Non-invasive diagnosis and follow-up of right ventricular overload

Henkens, I.R.

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Electrocardiographic monitoring of treatment response in pulmonary arterial hypertension patients

Ivo R. Henkens

C. Tji-Joong Gan

Serge A. van Wolferen

Miki Hew

Anco Boonstra

Jos W.R. Twisk

Otto Kamp

Ernst E. van der Wall

Martin J. Schalij

Anton Vonk Noordegraaf

Hubert W. Vliegen

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Abstract

Background

The potential use of the electrocardiogram for monitoring treatment effect in patients with pulmonary arterial hypertension (PAH) has not been investigated. We evaluated whether the ECG is useful for monitoring treatment response based on changes in pulmonary vascular resistance (PVR).

Methods

An ECG was recorded in 81 PAH patients at the time of diagnostic right heart catheterization, and after one year of treatment. Patients were treated according to the guidelines. Patients were divided into two groups based on PVR (<500 dynes·s·cm^{-5} or >500 dynes·s·cm^{-5}). A positive treatment response was defined as >25% decrease in PVR to an absolute PVR<500 dynes·s·cm^{-5}.

Results

At baseline, the 19 patients with a PVR<500 dynes·s·cm^{-5} had a significantly lower P amplitude in lead II, a less rightward oriented QRS axis, and a more rightward T axis than the 62 patients with a PVR>500 dynes·s·cm^{-5}. Overall (n=81), mean change in PVR was -143±360 dynes·s·cm^{-5} after one year of treatment (P<0.001). Twelve patients (19%) with a baseline PVR>500 dynes·s·cm^{-5} classified as responders. Receiver operating characteristics analysis determined that P amplitude in lead II (AUC=0.80, 95% CI, 0.67 - 0.94, P<0.01), QRS axis (AUC=0.70, 95% CI, 0.52 - 0.89, P=0.03), and T axis (AUC=0.90, 95% CI, 0.82 - 0.97, P<0.001) were important determinants of treatment response. Presence of P amplitude in lead II<0.175mV, and T axis≥25º combined, had a positive and negative predictive value for treatment response of 0.81(CI, 0.37 - 0.96) and 0.94 (CI, 0.86 - 0.99), respectively.

Conclusions

Routine ECG evaluation can be an important contribution in the assessment of treatment response in PAH patients.

Introduction

Pulmonary arterial hypertension (PAH) is a disease with intrinsic dismal prognosis [1], despite the advent of new PAH attenuating drugs [2-5]. Since treatment effect varies considerably among PAH patients, discriminating between 'responders' and 'non-responders' is often difficult [6-8]. Although considered of limited use for the diagnosis of PAH [1, 9, 10], an electrocardiogram (ECG) is routinely recorded in PAH patients and may be of use in the evaluation of treatment response after the diagnosis of PAH has been established. We therefore studied to what extent ECG variables might contribute in the repeated evaluation of PAH patients regarding treatment response.

Methods

The study procedures were in accordance with the Declaration of Helsinki. The local institutional review board did not require full approval, since this retrospective study included only patients familiar to the VU University Medical Center, and patient data were treated confidentially.

Patients

Between October 1999 and October 2007, 856 patients were evaluated for pulmonary hypertension. Patients were included in this study if concomitant resting ECGs before diagnostic right heart catheterization and before repeated right heart catheterization at follow-up were available. A mean pulmonary artery pressure (PAP)>25 mmHg with a pulmonary capillary wedge pressure≤15 mmHg was considered PAH [11, 12]. PAH was considered to be idiopathic when identifiable causes for pulmonary hypertension were excluded [11, 12]. Idiopathic PAH was identified in 109 patients, of whom 13 died before follow-up, and 15 did not have a repeated ECG or right heart catheterization at follow-up. Consequently, 81 patients were included in the study.

Electrocardiography

Standard 12-lead ECGs were recorded by certified ECG technicians with patients in supine position. Commercially available electrocardiographs (MAC VU and MAC 5000; GE Healthcare; The Netherlands), were used for ECG recording (paper speed=25 $mm \cdot s^{-1}$; sensitivity 1 mV=10 mm; sample frequency = 500 Hz). Heart rate, P axis, QRS axis, QRS duration, and T axis were directly derived from standard electrocardiographic calculations. P

amplitude in lead II was assessed from digitally stored ECGs, measured with the isoelectric PR-interval as reference point in steps of 0.025 mV (=0.25 mm on paper). ECGs were examined by an experienced cardiologist (HWV), blinded to the data.

