.8 ± 0.5	1.8 ± 0.6	0.23
E/e' ratio	14.4 ± 7.8	12.1 ± 4.5	12.4 ± 4.4	17.3 ± 10.3	0.13
RVGS, %	-11.5 ± 5.9	-13.3 ± 7.6	-10.8 ± 4.6	-11.2 ± 6	0.82
RVAS, %	-11.6 ± 5.9	-14.3 ± 6.3	-7.5 ± 5.6	-13.3 ± 4.3	< 0.001
RHC					
mPAP, mmHg	40.1 ± 17.5	20.9 ± 3	51.8 ± 20.6	40.9 ± 8.9	< 0.001
sPAP, mmHg	55.0 ± 17.6	35.3 ± 8.5	60.3 ± 17.4	53.5 ± 17.4	0.04
PCWP	16.1 ± 7.2	11.4 ± 4.1	11.4 ± 2.1	22.3 ± 6.3	< 0.001
CO, L/min	3.6 ± 3.8	3.3 ± 3.7	3.2 ± 3.3	3.4 ± 4.2	0.46
RV systolic pressure, mmHg	63.9 ± 26.3	37.1 ± 14.3	86.7 ± 25.4	66.3 ± 17.4	< 0.001
RV diastolic pressure, mmHg	5.3 ± 5.8	4.9 ± 5.3	4.3 ± 5.8	5.6 ± 5.8	0.07
RV mean pressure, mmHg	9.4 ± 8.6	7.5 ± 6.5	11.9 ± 12.1	8.6 ± 7.1	0.04
RA mean pressure, mmHg	13.5 ± 13.1	13.2 ± 9.3	12.7 ± 5.4	13.8 ± 14.7	0.69
WHO class					0.56
Ⅰ, n (%)	2 (4.3)	2 (20)	0 (0)	0 (0)	
Ⅱ, n (%)	10 (21.7)	3 (30)	2 (13.3)	5 (26.3)	
Ⅲ, n (%)	29 (63)	5 (50)	11 (73.3)	13 (68.4)	
Ⅳ, n (%)	3 (6.5)	0 (0)	2 (13.3)	1 (5.3)	

EF: Ejection fraction; EDV/ESV: End-systolic/diastolic volume; IVSd: Diastolic interventricular septum diameter; LAV: Left atrial volume; s/mPAP: Systolic/mean pulmonary arterial pressure; RVDs/d: Systolic/diastolic right ventricular diameter; TAPSE: Tricuspid annular plane systolic excursion; RVGS/RVAS: Global/apical right ventricular longitudinal strain; PCWP: Pulmonary capillar wedge pressure; CO: Cardiac output; RV/RA: Right ventricle/atrium; WHO: World Health Organization.

test for paired samples or Wilcoxon signed rank test for paired continuous variables. Categorical data was tested with Fisher's exact test. SPSS for Windows (PASW statistic, Version 21.0.0, SPSS Inc., Chicago, Illinois, United States) and MedCalc statistical software (MedCalc Software, Version 11.4.1.0, Mariakerke, Belgium) were utilized for statistical analysis.

Afterwards, a diagnostic model including RVAS, sPAP and E/e' ratio was generated by calculating associated ROC curves for the assumed possibilites. The corresponding AUCs along with 95%CI were calculated.

RESULTS

Six patients were excluded from the study population because of insufficient transthorathic image quality (n = 2), incomplete RHC results (n = 3) or withdrawal of consent (n = 1).

In total, 44 prospective patients [age 63.11 ± 14 years, 27 (61%), male], were consecutively included in our study. According to RHC, precapillary PH was diagnosed in 15 (34%), postcapillary PH in 19 (43%) and PH was excluded in 10 (23%) patients. Demographic baseline characteristics of the study cohort are shown in Table 2.

Echocardiography and speckle-tracking analysis

Echocardiographic measures on RV and LV functions differed significantly between patients with PH and those without PH concerning measures on LV diastolic function (E/e' ratio: Precapillary PH, 12.3 ± 4.4; postcapillary PH, 17.3 ± 10.3; no PH, 12.1 ± 4.5; P = 0.02), and LV volumes (ESV: 25.0 ± 15.0 mL, 49.9 ± 29.5 mL, 32.2 ± 13.6 mL, P = 0.027; EDV: 73.6 ± 24.0 mL, 110.6 ± 31.8 mL, 87.8 ± 33.0 mL, P = 0.021). Furthermore, sPAP showed significant differences between the patient groups (61.2 ± 22.3 mmHg, 53.6 ± 20.1 mmHg, 31.2 ± 24.6 mmHg, P = 0.001). Concerning RV function analysis, ST analysis of the RV free wall showed significant differences for apical RV longitudinal strain (RVAS: -7.5% ± 5.6%, -13.3% ± 4.3%, -14.3% ± 6.3%, P = 0.03), but not for global longitudinal RV strain (P > 0.05). All other measures on LV and RV function did not differ relevantly between the groups Table 1.

