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CLINICAL STUDY

ECG signs of right ventricular hypertrophy may help distinguish pulmonary arterial hypertension and pulmonary hypertension due to left ventricular diastolic dysfunction

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Abstract: *Objectives:* Distinguishing pulmonary arterial hypertension (PAH) and pulmonary hypertension due to left ventricular diastolic dysfunction (PHLDD) is essential for the correct disease management. We compared the importance of electrocardiographic (ECG) signs of right ventricular hypertrophy (RVH) in patients with similar degree PAH and PHLDD.
Methods: ECG analysis was retrospectively performed in 17 PHLDD and in 17 PAH patients with catheterization-confirmed moderate pulmonary hypertension. Sensitivity, specificity, and positive and negative predictive values for individual RVH signs were calculated.
Results: The PAH group showed a higher prevalence of the following: R/S ratio>1 in V1 ($p<0.001$), R in V1 + S in V6>1.05 mV ($p<0.01$), R wave peak time >0.035 s ($p<0.05$), right ventricular strain ($p<0.001$), and A+R–PL parameter (i. e. $R_{V1}+ S_{I} - S_{V1}$) =0.07 mV ($p<0.05$). The sensitivity and negative predictive value (NPV) of RVH signs for distinguishing PAH and PHLDD were low for all signs except right ventricular strain (sensitivity 71 %, NPV 77 %). The specificity and positive predictive value (PPV) of all six parameters were both 100 %.
Conclusions: In patients with pulmonary hypertension detected using echocardiography, ECG presence of RVH/overload may exclude LV diastolic dysfunction as a cause of PH and suggests the diagnosis of PAH *(Tab. 3, Ref. 19)*. Full Text in free PDF *www.bmj.sk.*
Key words: pulmonary arterial hypertension, pulmonary hypertension, right ventricle, left ventricular diastolic dysfunction, ECG, diagnosis.

Earlier diagnosis of pulmonary arterial hypertension (PAH) may be associated with an improved prognosis (1). The diagnostic algorithm of PAH involves ruling out all potential causes of pulmonary hypertension (PH) (2) and is often inefficient in identifying true cases of PAH. Right heart catheterization (RHC) is critical in the diagnosis of PAH. Due to a lack of availability and its invasive nature, however, it is not feasible for every patient with PH suspicion to undergo RHC. Accurate and timely identification of PH type is essential to select the most appropriate treatment because specific drug treatments have only been approved for patients with PAH (2, 3, 4).

PH due to left heart disease or pulmonary venous hypertension is the most frequent type of PH and represents up to 75 % of all PH cases (2). Systolic left ventricular (LV) dysfunction and left heart valvular diseases are usually not difficult to identify with echocardiography. However, PH due to LV diastolic dysfunction (PHLDD) remains a major diagnostic challenge. Several non-invasive parameters have been identified as markers of diastolic dysfunction (2, 3, 5). These parameters are nonspecific and have several limitations, and there remains a large amount of uncertainty in the proper diagnosis of diastolic heart failure (6). According to the ESC guidelines, diagnosis of PH due to left heart disease, including PHLDD, is defined as PWP >15 mmHg (2). An expert consensus document on LV diastolic dysfunction states the need for RHC confirmation in dubious cases with a suspicion of LV diastolic dysfunction, using a PWP of >12 mm Hg as a discriminative value for LV diastolic dysfunction, irrespective of the presence of PH (5). Even if we put this contradiction in borderline limits aside, there certainly remains a group of patients with higher borderline PWP values who probably have LV diastolic dysfunction but may be e. g. hypovolemic. These cases require the use of more sophisticated methods to rule out or confirm LV diastolic dysfunction as the most likely etiologic factor for their PH. The exact methodology for this approach, however, has not been standardized.

Simple, non-invasive tools are needed to assist clinicians in the evaluation of patients with possible PAH and help clinicians decide whether to proceed with additional invasive tests. An electrocardiogram (ECG) is a simple diagnostic tool. ECG signs of PH are represented by surrogate parameters of right ventricular hypertrophy (RVH) due to right ventricular pressure overload

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and the importance of ECG in the diagnosis of PH has already been established (7, 8, 9). In general, the sensitivity of these signs is low. However, the specificity of these parameters is high, although their accuracy for RVH seems to differ across underlying disorders (10). Echocardiography is currently the dominant method for PAH detection and screening. The role of ECG in the differential diagnosis and identification of the etiology of PH has not been evaluated.