Treatment

All patients underwent a vasoreactivity test [11, 13]. Patients with a positive response were started on calcium antagonists [11]. Before 2002, prostacyclin (epoprostenol) was prescribed to all patients in WHO class III and IV. From 2002 onward, patients in WHO class III received endothelin receptor antagonists (bosentan or sitaxsentan) or a phosphodiesterase-inhibitor (sildenafil), whereas patients in WHO class IV received prostacyclin (epoprostenol, treprostinil or iloprost).

Classification of responders

Based on recent studies, we assumed that compensatory right ventricular hypertrophy would be reflected by ECG changes over a limited range of PVR only [9, 14]. To allow categorization of patients based on ECG variables we first defined a cut-off point in pulmonary vascular resistance (PVR). Since a PVR of 240 dynes·s·cm^{-5} is considered the upper limit of normal [13], a PVR<500 dynes·s·cm^{-5} was considered a reasonable treatment goal for PAH patients. We hypothesized that a PVR<500 dynes·s·cm^{-5} (mild-to-moderate PAH) would be associated with less ECG abnormalities than a PVR>500 dynes·s·cm^{-5} (severe PAH), since the standard ECG lacks sensitivity for mild PAH [9, 10, 15]. At baseline, patients were compared for ECG variables based on a PVR above or below 500 dynes·s·cm^{-5}. Subsequently, in patients with mild–to-moderate PAH we evaluated differences in ECG characteristics at follow-up between patients with stable disease and patients who experienced a >25% increase in PVR to a PVR>500 dynes·s·cm^{-5}. Similarly, in patients with severe PAH at baseline we evaluated differences in ECG characteristics at follow-up between patients who experienced a >25% decrease in PVR to a PVR<500 dynes·s·cm^{-5} and patients without such a positive treatment response.

Statistical analyses

Normally distributed data are expressed as mean ± standard deviation or otherwise as median (interquartile range). The SPSS for Windows Software (version 12.0.1; SPSS Inc; Chicago, Ill) was used for data analysis. Correlation analyses (Pearson and Spearman) were used to determine relations between ECG variables, and catheterization variables. Paired t-tests were used for comparison of ECG variables over time. Receiver operating characteristics

(ROC) analyses were used to determine whether ECG variables could accurately classify patients as responders or non-responders. Comparison of the area under the curve (AUC) was performed according to the method described by Hanley and McNeil [16]. Binary logistic stepwise regression analysis (inclusion if $P<0.05$, removal if $P>0.10$) was used to construct an optimal model for classification of patients according to treatment response. A 95% confidence interval (CI) is provided for all estimates. A value of $P<0.05$ was considered to be statistically significant.

Results

Baseline PVR in patients surviving to follow-up (n=81) was considerably lower (891±466 vs.1612±753 dynes·s·cm^{-5}, $P<0.01$) than in patients who died before follow-up (n=13). Baseline characteristics for patients with mild-to-moderate PAH, patients with severe PAH, and deceased patients are presented in Table 1. Baseline ECG characteristics are presented in Table 2. The hemodynamic differences between patients with a PVR<500 dynes·s·cm^{-5} and patients with a PVR>500 dynes·s·cm^{-5} were predominantly reflected by P amplitude in lead II, and T axis, and to a lesser extent by QRS axis. Correlation analyses between the selected ECG variables and hemodynamic variables for both baseline and follow-up are described

Table 1

	PVR<500 (n=19)	PVR>500 (n=62)	Deceased (n=13)*	Between Groups	PVR<500 vs. PVR>500	PVR<500 vs. Deceased	PVR>500 vs. Deceased
Patient characteristics	Mean ± SD	Mean ± SD	Mean ± SD	*P*	*P*†	*P*†	*P*†
Age (years)	45 ± 12	43 ± 14	39 ± 16	0.72	1.00	0.74	1.00
Gender (male/female)	4/15	12/50	6/7	0.87	1.00	0.37	0.12
Body surface area (m²)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.86	1.00	1.00	1.00
RAP (mmHg)	5 ± 3	9 ± 5	16 ± 4	<0.01	0.01	<0.001	<0.001
mean PAP(mmHg)	37 ± 8	58 ± 11	67 ± 14	<0.001	<0.001	<0.001	0.07
Cardiac index (L·min^{-1}·m^{-2})	3.6 ± 0.7	2.3 ± 0.6	1.5 ± 0.3	<0.001	<0.001	<0.001	<0.01

