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Remembering the Occam's Razor: Could Simple Electrocardiographic Findings Provide Relevant Predictions for Current Hemodynamic Criteria of Pulmonary Hypertension?

ABSTRACT

Background: We evaluated the predictive value of electrocardiographic (ECG) findings for pulmonary hemodynamics assessed by right heart catheterization (RHC).

Methods: Our study population comprised 562 retrospectively evaluated patients who underwent RHC between 2006 and 2022. Correlations between ECG measures and pulmonary arterial systolic and mean pressures (PASP and PAMP) and pulmonary vascular resistance (PVR) were investigated. Moreover, receiver operating characteristic (ROC) curve analysis assessed the predictive value of ECG for pulmonary hypertension (PH) and precapillary PH.

Results: The P-wave amplitude (Pwa) and R/S ratio (r) in V1 and V2, Ra in augmented voltage right (aVR), right or indeterminate axis, but not P wave duration (Pwd) or right bundle branch block (RBBB) significantly correlated with PASP, PAMP, and PVR ($P < .001$ for all). The partial R2 analysis revealed that amplitude of R wave (Ra) in aVR, R/Sr in V1 and V2, QRS axis, and Pwa added to the base model provided significant contributions to variance for PASP, PAMP, and PVR, respectively. The Pwa > 0.16 mV, Ra in aVR > 0.05 mV, QRS axis > 100° and R/Sr in V1 > 0.9 showed the highest area under curve (AUC) values for PAMP > 20 mm Hg. Using the same cutoff value, Ra in aVR, Pwa, QRS axis, and R/Sr in V1 showed highest predictions for PVR > 2 Wood Units (WU).

Conclusion: In this study, Pwa, Ra in aVR, right or indeterminate axis deviations, and R/Sr in V1 and V2 showed statistically significant correlations with pulmonary hemodynamics, and Ra in aVR, R/Sr in V2 and V1, QRS axis, and Pwa contributed to variance for PASP, PAMP, and PVR, respectively. Moreover, Pwa, Ra in aVR, QRS axis, and R/Sr in V1 seem to provide relevant predictions for PH and precapillary PH.

Keywords: Electrocardiogram, QRS axis, pulmonary hypertension

INTRODUCTION

Pulmonary hypertension (PH) is a relentlessly progressive disease characterized by an increase in PVR resulting in right ventricular (RV) pressure overload and right-sided heart failure.[1-6] Among the various noninvasive methods reported to be utilized in the screening, suspicion, and confirmation phases of definitive PH diagnostic algorithm,[1-29] the data regarding the usefulness of electrocardiogram (ECG) have remained inconclusive.[10-26] Right ventricular and right atrial (RA) hypertrophy due to pressure and/or volume overload have been documented to be frequent in patients with PH.[1-6] Electrocardiogram has been considered to have only a supportive role in diagnosis because of its low sensitivity and specificity.[1-6] However, current data suggest significant associations between some ECG alterations indicating pressure strain in right heart structures and severity of the disease in different forms of PH.[10-26]

In this study, we aimed to evaluate the correlations between ECG findings of RV and RA pressure overload and pulmonary hemodynamics as assessed by right heart catheterization (RHC). Moreover, we also assessed the predictive value of the cutoff values of these ECG measures for current definitions for overall PH

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and pre-capillary PH according to the European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2022 PH Guidelines criteria.[3]

METHODS

Our study population comprised 562 retrospectively evaluated patients [female 62.3%, median age of 49 years (range: 31-66)] who underwent RHC with different indications between 2006 and 2022, in accordance with the recommendations of the European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2009 and 2015 PH guidelines.[1,2]

Pulmonary arterial systolic and mean pressures (PASP and PAMP) and pulmonary vascular resistance (PVR) were assessed in all RHC procedures. However, updated criteria of ESC/ERS 2022 PH Guidelines have been used for hemodynamic definitions of PH and precapillary PH. The PAMP > 20 mm Hg cutoff value have been utilized as diagnostic criteria for PH. While PAWP ≤ 15 mm Hg and PVR > 2 Wood Units (WU) criteria have been included in the pre-capillary PH definition.[3]

Correlations between ECG measures and PASP, PAMP, and PVR as assessed by RHC were investigated. Moreover, receiver operating characteristic (ROC) curve analysis and area under curve (AUC) were used to assess the predictive value of ECG measures for currently accepted definitive criteria of PH and precapillary PH.

The clinical and demographic characteristics, ECG recordings, and RHC data of the patients were obtained from the hospital database. Electrocardiogram was taken on the day of RHC. The patients with missing files were excluded from the study. Electrocardiographs with artifacts were excluded from the study. Group 2 PH patients with reduced EF have been followed by another team except us in our hospital; therefore, our data does not contain this group. Only 8 patients with group 2 PH due to heart valve abnormalities who underwent heart catheterization before surgery have been included in our study.

Written informed consent was obtained from each participant, and the study protocol was reviewed and approved by the Local Institutional Ethics Committee (approval date: January 31, 2023, approval number: 2023/02/668) in accordance with the Declaration of Helsinki.

Electrocardiographic recordings were performed with the standard 12-lead ECG (Schiller AT-2 plus, Switzerland) at rest on a paper speed of 25 mm/s and a sensitivity of 1 mV = 10 mm. The following parameters were analyzed: heart rhythm, rate, electrical QRS axis at the frontal plane, intraventricular conduction abnormalities, P-wave amplitude and duration (Pwa and Pwd) in lead II, R/S voltage ratio (R/Sr) in V1 and V2, amplitude of R-wave (Ra) in lead aVR, and QRS duration.

These were scanned for online analysis using the Cardio Calipers program (Version 3.2 for Windows, Iconico, www.iconico.com) (Supplementary Figure 1). A total of 3 consecutive cycles were measured in each of the standard 12 leads, and the mean of each parameter was calculated from these values and included in the analysis. The beginning of the P wave was defined as the point where the initial deflection of the P wave crossed the isoelectric line, and the end of the P wave was defined as the point where the final deflection of the P wave crossed the isoelectric line.