The aim of this study was to compare the presence of ECG signs of RVH in patients with PAH and PHLDD. The sensitivity, specificity and positive and negative predictive values of RVH signs in distinguishing these two types of PH were evaluated.

Patients and methods

Thirty-four patients were included in the study. All patients were initially admitted to the PAH center due to clinical and echocardiographic suspicion of PAH. LV ejection fraction was preserved in all patients, and no evidence of left heart valvular disease was present on echocardiography. PH due to lung or chronic thromboembolic disease was excluded using spirometry, lung HRCT, ventilatory-perfusion scans, and CT pulmoangiography.

The patients also underwent right heart catheterization, and the presence and character of PH was evaluated according to the European Society of Cardiology (ESC) criteria (2). Seventeen patients (13 women) were diagnosed with PAH. Among these patients, the final diagnoses were idiopathic PAH in 10 patients, connective tissue disease-associated PAH in four patients and "other" PAH in two patients. The PAH patients were included in the study consecutively.

Seventeen patients (16 women) were diagnosed with PH due to diastolic LV dysfunction. Among these patients, the final diagnoses were diastolic heart failure due to arterial hypertension in 11 patients, restrictive cardiomyopathy in 2 patients, and "other" in 4 patients. PHLDD was "out of proportion" (i.e., the transpulmonary gradient exceeded 12 mmHg) in 12 patients in this group. To exclude potential pulmonary pressure-related bias, patients in the PHLDD group were selected to match those in the PAH group in terms of pulmonary artery pressure (PAP) such that the mean PAP values were comparable between groups. They were also selected to match the PAH patients in terms of age and LV function. The patients' main characteristics are listed in Table 1.

Tab. 1. Patient characteristics (LVEF – left ventricular ejection fraction, mPAP – mean pulmonary arterial pressure, PCW – pulmonary wedge pressure, sPAP – systolic pulmonary arterial pressure, TPG – transpulmonary gradient, PVR pulmonary vascular resistance).

Characteristics	PAH group	PHLDD group	P value
N	17	17	n. s.
(females)	(13)	(16)	
Age (median, range) (years)	56.7 (28–73)	60.2 (35–75)	n.s.
WHO-functional class (No of pts)			
II	6	7	
III	10	8	
IV	1	2	
mean	2.7±0.6	2.7±0.7	n.s.
LVEF (%)	62.8±7.8	60.3±11.4	n.s.
mPAP(mmHg)	41.1±6.8	37.9 ± 8.1	n.s.
PCW (mmHg)	8.8±2.0	22±4.7	<0.001
sPAP(mmHg)	64.2±14.5	56.8±13.7	n.s.
TPG(mmHg)	32.9±7.1	15.9±5.1	<0.001
PVR (dyn.s.cm^{-5})	617±268	277±172	<0.001

A retrospective analysis of the ECGs was performed. Standard 12-lead ECGs in the supine position (Hewlett-Packard France Every, paper speed 25 mm/s, sensitivity 1 mV = 10 mm) were obtained within 24 hours before RHC. To minimize inter-individual bias, ECG analysis was performed by a single cardiologist who was experienced in ECG reading and blinded to the data.

The presence of 12 established parameters of RVH was recorded for both groups. Six of these parameters were recommended by the AHA/ACCF/HRS for diagnosis of RVH (10). The parameters recorded are summarized in Table 2.

The prevalence of individual RVH parameters was compared between groups with PAH and PHLDD. Statistical differences in categorical variables were evaluated using Fisher's exact test. Student's t-test was used for comparison of QRS axis deviation. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the individual parameters showing statistically significant difference in frequency between groups were calculated.

Results

In the PAH group, there was a higher prevalence of the following parameters with respect to the PHLDD group: R/S amplitude ratio >1 in lead V1 (52.9 vs 0.0 %, p<0.001), sum of the R amplitude in V1 and S amplitude in V5 or V6 >1.05 mV (41.2 vs 0.0 %, p<0.01), delayed time of onset of the intrinsicoid deflection (R wave peak time) (35.3 vs 0.0 %, p<0.05), and right ventricular strain (70.6 vs 0.0 %, p<0.001). The rate of the integrated parameter A+R-PL (i.e. **R** or **R'** in V1 or V2 + **S** in I or V6 – **S** in V1) was higher in the PAH group (29.4 vs 0.0 %, p<0.05). The PAH group also showed a marked rightward deviation of the frontal plane QRS electrical axis in comparison with the PHLDD group (81.8 ±66.4° vs 15.4 ±45.5°, p<0.01).