*Baseline characteristics for patients with a PVR<500 dynes·s·cm^{-5}, a PVR>500 dynes·s·cm^{-5}, and patients who died before follow-up. RAP = right atrial pressure. PAP = pulmonary artery pressure. * PVR in the deceased patients was 1612 ± 753 dynes·s·cm^{-5}. † Post-Hoc Bonferroni correction for the significance of the observed differences between the groups.*

TABLE 2

	PVR<500 (n=19)	PVR>500 (n=62)	Deceased (n=13)	Between Groups	PVR<500 vs. PVR>500	PVR<500 vs. Deceased	PVR>500 vs. Deceased
ECG variables	mean ± SD or median (IQR)	mean ± SD or median (IQR)	mean ± SD or median (IQR)	*P*	*P**	*P**	*P**
Heart rate (bpm)	75 ± 18	81 ± 16	94 ± 19	<0.01	0.53	<0.01	0.04
P amplitude in lead II (mV)	0.17 ± 0.07	0.22 ± 0.08	0.26 ± 0.07	0.01	0.04	<0.01	0.44
P axis (º)	65 (55 - 74)	65 (55 - 76)	69 (56 - 76)	0.75	1.00	1.00	1.00
QRS axis (º)	96 (65 - 115)	114 (97 - 128)	118 (99 - 133)	0.10	0.10	0.43	1.00
QRS duration (ms)	95 ± 21	92 ± 12	95 ± 15	0.67	1.00	1.00	1.00
T axis (º)	48 (29 - 70)	-9 (-40 - 38)	-23 (-39 - 57)	0.02	0.03	0.10	1.00

Baseline differences in ECG variables between PAH patients with a PVR<500 dynes·s·cm-5, a PVR>500 dynes·s·cm-5, and PAH patients who died before follow-up.
** Post-Hoc Bonferroni correction for the significance of the observed differences between the groups.*

TABLE 3

		RAP (mmHg)		mean PAP (mmHg)		Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)		PVR ($dynes \cdot s \cdot cm^{-5}$)	
ECG variables		1st	2nd	1st	2nd	1st	2nd	1st	2nd
Heart rate (bpm)	r	0.18	0.28*	0.23*	0.25*	-0.24*	-0.17	0.32†	0.31†
P amplitude in lead II (mV)	r	0.15	0.24*	0.43‡	0.45‡	-0.27†	-0.34†	0.45‡	0.52‡
P axis (º)	r	-0.08	-0.16	0.08	0.10	-0.02	-0.08	0.14	0.12
QRS duration (ms)	r	0.24*	-0.18	-0.02	-0.37‡	0.16	0.11	-0.11	-0.31†
QRS axis (º)	r	0.22	0.46‡	0.34†	0.53‡	-0.19	0.39‡	0.28*	0.48‡
T axis (º)	r	-0.30†	-0.21	-0.32†	-0.47‡	0.16	0.37†	-0.29*	-0.52‡

*Correlations between ECG-derived variables and hemodynamic parameters at baseline (1st) and at follow-up (2nd). Heart rate, P amplitude in lead II, and QRS duration were assessed in linear correlation analysis (Pearson) with hemodynamic parameters. P axis, QRS axis, and T axis were assessed in nonlinear correlation analysis (Spearman) with hemodynamic parameters. RAP = right atrial pressure. PAP = pulmonary artery pressure. PVR = pulmonary vascular resistance. * P<0.05, † P<0.01, ‡P<0.001*

in Table 3. The strongest linear relation was found between P amplitude and PVR (r=0.45, *P*<0.001 at baseline, and r=0.52, *P*<0.001 at follow-up, respectively, Figure 1). After 13.1 months of treatment (11.8-17.1 months) mean change in PVR was -143±360 dynes·s·cm^{-5} for all 81 patients (*P*<0.001).