Statistics

Continuous data were presented as medians and interquartile ranges, and categorical data were defined as frequency and percentage.

Outcome variables (dependent, Y): PASP, PAMP, and PVR as continuous variables.

Candidate predictors (independent, X): aVR R, QRS axis, Pwd, Pwa, RSV1, RSV2, and RBBB (all were continuous except RBBB).

We developed base a linear regression model that included age, sex, and presence of PH. The added value of ECG variables (aVR R, QRS axis, Pwd, Pwa, RSV1, RSV2, and RBBB) demonstrated the incremental contributions to the base model built in predicting the PASP, PAMP, and PVR. Results of regression models represented as regression coefficients and *P*-values. Model performances were evaluated by R squared (R2). The continuous ECG variables (aVR R, QRS axis, Pwd, Pwa, RSV1, and RSV2) were included in the model using restricted cubic spline (4 knots) and age using 3 knots. Adjusted relationship between dependent and independent variables were visualized by using partial effect plots.

To investigate the best cutoff of the ECG measurements to predict PASP > 20, PVR > 2, and PVR > 3, we also performed ROC curve analysis. An AUC value of 0.5 indicates a random chance, while an AUC value of 1.0 indicates a perfect discriminatory power. To find the best cutoff value for the ECG measurements, we used the Youden index, which maximizes the difference between the true positive rate and false positive rate. The Youden index is calculated as follows: Youden index = sensitivity + specificity − 1. We identified the cutoff value for the ECG measurements that maximize the Youden index.

The all-statistical analyses, two-tailed *P*-value less than .05 was set as statistical significance. Statistical analyses were

HIGHLIGHTS

- In electrocardiogram, P-wave amplitude (Pwa), amplitude of R-wave (Ra) in augmented voltage right (aVR), right or indeterminate axis deviations, and R/Sr in V1 and V2 showed statistically significant correlations with pulmonary hemodynamics.
- The Ra in aVR, R/S ratio (r) in V2 and V1, increase in QRS axis, and Pwa had significant and incremental contributions to variance for pulmonary arterial systolic pressure, pulmonary arterial mean pressures, and pulmonary vascular resistance, respectively.
- P-wave amplitude, Ra in aVR, rightward and extreme QRS axis deviations, and R/Sr in V1 seem to provide relevant predictions for pulmonary hypertension (PH) and precapillary PH.

performed using R version 4.2 software (Vienna Austria) with the "rms", "pROC", and "ggplot2" packages. R version 4.2 software (Vienna Austria) with "desctool" and "ggplot2" packages.

RESULTS

The patients' characteristics are given in Table 1. The ECG was evaluated in all 562 patients, and measures are summarized in Table 2. The rhythm was in sinus, persistent atrial flutter, and fibrillation in 499 (88.8%), 3 (0.5%), and 60 (10.7%) patients, respectively. The median frontal ECG axis was 60 (30; 120). The breakdown of the ECG axis were as follows: normal: 281 (50.1%), right deviation: 170 (30.3%), extreme: 22 (3.9%), and left deviation: 88 (15.7%). The incomplete and complete RBBB were noted in 62 and 39 patients, respectively. The 1st degree atrioventricular block was present in 11 patients (1.9%), while the left bundle branch block (LBBB) or higher degree atrioventricular block was not documented. The mean amplitude and duration of P wave in V1 derivations were 0.10 (0.10, 0.15), 0.08 (0.06, 0.10) mm and milliseconds, respectively.

In multiple linear regression model, there were significant association between invasively assessed PASP and "right or indeterminate axis deviations in frontal plane, Pwa, R/Sr in V1 and V2 and Ra in aVR" ($P < .001$ for all), but not with Pwd or RBBB ($P = .176$ and $P = .700$, respectively) (Figure 1). Similarly, PAMP also showed a significant relation to right or indeterminate axis deviations in frontal plane, Pwa, R/Sr in V1 and Ra in aVR ($P < .001$ for all) and R/Sr in V2 ($P = .002$), but not with Pwa or RBBB ($P = .069$ and $P = .427$, respectively) (Figure 2). Moreover, PVR showed a significant relation to right or indeterminate axis deviations in frontal plane, Pwa, R/Sr in V1 and V2, and Ra in aVR ($P < .001$) but not to Pwd or RBBB (0.991 and $P = .500$, respectively) (Figure 3). The importance of each predictor in a model was calculated as the proportion of explainable outcome variation contributed by each predictor assessed by partial R2, analysis revealed the incremental contributions of each ECG measures for variance in PASP, PAMP, and PVR (Figure 4). The aVR R amplitude and RBBB were the weakest variables, while Pwa and QRS axis were the strongest variables. Supplementary Figure 2 demonstrated that U-shaped curves of the patients PASP, PAMP, and PVR distribution along the QRS axis spectra. The PASP, PAMP, and PVR values were found to be increased with right or extreme/indeterminate axis deviations.

The ROC curve analysis was performed to evaluate the AUC values of the cutoff values of ECG variables predicting the PAMP > 20 mm Hg, PVR > 2 and PVR > 3 WU, respectively (Table 3). The 0.16 mV cutoff value of Pwa (AUC: 0.688, sensitivity: 0.564, specificity: 0.731) and 0.05 mV value of Ra in aVR (AUC: 0.683, sensitivity: 0.862, specificity: 0.424), 100° of QRS axis (AUC: 0.666, sensitivity: 0.361, specificity: 0.964), followed by 0.9 value of R/Sr in V1 showed the highest prediction for PAMP > 20 mm Hg. Moreover, the predictions for the novel definitive threshold of PVR > 2 WU for precapillary PH and the former definitive thresholds of PVR > 3 WU