There was no difference in the prevalence of increased P wave amplitude or duration, R amplitude in V1 =0.7 mV (11.8 vs 0.0 %), R amplitude in I =2 mm, a qR pattern in V1 (5.9 vs 5.9 %), R/S amplitude ratio in V5 or V6 =1 (29.4 vs 17.6 %), or an rSR' pattern in V1 with R' amplitude =1.0 mV (5.9 vs 0.0 %) between the two groups (p for all = n. s.). The prevalence of at least one of the above signs was higher in the PAH group (88.2 vs 23.5 %, p<0.05). Complete results are summarized in Table 2.

Seven patients from the PHLDD group had atrial fibrillation, and one patient from the PAH group had atrial flutter at the time of the ECG (p<0.05 for the presence of a sinus rhythm).

The sensitivity and NPV of RVH signs for distinguishing

Tab. 2. Endpoint parameters and results * Only for patients with sinus rhythm (see text).

Parameter	Discriminative value, positive finding	Reference	Presence in PAH group (n)	Presence in PHLDD group (n)	p value
P amplitude in II, III, aVF, V1 or V2	>0.25 mV	Butler, Leggett (8)	1	0	n. s.
R amplitude in I	≤2 mm	Butler, Leggett (8)	3	1	n. s.
R amplitude in V1	>7 mm	Sokolow, Lyon (7)	2	0	n. s.
R' amplitude in an rSR' configuration in V1	≥10 mm	Chou (17)	1	0	n. s.
qR pattern in V1	present	Chou (17)	1	1	n. s.
R/S amplitude in V1	>1	Sokolow, Lyon (7)	9	0	0.001
R/S amplitude in V5/6	< 1	Sokolow, Lyon (7)	5	3	n. s.
R in V1 + S in V5/6	>10.5 mm	Sokolow, Lyon (7)	7	0	0.007
Time of onset of QRS intrinsicoid deflection	>0.035 s	Myers (18)	6	0	0.018
QRS axis	>100°	Ahearn (16)	8	0	0.003
Right ventricular strain (negative T waves in V1-2)	present	Cabrera (19)	12	0	0.001
A+R-PL A = R or R' in V1 or V2 R = S in I or V6 PL = S in V1 or 2 (all amplitudes)	≥0.07 mV	Buttler, Leggett (8)	5	0	0.044

Tab. 3. Sensitivity, specificity, and positive and negative predictive values of selected parameters for distinguishing pulmonary arterial and pulmonary hypertension due to left ventricular diastolic dysfunction. NPV - negative predictive value, PPV - positive predictive value.

Parameter	Discriminative value, positive finding	sensitivity	specificity	PPV	NPV
R/S amplitude in V1	>1	0.53	1.00	1.00	0.68
R in V1+S in V5/6	>10.5 mm	0.41	1.00	1.00	0.63
Time of onset of QRS intrinsicoid deflection	>0.035 s	0.35	1.00	1.00	0.61
QRS axis	>100°	0.47	1.00	1.00	0.65
Right ventricular strain	present	0.71	1.00	1.00	0.77
A+R-PL	≥0.07 mV	0.31	1.00	1.00	0.61

PAH vs PHLDD were low for all signs except right ventricular strain (sensitivity 71 %, NPV 77 %). The specificity and PPV of all the parameters selected reached 100 % (Tab. 3).

Discussion

The merit of ECG signs of RVH in the diagnosis of PH has long been established. Prevalent markers of RVH have been shown to increase with rising systolic PAP and pulmonary vascular resistance (9, 11, 12) and might also be important in the long-term follow-up of patients at risk of developing PAH or in monitoring and assessing the response to treatment for PAH (12, 13). The presence of ECG signs of RVH before treatment has been associated with decreased survival in patients with primary PH (14).

Data on ECG signs of RVH in PH caused by LV diastolic dysfunction are scarce. In this case, the ECG pattern can be influenced by underlying conditions such as systemic arterial hypertension with LV remodeling or hypertrophy and hypertrophic or restrictive cardiomyopathy.