Three of the 19 patients with a baseline PVR <500 dynes·s·cm^{-5} experienced a >25% increase in PVR to a PVR>500 dynes·s·cm^{-5}; eleven remained stable, and five patients experienced a >25% decrease in PVR. An example of ECG leads I, II, and aVF derived from a patient in whom PAH progressed is depicted in Figure 2 (A+B). Patients who deteriorated had a more rightward oriented QRS axis at follow-up compared to the other patients with a baseline PVR<500 dynes·s·cm^{-5} (129±16º vs. 79±29º, *P*=0.01). ROC analysis defined a QRS axis>116º to have 100% sensitivity and 100% specificity (CI, 1.00 - 1.00 for both) for patients with >25% increase in PVR to a PVR>500 dynes·s·cm^{-5} (*P*<0.01). Other ECG variables, medication use or gender distribution were not statistically different between patient groups with an initial PVR <500 dynes·s·cm^{-5}.

Twelve (19%) out of 62 patients with severe PAH at baseline demonstrated a positive treatment response. Responders had a significantly lower PVR than non-responders both at baseline

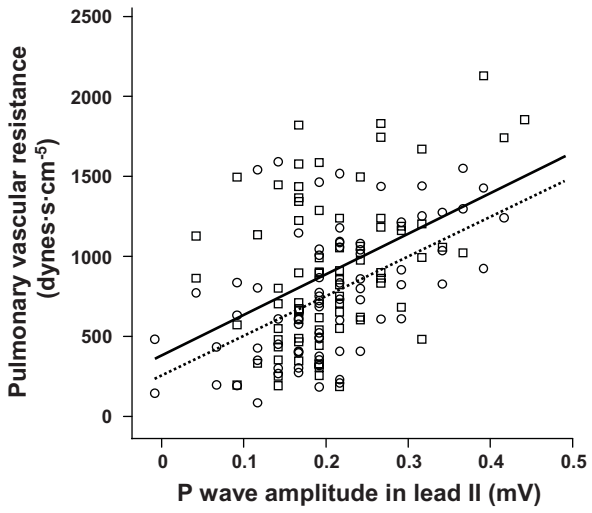

Figure 1

ECG data and hemodynamic data from all 81 patients from baseline (open squares, solid line) and follow-up (open circles, dotted line) combined. There was a linear relation between P amplitude in lead II and PVR both at baseline and at follow-up: r=0.45, P<0.001 and r=0.52, P<0.001, respectively).

