# Chapter 9

## Pulmonary Hypertension: The Role of the Electrocardiogram

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## ABSTRACT

A 54-year-old female was referred to our centre for further evaluation of recently established severe pulmonary hypertension. Six months prior to presentation to the cardiologist of the referring centre, the patient had first experienced exertional dyspnoea. At the time of presentation to the referring cardiologist, the patient's ECG showed signs of an increased right heart load. Interestingly, this patient had undergone a thorough cardiac evaluation in the referring centre seven years before when she presented with severe hyperthyroidism. At that time there were no symptoms or signs of pulmonary hypertension on ECG, echocardiography, or at heart catheterisation. Thorough evaluation in cooperation with the referring centre demonstrated that this patient was suffering from idiopathic pulmonary arterial hypertension, a rare form of pulmonary hypertension. We conclude this report with a discussion on the potential use of the ECG for the diagnosis of increased right heart load.

## CASE

In August 2005, a 54-year-old female was referred to our centre for additional evaluation into the aetiology of recently established severe pulmonary arterial hypertension (PAH). The patient had first experienced exertional dyspnoea six months prior to presentation to the referring cardiologist. There was no history of cardiac or pulmonary disease, but this patient had undergone an extensive cardiac evaluation seven years before, after a single episode

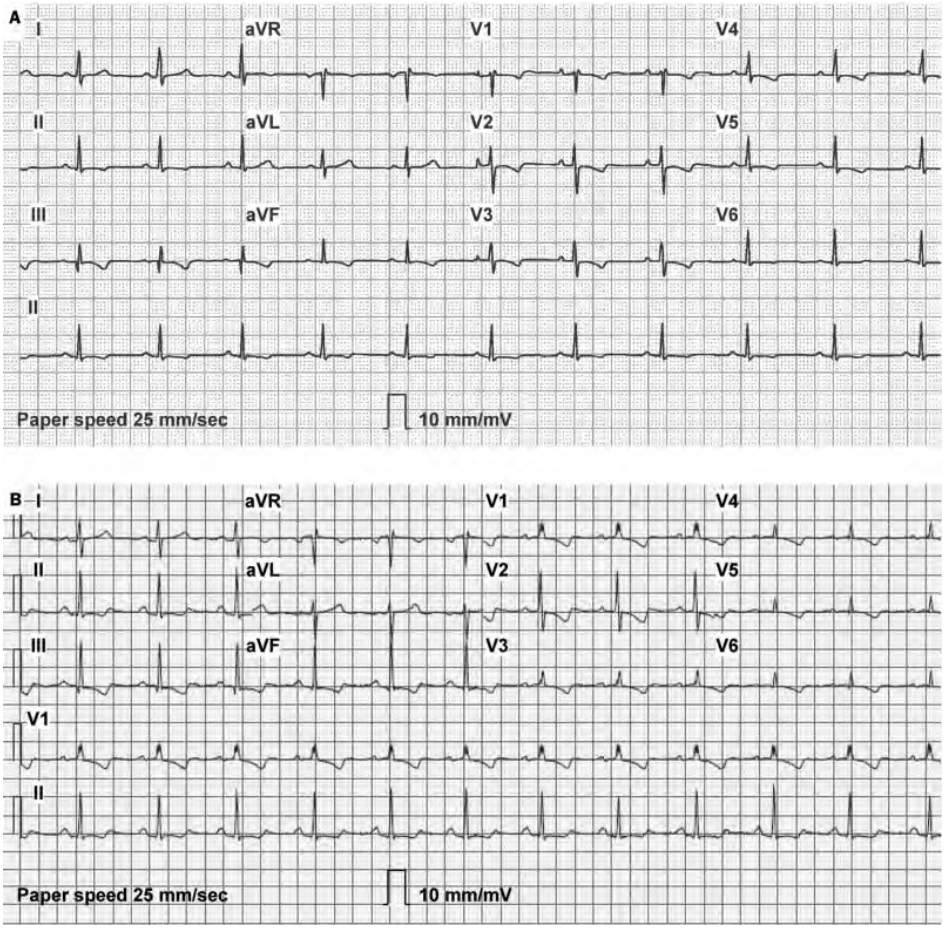


**Figure 1.** A. ECG of the patient at first presentation, seven years before the diagnosis of PAH, demonstrated a regular sinus rhythm of 65 beats/min, a QRS axis of 36°, normal P waves, conduction intervals within normal limits, and an inverted T waves in leads II, III, aVF and V1 to V6. In short, there was no reason to suspect an increased right heart load at the time, based on this ECG. B. The ECG recorded at the time of renewed presentation showed a regular sinus rhythm of 84 beats/min, a QRS axis of 90°, the R wave in lead V1 measured 6 mm in the absence of an S wave, and there were diffuse repolarisation abnormalities, all in agreement with an increased right heart load. Given this second ECG, especially with an ECG available from several years before, further investigation regarding an increased right heart load is warranted.