Functional testing and non-invasive measurements

Patients with precapillary PH presented significantly more often with ECG changes indicating RV stress (precapillary PH: 87%, postcapillary PH: 58%, no PH: 20%, P = 0.001). Functional status did not differ between patients with or without PH when comparing measures on 6MWD (375.3 ± 187.8 m, 319.5 ± 132.0 m, 372.5 ± 127.5 m,

Table 2 Baseline characteristics

	All patients (*n* = 44)	No PH (*n* = 10)	Precapillary PH (*n* = 15)	Postcapillary PH (*n* = 19)	*P*
Age, yr	63.11 ± 14.2	60.3 ± 16.9	60.2 ± 13	66.9 ± 13.3	0.71
Male gender, *n* (%)	27 (61)	5 (50)	8 (53)	14 (74)	0.33
AHT, *n* (%)	30 (60)	8 (61)	7 (53)	15 (62)	0.82
Diabetes mellitus, *n* (%)	11 (22)	2 (15)	3 (23)	6 (25)	0.57
CAD, *n* (%)	26 (52)	7 (53)	7 (53)	12 (50)	0.44
HLP, *n* (%)	15 (30)	4 (31)	6 (25)	5 (38)	0.33
Nicotine, *n* (%)	10 (20)	3 (23)	5 (21)	2 (15)	
Specific PAH Therapy, *n* (%)	15 (34)	0 (0)	15 (100)	0 (0)	< 0.001
ECG RV strain, *n* (%)	26 (59)	2 (20)	13 (87)	11 (58)	0.001
NT pro-BNP (pg/mL)	2778.3 ± 5681.3	367.5 ± 420.4	1980.3 ± 3432.1	4677 ± 7764.8	0.44
Hemoglobine, mg/dL	12.8 ± 3.6	11.4 ± 0.9	12.2 ± 2.5	12.6 ± 3.4	0.09
Bilirubin, mg/dL	0.7 ± 0.5	0.5 ± 0.2	0.9 ± 0.8	0.8 ± 0.3	0.08
Uric acid, mg/dL	7.1 ± 2.6	6.0 ± 1.7	6.9 ± 2.6	7.9 ± 2.8	0.13
Serum creatinine, mg/dL	1.3 ± 0.3	1.0 ± 0.2	1.3 ± 0.4	1.2 ± 0.2	0.25
Creatinine clearance, mL/min	55.3 ± 13.4	53.2 ± 8.9	50.5 ± 11.4	57.2 ± 6.3	0.48
6MWD, m	351.9 ± 153.2	372.5 ± 127.5	375.3 ± 186.8	319.5 ± 131.9	0.55

AHT: Arterial hypertension; CAD: Coronary artery disease; HLP: Hyperlipoproteinemia; PAH: Pulmonary arterial hypertension; ECG: Electrocardiogram; RV: Right ventricular; NT pro-BNP: N-terminal pro brain-natriuretic-peptide; 6MWD: 6 min walking distance.