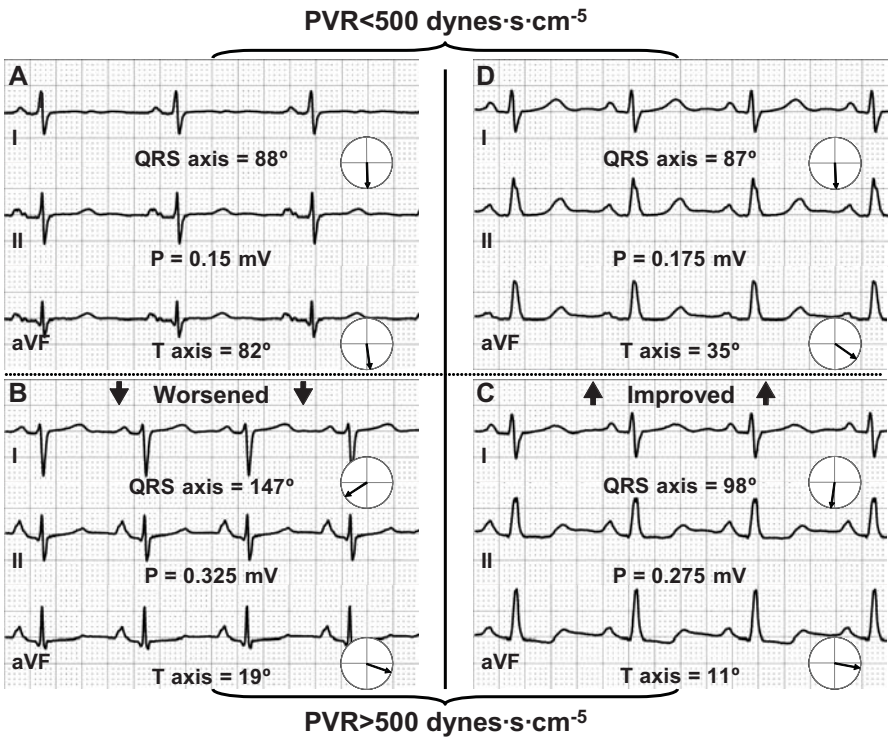

Figure 2

Left: representative example of leads I, II, and aVF of standard 12-lead ECGs from a patient with a PVR of 330 dynes·s·cm^{-5} before treatment (A), and a PVR of 600 dynes·s·cm^{-5} at follow-up (B) demonstrating an increase in P amplitude in lead II (0.15 mV to 0.325 mV), a more rightward QRS axis orientation (88º to 147º), and a less rightward T axis orientation (82º to 19º). Right: representative example of leads I, II, and aVF of standard 12-lead ECGs from a patient with a PVR of 540 dynes·s·cm^{-5} before treatment (C), and a PVR of 300 dynes·s·cm^{-5} at follow-up (D) demonstrating a decrease in P amplitude in lead II (0.275 mV to 0.175 mV), a less rightward QRS axis orientation (98º to 87º), and a more rightward T axis orientation (11º to 35º). The initial strain pattern, most evident in lead aVF (C) was no longer present (D).

(762±240 dynes·s·cm^{-5} vs. 1120±406 dynes·s·cm^{-5}, P<0.01) and at follow-up (370±100 dynes·s·cm^{-5} vs. 976±307 dynes·s·cm^{-5}, P<0.001). Responders did not differ from non-responders with respect to age (44±13 vs. 43±15, P=0.81), gender distribution (3:9 vs. 9:41, male:female, P=0.59), treatment with calcium-channel blockers (n=1:11 vs. n=3:47, P=0.77), endothelin receptor antagonists (n=7:5 vs. n=23:27, P=0.45), phosphodiesterase-5 inhibitors (n=2:10 vs. n=8:42, P=0.96), or prostacyclin (n=4:8 vs. n=23:27, P=0.44). In responders,

mean PAP decreased by 14±8 mmHg to 39±6 mmHg (P<0.001), whereas in non-responders mean PAP changed by 1±11 mmHg to 57±10 mmHg (P=0.48). In responders, cardiac index increased by 1.1±1.2 L·min^{-1}·m^{-2} to 3.9±1.4 L·min^{-1}·m^{-2} (P=0.02). In non-responders, cardiac index also increased by 0.3±0.6 L·min^{-1}·m^{-2} to 2.5±0.7 L·min^{-1}·m^{-2} (P<0.01). An example of ECG leads I, II, and aVF from a responder is depicted in Figure 2 (C+D).

Hemodynamic differences between responders and non-responders were again best reflected by P amplitude in lead II, QRS axis, and T axis (Table 4). Results of ROC analysis for these ECG variables for discrimination between responders and non-responders are depicted in Figure 3. Given the observed a priori chance of 0.19 (12/62 patients) for a positive treatment

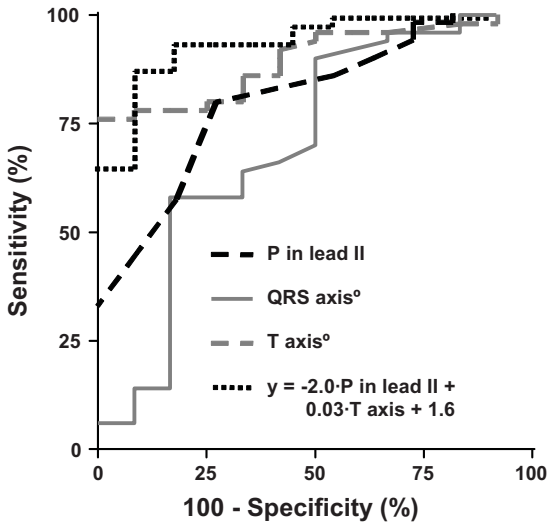

Figure 3

Receiver operating characteristics analysis for determination of treatment response in PAH patients. P amplitude had a sensitivity and specificity of 73% (CI, 39 - 94%) and 80% (CI, 66 - 90%) respectively for a cut-off point of 0.175 mV (AUC=0.80, CI, 0.67 - 0.94, P<0.01), QRS axis had a sensitivity and specificity of 42% (CI, 15 - 72%) and 92% (CI, 81 - 98%) respectively for a cut-off point of 90° (AUC= 0.70, CI, 0.52 - 0.89, P=0.03), and T axis had a sensitivity and specificity of 100% (CI, 74 - 100%) and 76% (CI, 62 - 87%) respectively for a cut-off point of 25° (AUC= 0.90, CI, 0.82 - 0.97, P<0.001). Binary logistic regression analysis rendered the following formula for prediction of a positive treatment response: y=-2.0·P amplitude in lead II + 0.03·T axis + 1.6 (AUC=0.94, CI, 0.87 - 1.01, P<0.001). Although according to binary logistic regression analysis the latter formula performed better than assessment of T axis alone, the AUC was not significantly larger than that of T axis alone (P=0.12), according to the method described by Hanley and McNeil [16]. By the same method, however, the regression formula was better than using either P amplitude (P=0.01) or QRS axis (P<0.01).