Table 1. Patients' Characteristics

Characteristics	n = 562
Age (years)	49 (34-64)
Sex (male)	212 (37.7%)
Group 1 PAH (n)	274 (48.7%)
APAH—congenital heart disease	126 (45.9%)
IPAH	129 (47%)
APAH—connective tissue disease	15 (5.5%)
APAH—drug	1 (0.4%)
Portopulmonary hypertension	3 (1.1%)
Group 2 PH (n)	8 (1.4%)
Group 3 PH (n)	5(0.9%)
Group 4 PH (CTEPH) (n)	96 (17%)
Group 5 PH* (n)	8 (1.4%)
Patients without pulmonary hypertension (n)	171 (30%)
PASP (mm Hg)	62 (37-92)
PAMP (mm Hg)	37 (22-56)
PAWP (mm Hg)	12.0 (9-14)
PVR (WU)	4.7 (1.8-9)
SVR (WU)	19.7 (16.0-24.0)
TAPSE (cm)	2.00 (1.60-2.30)
LVEF (%)	65.0 (65.0-65.0)
Moderate-to-severe MR (n)	53 (9.4%)
Moderate-to-severe TR (n)	266 (47.3%)
AF (n)	74 (13.3%)
QRS axis (°)	60° (0-105°)
Clockwise rotation, yes (n)	62 (11%)
P-wave duration on V1 (ms)	0.10 (0.08-0.12)
P-wave amplitude on V1 (mV)	0.16 (0.10-0.20)
P-wave amplitude on V2 (mV)	0.10 (0.10-0.15)
PR duration on V1 (ms)	0.160 (0.140-0.180)
Biphasic P wave on V1 (n)	140 (24.9%)
P-wave duration on D2 (ms)	0.100 (0.080-0.120)
P-wave amplitude on D2 (mV)	0.20 (0.15-0.24)
PR duration on D2 (ms)	0.160 (0.140-0.180)
QRS duration (ms)	0.08 (0.08-0.100)
RBBB (n)	
Incomplete	88 (15.9%)
Complete	46 (8.3%)
qR in V1 (n)	78 (13.8%)
R-wave amplitude on V1 (mV)	0.20 (0.10-0.50)
R-wave amplitude on V2 (mV)	0.50 (0.30-0.80)
R/S ratio on V1	0.25 (0.16-0.50)
R/S ratio on V2	0.50 (0.30-1.00)
V1-2 T-wave inversion (n)	
v1	5 (1.4%)
vV1	159 (43.3%)
V1 v2	83 (22.6%)
V2	23 (6.3%)

(*Continued*)

Table 1. Patients' Characteristics (*Continued*)

Characteristics	n = 562
V2 v1	97 (26.4%)
Amplitude of T-wave inversion on V1-V2 (mV)	0.20 (0.1-0.30)
aVR Ra (mV)	0.25 (0.10-0.40)

Continuous variables given as median and interquartile range (25^{th}-75^{th}).
AF, atrial fibrillation; APAH, associated pulmonary arterial hypertension; aVR Ra, R amplitude of lead aVR; cm, centimeter; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; ms, millisecond; mV, millivolt; PAH, pulmonary arterial hypertension; PAMP, pulmonary artery mean pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RBBB, right bundle branch block; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.
*One of the patients had histiocytosis; others had segmental pulmonary arterial hypertension due to truncus arteriosus or complex congenital heart disease like single ventricle.

were compared. For PVR > 2 WU, 0.05 cutoff value of Ra in aVR (AUC: 0.710, sensitivity: 0.889, specificity: 0.459) 0.16 mV cutoff value of Pwa (AUC: 0.680, sensitivity: 0.572, specificity: 0.732), 100° of QRS axis (AUC: 0.658, sensitivity: 0.37, specificity: 0.93), and 0.16 value of R/Sr in V1 (AUC: 0.635, sensitivity: 0.818, specificity: 0.407) showed highest predictions. For PVR > 3 WU, a 0.05 cutoff value of Ra in aVR (AUC: 0.696, sensitivity: 0.899, specificity: 0.413), 0.16 mV cutoff value of Pwa (AUC: 0.665, sensitivity: 0.587, specificity: 0.702), 100° of QRS axis (AUC: 0.654, sensitivity: 0.378, specificity: 0.899), and 0.16 value of R/Sr in V1 (AUC: 0.662, sensitivity: 0.840, specificity: 0.400) were most powerful predictors (Table 3). Figure 5A, B, and C demonstrate the AUC values of these cutoff values, predicting the PAMP > 20 mm Hg, PVR > 2 and ≥ 3 WU, respectively.

DISCUSSION

In this retrospective study, some of the simple ECG parameters were found to be related with RHC measures of pulmonary circulation and right ventricular pressure strain. The PASP, PAMP, and PVR showed significant, consistent, and clinically relevant correlations to Pwa, Ra in aVR, right or indeterminate axis deviations in the frontal plane, and R/Sr in V1 and V2, but not to Pwd or RBBB. The partial R2 analysis revealed that Pwd or RBBB pattern did not provide any contribution to the base model, while Ra in aVR, R/Sr in V2 and V1, increase in QRS axis, and Pwa had stepwise and concordant contributions to variance for PASP, PAMP, and PVR, respectively. The Pwa > 0.16, Ra in aVR > 0.05 mV, QRS axis > 100°, and R/Sr in V1 > 0.9 showed the highest prediction for overall PH and precapillary PH diagnosis according to the ESC/ERS 2022 PH definitive RHC criteria.

The ECG has been utilized as one of the basic noninvasive tools in PH diagnostic algorithms, and relationship between ECG parameters and hemodynamic and clinical status have been investigated in some studies.[10-26] However, the diagnostic and prognostic impact of ECG measures have seemed to be understated.