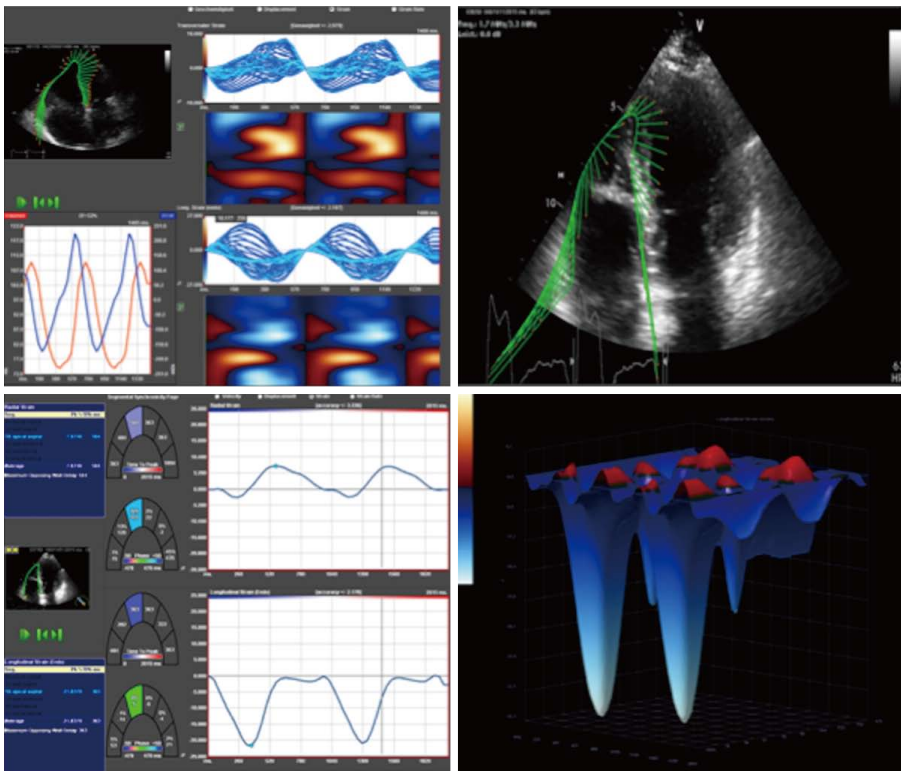

Figure 1 Example of right ventricular speckle tracking and three dimensional visualisation of longitudinal right ventricular strain values. RV: Right ventricular; 3D: Three dimensional; RVSI: Right ventricular longitudinal strain.

P > 0.05) and pulmonary function (Table 2).

Serum NT pro-BNP was significantly higher in patients with postcapillary PH (4677.0 ± 7764.1 pg/mL) as compared to patients with (precapillary PH (1980.3 ± 3432.1 pg/mL), or no PH (367.5 ± 420.4 pg/mL, *P* = 0.03). All other laboratory values did not show significant differences between the subgroups (Table 1). Notably, patients with elevated pulmonary pressures had a higher WHO functional class compared to patients without PH (*P* = 0.04) (Table 1, Figure 2).

Factors predicting PAH

In order to define cut-off values for the identification of precapillary PH, ROC analyses of variables with significant differences between the patient groups were done subsequently. Only measures on regional RV function with

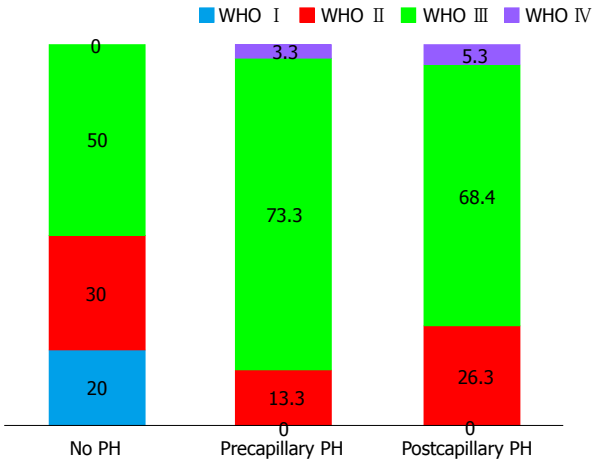

Figure 2 Distribution of World Health Organization classes in the study cohort, separated by etiology of pulmonary hypertension.

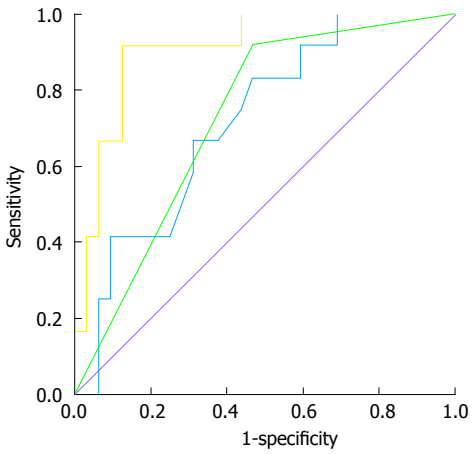

Figure 3 Incremental diagnostic value of the combination of non-invasive measures for identification of patients with precapillary pulmonary hypertension. Green curve, ECG RV stress signs alone; blue curve, apical right ventricular longitudinal strain alone; sand-colored curve, combination of non-invasive measures. RV: Right ventricle; ECG: Electrocardiograph.

strain imaging [RVAS: cut-off < -6.5%, area under the curve (AUC) 0.91, $P < 0.001$], RV hemodynamics (sPAP: cut-off > 33 mmHg, AUC 0.86, $P < 0.001$) and ECG RV stress signs (AUC 0.83, $P < 0.001$) were associated with precapillary PH.