Overall, the prevalence of RVH signs was high (88.2 % for at least one sign) in the PAH group at the mean PAP level and low in the PHLDD group (23.5 %). The prevalence of "P pulmonale" was low (6 % in the PAH group vs 0 % in the PHLDD group). These findings are in agreement with those of Henkens et al. who found that the P amplitude in a group of 19 patients with pulmonary vascular resistance <500 dyne.s.cm^{-5} and a mean PAP of 37±8 mm Hg was 0.17 ±0.7 mV, suggesting a lower cut-off point for P wave amplitude than 0.25 mV (12), which would likely increase sensitivity at the cost of reduced specificity for this sign.

PAH patients showed a significant rightward shift in the frontal plane QRS axis with respect to PHLDD patients. Several au-

thors have found moderate correlation between rightward QRS axis deviation and PAP in mitral stenosis, primary PH, and connective tissue disease-associated PAH (15, 16). The sensitivity of a cut-off value of 100°, recently proposed by Ahearn et al., was low among our patients with moderate PAH (47 %). In a retrospective analysis of patients with PAH by Ahearn et al., this parameter reached 89 % sensitivity for detecting RV enlargement, 100 % specificity for a PVR of >5 Wood units and 83 % specificity for RV enlargement. The sensitivity and specificity of a mean PAP value >50 mmHg were moderate (73 % and 70 %, respectively) (16). Interestingly, none of our patients in the PHLDD group showed a QRS frontal axis >100°. The results for other QRS complex components that suggest right ventricular dominance in the transverse plane were mixed. An R amplitude >7 mm in V1 was present in 3 of 17 patients with PAH vs 1 of 17 in the PHLDD group, making it a parameter with very low sensitivity. However, an R/S amplitude ratio =1 in V1 showed higher prevalence in the PAH group vs. zero prevalence in PHLDD group, resulting in high specificity of this parameter but sensitivity of only 53 %. The difference in the rate of R' amplitude =10 mm in an rSR' pattern in V1 was not significant, but the overall prevalence of an rSR' pattern was very low among our patients. Parameters that took into account S wave amplitude in the precordial V5 or V6 leads could have been influenced by intraventricular conduction abnormalities such as left anterior hemiblock that can be more frequent in underlying conditions that result in LV diastolic dysfunction. The integrated Butler-Leggett A+R-PL parameter (Tab. 2) was only observed among PAH patients; however, the sensitivity of this parameter was lower than expected (35 %).

A repolarization disorder represented by the presence of right ventricular strain was the most frequent parameter observed in the PAH group, with 71 % sensitivity, 100 % specificity and PPV, and 77 % negative predictive value for prediction of PAH vs PHLDD. These findings correspond with those of Henkens et al. In their cohort, the T wave axis at baseline showed a significant leftward shift in patients with more severe PH (median of –9° for PVR >500 dyne.s.cm^{-5} and mean PAP 58±11 mm Hg vs 48° for PVR <500 dyne.s.cm^{-5} and mean PAP 37±8 mm Hg) (12). We did not evaluate the continuous variable of T wave axis in our group.

The limitations of this study include the retrospective nature of the data acquisition and the relatively low number of patients, which was a consequence of the low prevalence of PAH in the general population, as well as single centre character of the study. Thus, the definitive confirmation of our results requires verification in a larger population sample defined according to these specific criteria.

Conclusion

In summary, our results confirm the low sensitivity and high specificity of established parameters of RVH for predicting moderate PAH versus PHLDD. There were significant differences in the occurrence of these parameters between patients with PAH and those with PHLDD due to LV diastolic dysfunction (with the majority being "out of proportion") who had a similar mean PAP. We believe our results could have an impact in at least the following two clinical situations:

1) In patients with PH detected using echocardiography, when LV systolic dysfunction as well as lung and chronic thromboembolic pulmonary diseases are excluded noninvasively, the presence of ECG signs of RV hypertrophy/overload excludes LV diastolic dysfunction as a cause of PH and suggests the diagnosis of PAH. This could shift the diagnostic process towards RHC.

2) Our groups clearly had unequivocal pre-capillary (PWP = 8.8 ± 2.0 mmHg for PAH) and post-capillary (22 ± 4.7 mm Hg) PH. Thus, in patients with PWP in the upper borderline values for PAH as assessed by RHC, the presence of ECG signs of PH/RVH could further support the diagnosis of PAH. However, the absence of these signs supports the diagnosis of PH due to left ventricular diastolic failure.

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