Table 2. Regression Coefficients and *P*-values of Electrocardiographic Variables Demonstrating the Incremental Contributions to Base Model Built by Using Age, Sex, Presence of PH in Predicting the PASP, PAMP, and PVR

	Regression Coefficient	95% Lower CI	95% Upper CI	*P*
PASP				
Base + Pwd from 0.08 to 0.12 sec	1.55	−3.51	6.61	.176
Base + Pwa from 0.15 to 0.25	7.01	2.55	1146	<.001
Base + QRS axis				<.001
From −100 to 0	−13.85	−20.26	−7.44	
From 0 to +100	9.93	4.46	15.4	
Base + aVR Ra from 0.1 to 0.3	4.49	1.76	7.22	<.001
Base + RBBB				.505
Incomplete vs. No	4.04	−2.92	11.01	
Complete vs. No	−0.27	−5.53	4.98	
Base + R/Sr in V1 from 0.2 to 0.8	1.18	−1.20	3.57	<.001
Base + R/Sr in V2 from 0.3 to 1	2.00	−0.61	4.62	<.001
PAMP				
Base + Pwd from 0.08 to 0.12 seconds	3.04	−0.32	6.40	.069
Base + Pwa from 0.15 to 0.25	5.57	2.63	8.51	<.001
Base + QRS axis				<.001
From −100 to 0	−8.36	−12.54	−4.17	
From 0 to +100	6.10	2.52	9.67	
Base + aVR Ra from 0.1 to 0.3	2.62	0.83	4.41	<.001
Base + RBBB				.427
Incomplete vs. No	2.97	−1.57	7.51	
Complete vs. No	0.70	−2.71	4.11	
Base + R/Sr in V1 from 0.2 to 0.8	0.42	−1.14	1.99	<.001
Base + R/Sr in V2 from 0.3 to 1	1.21	−0.51	2.93	.002
PVR				
Base + Pwd from 0.08 to 0.12 seconds	0.12	−1.03	1.28	.991
Base + Pwa from 0.15 to 0.25	1.76	0.76	2.76	<.001
Base + QRS axis				<.001
From −100 to 0	−2.44	−3.88	−1.01	
From 0 to +100	1.22	0.04	2.40	
Base + aVR Ra from 0.1 to 0.3	1.01	0.41	1.60	.001
Base + RBBB				.634
Incomplete vs No	0.20	−1.40	1.79	
Complete vs No	−0.51	−1.64	0.62	
Base + R/Sr in V1 from 0.2 to 0.8	0.57	0.11	1.03	<.001
Base + R/Sr in V2 from 0.3 to 1	0.52	−0.05	1.09	<.001

*Base models were built by using age, sex, presence of pulmonary hypertension.
PASP, pulmonary artery systolic pressure; PAMP, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; Pwa, P-wave amplitude; Pwd, P-wave duration; RBBB, right bundle branch block; R/Sr, R/S ratio.

The ECG parameters have been reported to be strongly correlated with echocardiographic markers of pulmonary arterial pressure burden, RV and RA overload, hypertrophy and dysfunction, functional status, 6-minute walk distance, and cardiopulmonary exercise parameters of respiratory response as defined by minute ventilation to carbon dioxide

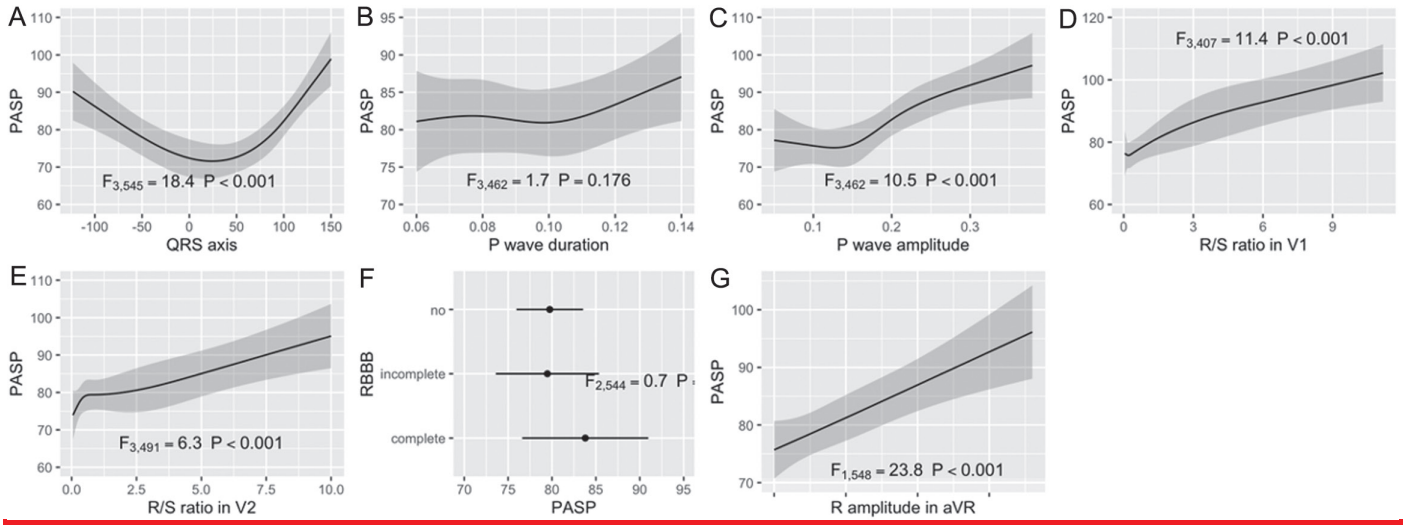

Figure 1. Summary of relationship between continuous measures of ECG and PASP. ECG: electrocardiogram; PASP, pulmonary artery systolic pressure; RBBB, right bundle branch block.

production slope (VE/VCO2) and hemodynamic measures of pulmonary circulations as assessed by RHC.[10-26]

In a study by Michalski et al[17], Pwa in lead II correlated to VE/VCO2 slope and echocardiographic estimates of RA pressure. Seyyedi et al reported that P-pulmonale was frequent in patients with severe RV dysfunction but not related to NT-proBNP concentration or 6-minute walk distance.[22] However, Bossone et al found that the presence of P-pulmonale was associated with a decreased survival rate.[21] These results seem to be consistent with our data showing the relationship between Pwa and higher PASP, PAMP, and PVR. The lack of correlation between Pwa and these hemodynamic measures is another important finding of our study. Furthermore, we found that 0.16 mV cutoff value of Pwa was the strongest predictor of PAMP > 20 mm Hg and among the most powerful predictors for PVR > 2 and > 3 WU, respectively.