A combination of the cut-off values showed a sensitivity of 82.8% and a specificity of 17.2% for the confirmation of precapillary PH (Figure 3).

DISCUSSION

According to current guidelines invasive testing with RHC is necessary for the diagnosis of PAH and the indication for RHC is based only on functional and clinical status in patients with persistent dyspnea of unknown cause.

Therefore, there is an unmet need for patient identification with a widespread, cost-effective and non-invasive tool[7]. Our group showed recently, that echocardiography might enable direct, easy and noninvasive diagnosis of PAH by combining non-invasive measures on RV hemodynamics utilizing sPAP, RV function RVAS and E/e' ratio as a parameter for LV diastolic function. In this study we intended to verify and extend this approach in a prospective fashion, integrating it into the newly suggested screening model for PAH in order to prove its clinical applicability.

Most importantly, the present study indicates that (1) the combined consideration of sPAP, RVAS, E/e' ratio and ECG RV stress signs seems to be a promising and easily applicable tool to discriminate between pre-, post-capillary and to some extent no PH; and (2) our data provide preliminary evidence that there does not seem to be an additional clinical benefit of functional testing with 6MWD, and/or pulmonary function tests in a preselected, severely ill patient cohort.

Need for early diagnosis of PAH

Current studies suggest the possibility of an improved long-term outcome in PAH patients when diagnosed and treated early[15,16]. Due to the unspecific symptoms of early stage PH and the limitations of routinely used screening methods, definite diagnosis is often delayed. Despite increased efforts in the early detection of PAH associated with connective tissue disease[17] and other known risk factors including bone morphogenic protein receptor 2 mutations[18], there is still a lack of general recommendations concerning screening algorithms for PAH in non-high risk populations. While 6MWD, NT pro-BNP and changes in WHO functional class have been described as significant predictors of outcome in patients with idiopathic PAH[19], Graspa *et al*[20] could demonstrate, that RV dysfunction, moderate to severe tricuspid regurgitation, a low cardiac index and elevated right atrial pressures are independent predictors in mortality in a large prospective study with patients suffering from PAH. The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) detected an elevated pulmonary vascular resistance (PVR), WHO functional class Ⅲ-Ⅳ, elevated mean right atrial pressure, 6MWD and Brain Natriuretic Peptide as predictive factors in PAH[21].

Right ventricular speckle-tracking in patients with pulmonary hypertension

Although clinical trials on RV strain analysis are rare, evidence proving its feasibility and prognostic value is constantly growing[5-8,13,22,24,28]. Whilst this study failed to show a significant correlation between RVGS and PH status, Rajagopal *et al*[5] were able to detect a sufficient relation between RVGS and functional status of patients suffering from PH applying a RV-centered echocardiographic approach. However, they included 40, mainly female (85%), patients, who in contrast to our cohort had a lower WHO functional class (73% WHO FC Ⅰ and Ⅱ, 27% WHO FC Ⅲ and Ⅳ). More importantly, other studies confirmed the diagnostic value of measuring regional alterations in strains derived from the RV free wall[22], namely the averaged RV peak strain as functional measure for RV ejection fraction

in adults and children suffering from different etiologies of RV impairment. However, there is still no study to verify the correlation between RV-derived strain and WHO functional class in a large patient cohort with determined PH.

Fukuda *et al*[6] were able to show a significant correlation between ST of the RV free wall with invasively measured mPAP and PVR as well as RV ejection fraction and RV end-systolic volume determined by cardiac magnetic resonance imaging and exercise tolerance by 6MWD thus implying RV ST as a suitable method to assess patients with PH. More recently, Sano *et al*[23] established RV ST analysis to describe reverse remodeling as a marker for long-term outcome of PH and Vitarelli *et al*[24] were able to affirm the diagnostic accuracy of two- and three-dimensional ST parameters, including RVAS as a surrogate for hemodynamic assessment and thus predictor of outcome in chronic pulmonary hypertension.

Screening for PAH

Humbert *et al*[18] suggested an elaborated screening algorithm for patients at risk for developing pulmonary hypertension, clearly delineating the lack of a standardized diagnostic approach in unselected patients.

