



## ECG Monitoring of Treatment Response in Pulmonary Arterial Hypertension Patients\*

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**Background:** The potential use of the ECG for monitoring treatment effects 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 1 year of treatment. Patients were treated according to the guidelines. Patients were divided into two groups based on PVR (ie,  $< 500$  or  $> 500$  dyne  $\cdot$  s  $\cdot$  cm $^{-5}$ ). A positive treatment response was defined as a  $> 25\%$  decrease in PVR to an absolute PVR of  $< 500$  dyne  $\cdot$  s  $\cdot$  cm $^{-5}$ .

**Results:** At baseline, the 19 patients with a PVR of  $< 500$  dyne  $\cdot$  s  $\cdot$  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 of  $> 500$  dyne  $\cdot$  s  $\cdot$  cm $^{-5}$ . Overall ( $n = 81$ ), the mean ( $\pm$  SD) change in PVR was  $-143 \pm 360$  dyne  $\cdot$  s  $\cdot$  cm $^{-5}$  after 1 year of treatment ( $p < 0.001$ ). Twelve patients (19%) with a baseline PVR of  $> 500$  dyne  $\cdot$  s  $\cdot$  cm $^{-5}$  were classified as responders. Receiver operating characteristic analysis determined that the P amplitude in lead II (area under the curve [AUC], 0.80; 95% confidence interval [CI], 0.67 to 0.94;  $p < 0.01$ ), QRS axis (AUC, 0.70; 95% CI, 0.52 to 0.89;  $p = 0.03$ ), and T axis (AUC, 0.90; 95% CI, 0.82 to 0.97;  $p < 0.001$ ) were important determinants of treatment response. The presence of a P amplitude in lead II of  $< 0.175$  mV and a T axis of  $\geq 25^\circ$  combined had a positive and negative predictive value for treatment response of 0.81 (95% CI, 0.37 to 0.96) and 0.94 (95% CI, 0.86 to 0.99), respectively.

**Conclusions:** Routine ECG evaluation can be an important contribution in the assessment of treatment response in PAH patients. (CHEST 2008; 134:1250–1257)

**Key words:** ECG; monitoring; pulmonary circulation; pulmonary hypertension

**Abbreviations:** AUC = area under the curve; CI = confidence interval; IQR = interquartile range; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; ROC = receiver operating characteristics; RV = right ventricle/ventricular; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is a disease with an intrinsic dismal prognosis,<sup>1</sup> despite the advent of new PAH-attenuating drugs.<sup>2–5</sup> Since the treatment effect varies considerably among PAH patients, discriminating between “responders” and “nonresponders” is often difficult.<sup>6–8</sup> Although it is considered to be of limited use for the diagnosis of PAH,<sup>1,9,10</sup> an ECG is routinely recorded in PAH patients and may be of use in the evaluation of the treatment response after the diagnosis of PAH has been established. We there-

fore studied to what extent ECG variables might contribute in the repeated evaluation of PAH patients regarding treatment response.

### MATERIALS AND 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 evaluated at the VU University Medical Center and patient data were treated confidentially.

Between October 1999 and October 2007, 856 patients were evaluated for PAH. Patients were included in this study if the results of concomitant resting ECGs that had been performed before diagnostic right heart catheterization and before repeated right heart catheterization at follow-up were available. A mean pulmonary artery pressure (PAP) of  $> 25$  mm Hg with a pulmonary capillary wedge pressure of  $\leq 15$  mm Hg was considered to be PAH.<sup>11,12</sup> PAH was considered to be idiopathic when identifiable causes for PAH were excluded.<sup>11,12</sup> 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.

## ECG

Standard 12-lead ECGs were recorded by certified ECG technicians with patients in the supine position. Commercially available ECGs (MAC VU and MAC 5000; GE Healthcare; Den Bosch, the Netherlands) were used for ECG recording (paper speed, 25 mm/s; 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 ECG calculations. The P amplitude in lead II was assessed from digitally stored ECGs, measured with the isoelectric PR interval as the reference point in steps of 0.025 mV (0.25 mm on paper). ECGs were examined by an experienced cardiologist (H.W.V.) who was blinded to the data.

## Treatment

All patients underwent a vasoreactivity test.<sup>11,13</sup> Patients with a positive response were started on therapy with calcium antagonists.<sup>11</sup> Before 2002, prostacyclin (epoprostenol) was prescribed to all patients in World Health Organization (WHO) class III and IV. From 2002 onward, patients in WHO class III received therapy with endothelin receptor antagonists (bosentan or sitaxentan) or a phosphodiesterase inhibitor (sildenafil), whereas patients in WHO class IV received prostacyclin (epoprostenol, treprostinil, or iloprost).

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The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Manuscript received February 27, 2008; revision accepted June 9, 2008.

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DOI: 10.1378/chest.08-0461

## Classification of Responders

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

## Statistical Analysis

Normally distributed data are expressed as the mean  $\pm$  SD or otherwise as median (interquartile range [IQR]). A statistical software package (SPSS for Windows, version 12.0.1; SPSS Inc; Chicago, IL) was used for data analysis. Correlation analyses (Pearson and Spearman) were used to determine the relations between ECG variables and catheterization variables. Paired *t* tests were used for the comparison of ECG variables over time. Receiver operating characteristic (ROC) analyses were used to determine whether ECG variables could accurately classify patients as responders or nonresponders. Comparison of the area under the curve (AUC) was performed according to the method described by Hanley and McNeil.<sup>16</sup> Binary logistic stepwise regression analysis (inclusion if  $p < 0.05$ , removal if  $p > 0.10$ ) was used to construct an optimal model for the 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

The baseline PVR in patients surviving to follow-up ( $n = 81$ ) was considerably lower ( $891 \pm 466$  vs  $1,612 \pm 753 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ , respectively;  $p < 0.01$ ) than in patients who died before follow-up ( $n = 13$ ). The 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 of  $< 500 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$  and patients with a PVR of  $> 500 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$  were predominantly reflected by P amplitude in lead II, T axis, and to a lesser extent by QRS axis. Correlation analyses among the selected ECG variables and hemodynamic variables for both baseline and follow-up are

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