The R-wave in lead aVR, reflecting RV hypertrophy and extreme/indeterminate QRS axis deviation, seems to be another controversial issue in this setting. We found a highly significant and clinically relevant correlation between the amplitude of R-wave in lead aVR and PASP, PAMP, and PVR. Therewithal 0.05 mV value of Ra in aVR was the strongest predictor for PAMP > 20 mm Hg, PVR > 2 and > 3 WU. Michalski et al[17] reported that R-wave in lead aVR were correlated with RV function, RV free wall thickness, overload, tricuspid regurgitation pressure gradient, VE/VCO2 slope, and invasively assessed PAMP and other hemodynamic measures of pulmonary arterial hypertension (PAH) diagnosis. Cheng et al[24] reported that R-wave in lead aVR > 0.40 mV was an independent predictor of mortality. The RV Sokolow–Lyon index was correlated with RV function, RV free wall thickness, overload, tricuspid regurgitation pressure gradient, VE/VCO2 slope and invasively assessed PAMP and other hemodynamic measures of PAH diagnosis.[17] The RV

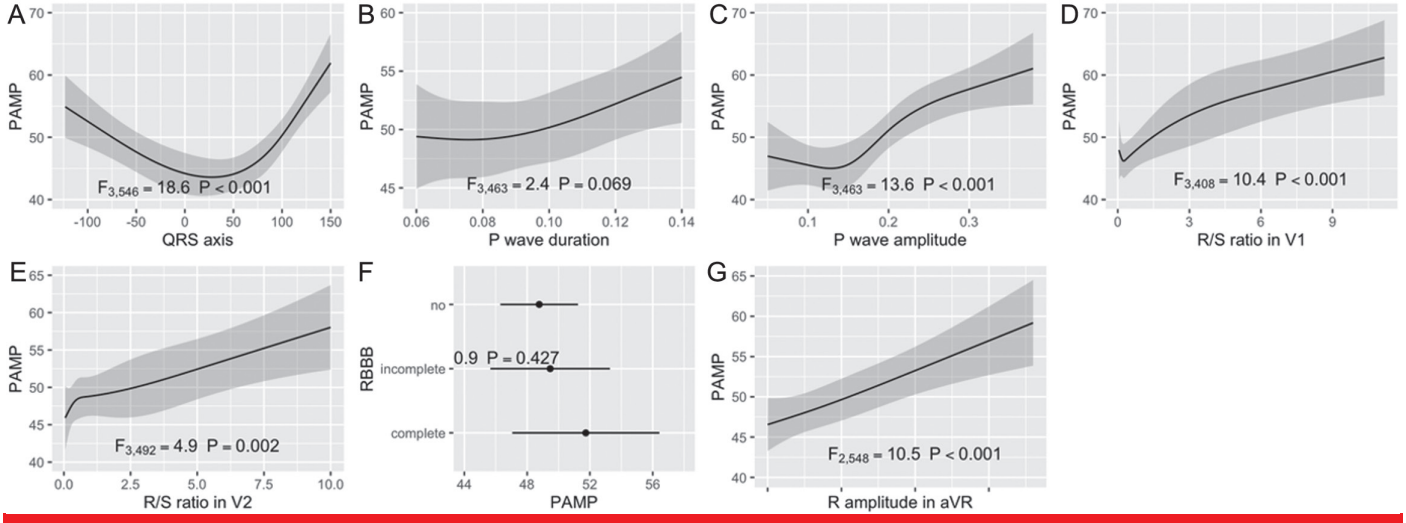

Figure 2. Summary of relationship between continuous measures of ECG and PAMP. ECG, electrocardiogram; PAMP, pulmonary artery mean pressure; RBBB, right bundle branch block.

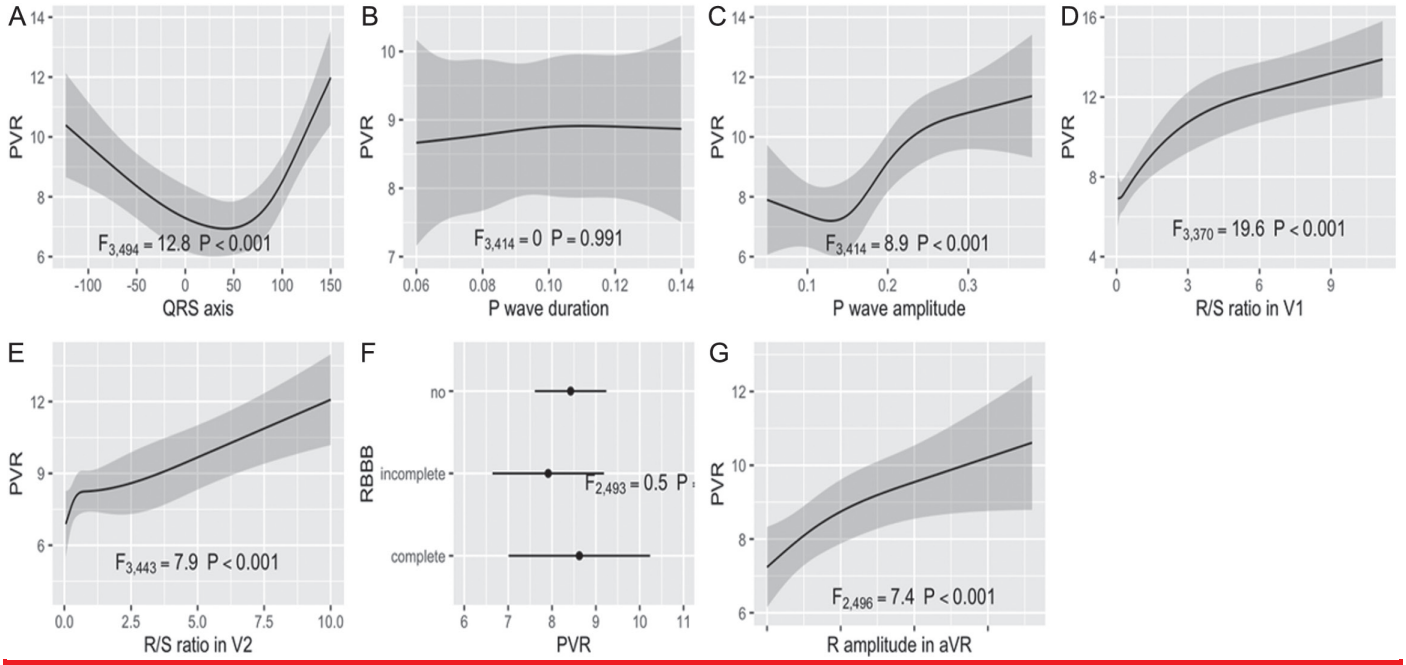

Figure 3. Summary of relationship between continuous measures of ECG and PVR. ECG, electrocardiogram; PVR, pulmonary vascular resistance; RBBB, right bundle branch block.