Parent *et al*[25] found evidence for a combination of echocardiographic markers, 6MWD and NT-proBNP in patients with sickle-cell anemia associated PAH, whereas Allanore *et al*[26] proposed a combination of echocardiographic assessment of sPAP, serum NT-pro BNP, erythrocyte sedimentation rate and the diffusing capacity for carbon monoxide/alveolar volume in patients with systemic sclerosis. Although annual echocardiography is recommended in high risk populations[14,27], implementation of ST based RV functional analysis has not yet found consideration in order to refine the diagnostic value of TTE. Of note, the prognostic value of RV ST has been demonstrated for patients suffering from PH irrespective of its etiology by Haeck *et al*[28].

The drawbacks of all studies are the relatively small patient numbers, which may lead to biased conclusions and thus may lack general extrapolation. Therefore, the findings of the prospective DELPHI-2 study, which follows asymptomatic carriers of the bone morphogenic protein receptor 2 mutation and will provide their hemodynamic, echocardiographic and functional characteristics, will elucidate this topic in a relevant bigger cohort of patients at high risk of developing PAH.

COMMENTS

Background

Definite diagnosis of pulmonary hypertension (PH) in general and the distinction between the precapillary and postcapillary form of this disease in is often delayed due to unspecific symptoms and the necessity of invasive testing. The authors' study results verified a useful estimation of pulmonary pressure with transthorathic echocardiography (TTE). Combined with speckle-tracking (ST) analysis of the apical right ventricle (RV) and electrocardiogram (ECG) RV stress signs it seems to be of value to strengthen the suspicion of the rare but malignantly proceeding precapillary form of PH and therefore should be considered as a diagnostic tool in patients with suspected pulmonary arterial hypertension (PAH).

Research frontiers

Although the ST assessment of our cohort was performed blinded to the results of right heart catheterization (RHC), our approach was still retrospective. Therefore, confirmation of the study result needs to be acquired in a fully prospective study. Another weakness of this trial is the relatively small number of patients included, in order to reaffirm our findings, future research should aim to comprise larger numbers of patients of the different PH subgroups. Since there are multiple differential diagnoses to pulmonary hypertension that lead to RV strain and alterations of the RV geometry and contractility that have not been considered in our analysis, a prospective study design could compare RV speckle-tracking analysis of patients with PH ideally scrutinizing the diverse etiologies of PH and disparate right heart impairments. Ultimately, as the software available to perform ST-analysis was primarily produced for the left ventricle, newly developed software specialized on the complex geometry of the RV could refine the data.

Innovations and breakthroughs

The data in this study suggests that a combination of non-invasive measurements including echocardiography and speckle-tracking analysis allows feasible estimation of PH with a sensitivity of 82.8%. Taking into consideration all our findings a model for future assessment of suspected PH could provide an incrementally invasive examination beginning with TTE and ECG on the first level, adding NT pro-BNP on a second level and only after evaluating these results, a recommendation for timely RHC should be given.

Applications

In this study, ST showed only a specificity of 17.2% for detection of precapillary PH. Therefore, it does not seem to reliably identify PAH at this point and the definite diagnosis has still to be made by invasive RHC. However, ST has become more applicable in echocardiographic examination and it should be considered as an additional diagnostic tool for patients before invasive RHC. Our study results indicate a necessity for timely RHC assessing PAH if a patient shows RVAS < -6.5%, sPAP > 33 mmHg and electrocardiographic RV stress signs. In a second step, NT pro-BNP could help to determine the necessity of RHC in patients with RVAS > -6.5%. Since sPAP < 33 mmHg, no signs of RV stress in ECG and NT pro-BNP < 1000 pg/mL seemed not to correlate with PH, suggestion for RHC should be made reluctantly and other causes of dyspnea should be considered. However, given our small sample size, this model has yet to be tested in a larger patient cohort.

Terminology

The clinical classification of PAH comprises a heterogenous group of disease patterns that show unspecific clinical presentation due to elevated pulmonary pressures and right ventricular stress. ST is a relatively novel ultrasound technique that allows estimation of myocardial deformation as thus assessment of right ventricular function which is compromised in both pre- and post-capillary forms of pulmonary hypertension.

Peer-review

Recent studies focus on the value of ST-analysis in patients with suspected pulmonary hypertension, especially as to its potential to discriminate between pre- and postcapillary forms of PH. This work provides a comprehensive literature review on this topic. PAH is caused by heterogenous etiologies and often associated with rare diseases, therefore, the majority of papers available on ST in patients with PAH are centered on a specific etiology. The study included patients with suspected PAH regardless its etiology. The results are interesting and provide evidence of the utility of right ventricular ST in patients with suspected PAH.

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