response, the respective positive and negative predictive values for a positive treatment response were 0.46 (CI, 0.21 - 0.69) and 0.93 (CI, 0.82 - 0.98) for P amplitude >0.175mV, 0.55 (CI, 0.16 - 0.89) and 0.87 (CI, 0.80 - 0.94) for QRS axis >90º, and 0.48 (CI, 0.31 - 0.64) and 1.00 (CI, 0.91 - 1.00) for T axis<25º. Binary logistic regression analysis determined that only P amplitude in lead II had additional value after assessing T axis (Figure 3). A stepwise prediction model was constructed with sequential assessment of T axis and P amplitude in lead II. Since a T axis <25º had a negative predictive value of 1.00 (CI, 0.91 - 1.00) for a PVR<500 dynes·s·cm^{-5} all patients with a T axis <25º were classified as non-responders. Patients with a T axis ≥25º and a P amplitude in lead II ≤0.175 mV were classified as responders. This algorithm had a sensitivity and specificity of 75% (CI, 43 - 95%) and 96% (CI 83 - 99%), respectively, for detection of a positive treatment response. Positive and negative predictive values of this two-step treatment response assessment were 0.81 (CI, 0.37 - 0.96) and 0.94 (CI, 0.86 - 0.99), respectively.

Discussion

Key finding of this study is that there is a robust correlation between PVR and the ECG-derived P amplitude, QRS axis, and T axis. Repeated ECG analysis may therefore be of use in both early and late evaluation of treatment response, and hence facilitate targeted treatment adjustment in patients not reaching their treatment goal.

We detected a linear relation between P amplitude in lead II and PVR. For P amplitude in lead II 0.175 mV was defined as the best cut-off point in ROC analysis for discrimination between responders and non-responders. This cut-off point is still below the 0.25mV threshold for a 'P pulmonale' which has good specificity, yet poor sensitivity for mild-to-moderate RV hypertrophy [17]. The prognostic value of P amplitude in PAH reportedly increases with its amplitude [18], stressing its clinical value in singling out PAH patients with advanced disease and a dismal prognosis. PAH-induced RV hypertrophy and RV dilation associated tricuspid regurgitation are considered causative factors of increased systolic and diastolic atrial load responsible for the increased P amplitude in lead II [19]. In healthy men, Karliner et al. observed an increase in P amplitude in lead II from sea level to a few months later at a height of 6300 meters above sea level on Mount Everest.[19] This report concurs with the recent overview on the heart and pulmonary circulation in highlanders by Penaloza and Aries-Stella who link an elevated P amplitude, a rightward oriented QRS axis, and inverted T waves to increased pulmonary pressures [20]. They elegantly demonstrate that QRS axis reflects RV hypertrophy in individuals with a hypoxia-induced

elevation of pulmonary vascular resistance at high altitude, and that QRS axis increases over time in accordance with increases in pulmonary vascular resistance or vice versa. For different populations, different cut-off values have been proposed for QRS axis for optimal diagnosis of RV hypertrophy [17]. Although the relatively wide normal range for QRS axis hampers diagnostic accuracy for RV hypertrophy in a cross-sectional study of the general population [21], QRS axis is a useful tool for follow-up of patients with established PAH, as was shown in our population. Rich and Brundage demonstrated a reduction in rightward QRS axis orientation in PAH patients with a long-term positive response to high-dose calcium channel blockers [22]. A more recent study reported a QRS axis>100º to be highly predictive of a PVR>400 dynes·s·cm^{-5} [10]. This cut-off point for QRS axis lies in between the QRS axis>116º we found for PAH patients with a baseline PVR<500 dynes·s·cm^{-5} yet progressive disease, and the QRS axis>90º we found for PAH patients with a baseline PVR>500 dynes·s·cm^{-5} with a positive treatment response. The observed importance of the T axis in our population concurs with T wave abnormalities registered in patients with RV hypertrophy due to residence at high altitudes [20]. Furthermore, Kawaguchi et al. found the T wave to discriminate best between patients with and without RV hypertrophy [23]. In selected PAH patients the T axis is therefore a valuable indicator of disease burden.