Sokolow–Lyon index > 1.54 mV was found to predict severe PAH defined as invasively assessed PAMP > 35 mm Hg.[17] In same study, QRS duration correlated with right atrial pressure estimate, right atrial area, vena cava inferior diameter, deterioration in cardiopulmonary exercise parameters, and 6-minute walk distance. Moreover, RV Sokolow–Lyon index (cutoff point: 1.57 mV, AUC: 0.771) and QRS duration (cutoff points: 0.09 seconds, AUC: 703 and 0.1 seconds, AUC: 0.759) were reported as independent predictors of 1-year mortality estimates according to the ESC/ERS PH risk table.[17] Similarly, Krämer et al[23] documented a significant relation between the RV Sokolow–Lyon Index > 2.1 mV and the increased risk of cardiac events in children with idiopathic PAH.[23] In addition to the R-wave in lead aVR, our results regarding the QRS axis and R/Sr in V1 and V2 are also consistent with these results, and the QRS axis > 100° and R/Sr > 0.9 in V1 were able to predict PAMP > 20 mm Hg, and PVR > 2 WU and > 3 WU, respectively. All these alterations should be considered to reflect pressure overload resulting in RV hypertrophy and dilation and deviations of the frontal electrical axis to right or extreme/indeterminate zones.

The QRS duration might reflect intraventricular conduction disturbances due to alterations in the RV myocardial

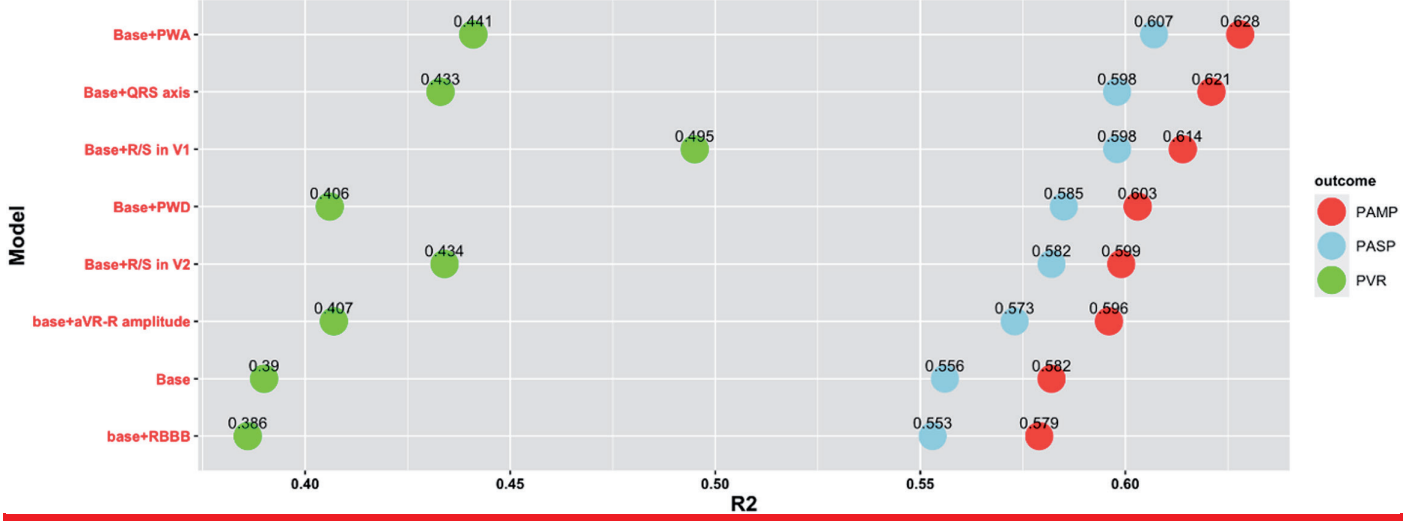

Figure 4. Each electrocardiogram measures for variance in PASP, PAMP, and PVR. PAMP, pulmonary arterial mean pressure; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; Pwa: P-wave amplitude; Pwd, P-wave duration; RBBB, right bundle branch block.

Table 3. Cutoff Values, AUC and *P*-Values, Sensitivity, and Specificity of ECG Variables Predicting the PAMP > 20 mm Hg, PVR > 2 and PVR > 3 WU, Respectively

	AUC (*P*)	Cutoff	Sensitivity	Specificity
PAMP mean > 20 mm Hg				
Pwd	0.461 (.185)	-	-	-
Pwa	0.688 (<.001)	0.16	0.564	0.731
QRS axis (°)	0.666 (<.001)	100	0.361	0.964
aVR Ra	0.683 (<.001)	0.05	0.862	0.424
R/Sr in V1	0.617 (<.001)	0.9	0.211	0.968
R/Sr in V2	0.555 (.094)	0.25	0.825	0.286
PVR > 2 WU				
Pwd	0.498 (.963)	0.1	0.664	0.400
Pwa	0.680 (<.001)	0.16	0.572	0.732
QRS axis (°)	0.658 (<.001)	100	0.367	0.934
aVR Ra	0.710 (<.001)	0.05	0.889	0.459
R/Sr in V1	0.635 (<.001)	0.16	0.818	0.407
R/Sr in V2	0.587 (.005)	0.37	0.681	0.472
PVR > 3 WU				
Pwd	0.494 (.818)	0.1	0.646	0.397
Pwa	0.665 (<.001)	0.16	0.587	0.702
QRS axis (°)	0.654 (<.001)	100	0.378	0.899
aVR Ra	0.696 (<.001)	0.05	0.899	0.413
R/Sr in V1	0.662 (<.001)	0.16	0.840	0.400
R/Sr in V2	0.606 (<.001)	0.37	0.699	0.477

aVR Ra, R amplitude of lead aVR; PAMP, pulmonary artery mean pressure; PVR, pulmonary vascular resistance; Pwa, P-wave amplitude; Pwd, P-wave duration, R/Sr, R/S ratio.

structure caused by pressure overload, and QRS prolongation was reported to be correlated with measures of RV pressure overload, hypertrophy and dysfunction assessed with imaging and exercise tests, and worst outcome.[17,24-26] Although we did not find a relation between QRS duration or right bundle branch block and pulmonary hemodynamic measures, QRS prolongation was reported to be associated with a worsening in functional class and 6-minute walk distance.[17,26] Moreover, prolongation in QRS (> 0.12 seconds) was reported to be associated with a 2.5-fold increased risk of mortality in idiopathic PAH.[26]

Beyond the correlations between ECG variables and PASP, PAMP, and PVR, we also confirmed the predictive value of these measures for updated RHC criteria for overall PH and precapillary PH diagnosis according to the ESC/ERS 2022 PH Guidelines. For the first time, we found that P-wave amplitude > 0.16, R amplitude in aVR > 0.05 mV, QRS axis >100°, and R/Sr in V1 > 0.9 showed the highest prediction for the presence of overall PH and precapillary PH. Furthermore, the AUC values of these ECG measures were not found to be different for PVR > 2 WU and PVR ≥ 3 WU. Prior to this study, we also compared the echocardiographic screening algorithm for PAMP >20 mm Hg and PAMP ≥ 25 mm Hg.[29] In contrast to those in predicting the PAMP ≥ 25 mm Hg, suggestive echocardiographic findings did not provide a significant contribution to the probability of PAMP > 20 mm Hg predicted by Tricuspid regurgitation maximum velocity (TRVmax) solely. The TRVmax > 2.8 m/s and TRVmax > 3.4 m/s were associated with 70% and 84% probability of PAMP > 20 mm Hg and 60% and 76% probability of PAMP ≥ 25 mm Hg, respectively.[29] Whether the 4 mm Hg reduction in the definitive threshold of PAMP may also require echocardiographic algorithms remains to be clarified by future studies. However, it should be kept in mind that a normal ECG does not exclude the presence of PH in adults with unexplained dyspnea on exertion. But combination of normal ECG with biomarkers (BNP/NT-proBNP) remaining within the normal limits is associated with a low likelihood of PH in patients referred for suspected PH or at risk of PH.[1-3,27]

Study Limitations

Our single-center study suffered from retrospective nature of the data extraction, and most of the study population was composed of group 1 pulmonary hypertension patients. The time delay between ECG recordings and hemodynamic assessment might exceed a 24-hour period in some patients and may be considered a methodologic shortcoming of this analysis. Because our analysis was limited to cross-correlations between the ECG variables and hemodynamic measures of pulmonary circulation, the questions regarding the ECG measures in relation to clinical and echocardiographic characteristics and survival prediction remain to be answered. However, these issues are going to be evaluated in a second study. Some values, like 0.05 mV amplitude of R wave, are difficult to use in clinical practice. These values would have an impact on machine learning algorithms in the future.

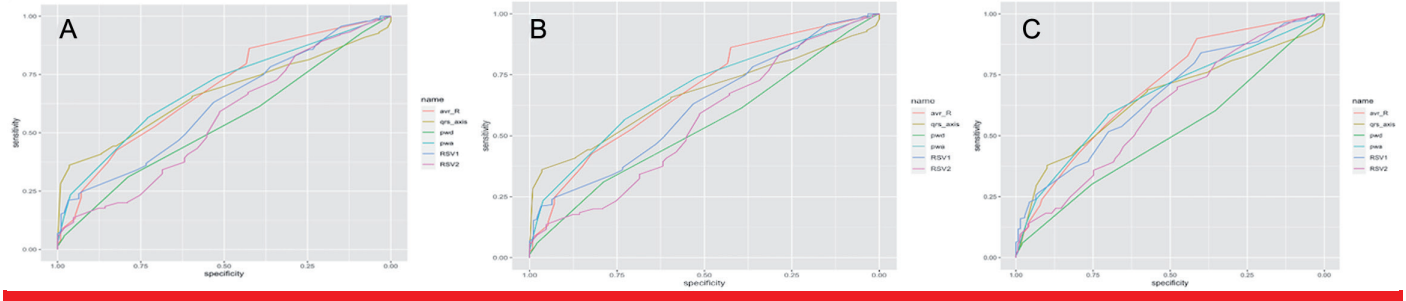

Figure 5. The area under curve (AUC) values of the cutoff values of ECG variables predicting the PAMP > 20 mm Hg (Figure 5A), PVR > 2 WU (Figure 5B), and PVR > 3 WU (Figure 5C), respectively. ECG, electrocardiogram; PAMP, pulmonary artery mean pressure, PVR, pulmonary vascular resistance.

CONCLUSION

In this study, ECG parameters including Pwa, Ra in aVR, right or indeterminate axis deviations in frontal plane, and R/Sr in V1 and V2, but not Pwd or RBBB patterns, showed statistically significant and clinically relevant correlations with PASP, PAMP, and PVR. The partial R2 analysis revealed that the Pwd or RBBB pattern did not provide any contribution to the base model while Ra in aVR, R/Sr in V2 and V1, increase in QRS axis, and Pwa had stepwise and concordant contributions to variance for PASP, PAMP, and PVR, respectively. The Pwa > 0.16, Ra in aVR > 0.05 mV, QRS axis > 100°, and R/Sr in V1 > 0.9 showed the highest prediction for overall PH and precapillary PH diagnosis according to the ESC/ERS 2022 PH definitive RHC criteria.

Ethics Committee Approval: The approval for the study was obtained from the Ethics Committee on January 31, 2023, approval number: 2023/02/668.