Our definition of treatment response was based on PVR, a robust measure of interplay between cardiac output and RV afterload [13]. Using PVR secures unambiguous results, whereas sequential measurement of mean PAP or cardiac output alone might underestimate or overestimate treatment effect [11, 13]. The PVR cut-off point of <500 dynes·s·cm^{-5} and the >25% decrease in PVR may be considered 'aiming high' given our results and those of others [6, 24]. Given the suboptimal sensitivity of the standard ECG [10], we considered such an important change in disease burden necessary for any effect in the

Table 4

ECG variables	PVR<500 dynes·s·cm^{-5} (n=12)	PVR>500 dynes·s·cm^{-5} (n=50)	*P*
Heart rate (bpm)	77 ± 12	84 ± 17	0.07
P amplitude in lead II (mV)	0.14 ± 0.08	0.24 ± 0.08	<0.001
P axis (º)	61 (23 - 74)	64 (15 - 73)	0.20
QRS axis (º)	98 (62 - 108)	114 (101 - 121)	<0.01
QRS duration (ms)	95 ± 10	95 ± 12	0.87
T axis (º)	60 (34 - 76)	-5 (-33 - 25)	<0.001

Differences in ECG variables at follow-up between responders and non-responders in pulmonary arterial hypertension patients with a baseline PVR>500 dynes·s·cm^{-5}

ECG to be observed. Because the range of normal ECG values is relatively wide [25], we categorized PAH patients as having mild–to-moderate PAH or severe PAH. ECG variables in patients with mild-to-moderate PAH approximated normal values in the majority of patients. Similarly, ECGs variables of patients with severe PAH and a positive treatment response regressed to a (near-)normal situation, whereas the opposite was true for PAH patients with mild-to-moderate PAH with progressive disease (Table 4, Figure 2).

Since PAH is essentially a hemodynamic diagnosis, right heart catheterization remains the gold standard for diagnosis of PAH [11, 15]. Although the inherent risk of this invasive procedure is low [26], clinicians are exploring and validating other ways of patient monitoring.

Ubiquitous use of the 6-minute walk test [27], biomarkers [28, 29], and non-invasive imaging [30, 31] for evaluation of PAH has greatly improved understanding prognosis, yet clear cut-off values for timely detection of treatment response are lacking. This is likely explained by the considerable inter-individual variation in PAH-related variables as well as their intrinsic optimal discrimination range of PAH severity; e.g. the ECG was only useful for discrimination between mild-to-moderate PAH and severe PAH (Table 2), whereas the 6-minute walk distance becomes increasingly important in end-stage disease. Importantly, the ECG correctly classified the majority of PAH patients that worsened from a favorable baseline situation or improved from an unfavorable baseline situation.

Clinical implications

Randomized clinical trials have demonstrated that after 12-16 weeks of treatment, there is generally a modest, though overall significant beneficial effect of PAH attenuating drugs [2, 4, 5, 32-35]. However, the individual treatment effect is difficult to evaluate non-invasively, and patients generally require treatment indefinitely. Currently, patients with a suboptimal effect of monotherapy would receive additional PAH attenuating therapy [36, 37]. Evaluation of treatment effect could therefore ascertain earlier initiation of tailored combination therapy in these patients. Assessing the ECG at follow-up for disease progression and treatment response in PAH patients is simple, and requires merely an additional evaluation of the P amplitude in lead II, QRS axis, and T axis. The robustness and reproducibility of ECG recordings as well as the ease of interpretation render the ECG an excellent tool for longitudinal evaluation of treatment effect by any clinician familiar with PAH. Implementation of routine ECG evaluation in all PAH patients may therefore be an important contribution to clinical assessment of these patients.

Limitations

Although the choice for a cut-off point of <500 dynes·s·cm^{-5} for PVR was based on recent studies regarding diagnostic accuracy of the ECG [9], and consequences of an increasing PVR [14], it remains arbitrary. Furthermore, it resulted in an unequal distribution of patients with mild-to-moderate PAH and patients with severe PAH. However, this resembles the common clinical situation where most PAH patients already have advanced disease at the time of diagnosis. A certain caution in interpretation of these data is therefore warranted, especially in the smaller group with a baseline PVR<500 dynes·s·cm^{-5}.

Conclusion

Routine ECG evaluation can be an important contribution in the assessment of treatment response in PAH patients.

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