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.C.T., N.Ö., C.K.; Design – H.C.T, C.K.; Supervision – N.Ö., C.K.; Resources – H.C.T., B.E.Ö., Y.C.E.; Materials – H.C.T., C.K., S.T.Ü.; Data Collection and/or Processing – H.C.T., C.K., B.E.Ö., Y.C.E., A.T., D.S., Ş.K., A.S., Z.B., B.K., B.K., Ç.B., S.T.Ü.; Analysis and/or Interpretation – İ.H.T., A.K., C.K.; Literature Search – H.C.T., C.K., İ.H.T., A.K.; Writing – C.K., H.C.T., İ.H.; Critical Review – H.C.T., A.S., İ.H.T., N.Ö., C.K.

Declaration of Interests: The authors have no conflict of interest to declare.

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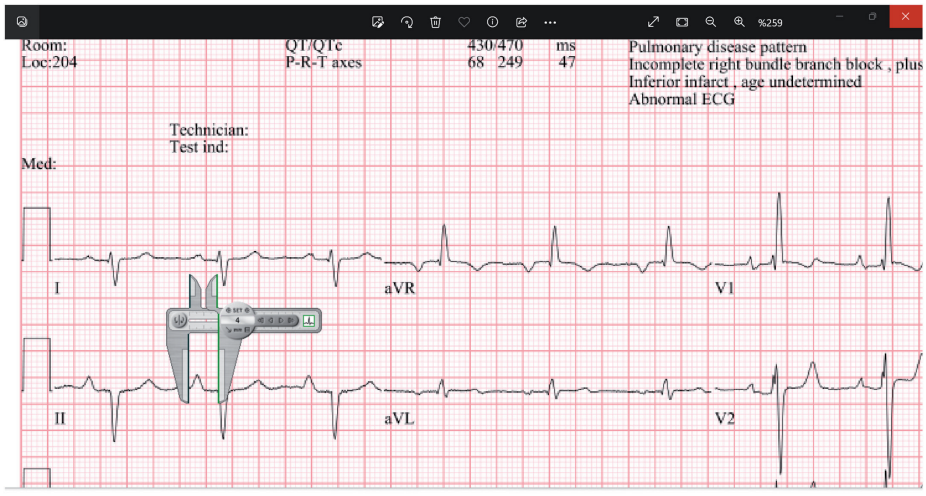
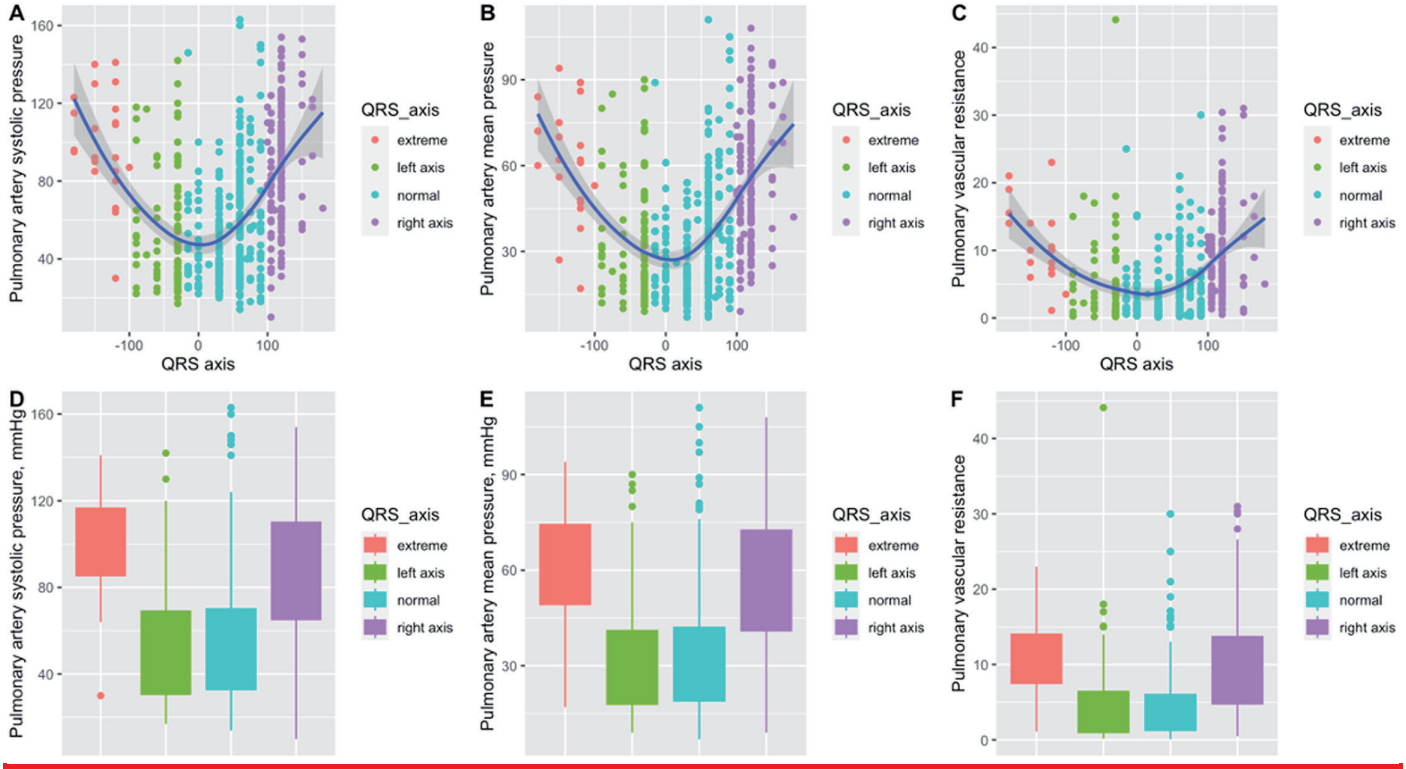


Supplementary Figure 1. ECG of a patient with PH, measurements were done using CardioCalipers software.



Supplementary Figure 2. Distributions of PASP, PAMP and PVR values along the QRS axis spectra. PAMP, pulmonary arterial mean pressure; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; Pwa: P-wave amplitude; Pwd, P-wave duration; RBBB, right bundle branch block.