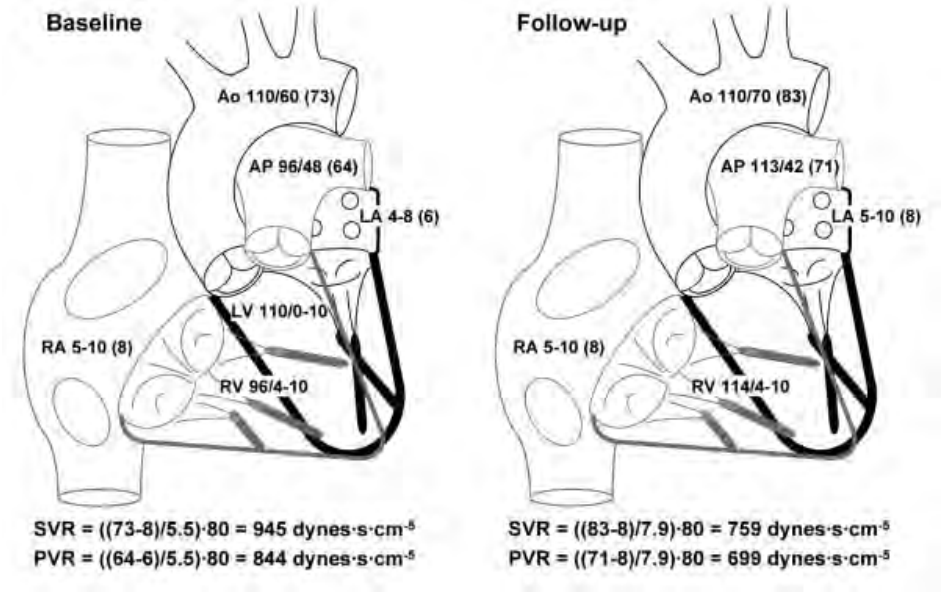


**Figure 2.** Haemodynamics recorded at baseline (left) and at follow-up (right). Despite the fact that the systolic pulmonary artery pressure is increased after one year of treatment, PVR has decreased due to an improved cardiac output (from 5.5 l/min to 7.9 l/min). Essentially, right ventricular function seems improved, generating higher pulmonary artery pulse pressures and an increased cardiac output.

of syncope. At that time, the ECG showed a sinus rhythm, a QRS axis of 36°, normal P waves, conduction intervals within normal limits, and inverted T waves in leads I, III, aVF and V1 to V6 (figure 1A). Because of the observed repolarisation abnormalities, a series of additional tests was performed. Apart from severe hyperthyroidism, there were no cardiac or pulmonary abnormalities found at echocardiography (tricuspid and pulmonary valve regurgitation gradients were within normal limits, there was no right atrial or ventricular dilatation, right ventricular hypertrophy, or paradoxical septal bowing), left heart and coronary catheterisation, or pulmonary function tests. At renewed presentation, the ECG now showed a QRS axis of 90°, the R wave in lead V1 measured 6 mm in the absence of an S wave, and there were diffuse repolarisation abnormalities, all in agreement with an increased right heart load (figure 1B). At bicycle ergometry the patient performed 120 W (88% of predicted), without evidence of exercise-induced ischaemia. A pulmonary perfusion scan showed no signs of pulmonary embolism. Coronary angiography again revealed normal coronary arteries. The patient (height: 170 cm, weight: 90 kg) now had a normal thyroid function, and was not taking any medications. Haemodynamics at right heart catheterization are presented in figure 2. Pulmonary pressures and pulmonary vascular resistance approached systemic values, signifying that the degree of right heart load was severely elevated in this patient.

According to the guidelines, [1] the patient was further evaluated, eliminating possible aetiological factors in a stepwise fashion. Our patient denied past use of anorexigens or

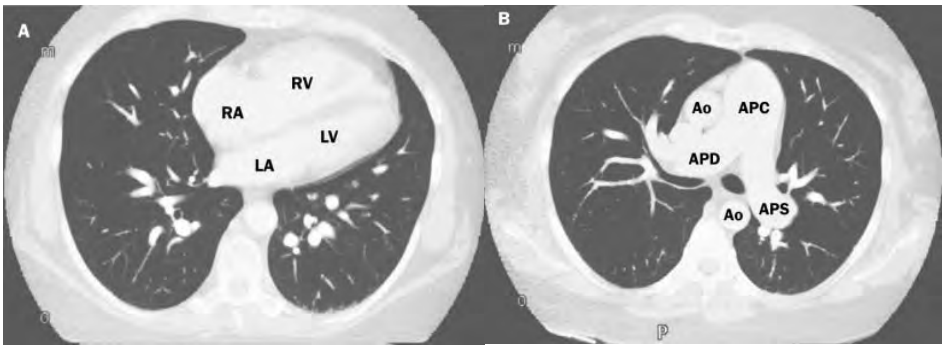


**Figure 3.** A. CT image which clearly shows the marked dilation of the right atrium and right ventricle, whereas the left atrium and left ventricle are considerably smaller. B. CT image of the aorta and pulmonary arteries. The diameter of the common pulmonary artery is almost twice that of the ascending aorta, and the right and left pulmonary arteries are also dilated. The severe dilatation of the pulmonary arteries indicates that the pulmonary arterial hypertension is not of recent onset, but a chronic condition. RA=right atrium, RV=right ventricle, LA=left atrium, LV=left ventricle, Ao=aorta, APC=common pulmonary artery, APD=right pulmonary artery, APS=left pulmonary artery.

intravenous drugs. There were no relatives with similar symptoms or established pulmonary hypertension. There was a history of alcohol abuse, but our patient had managed to refrain from drinking alcohol for several years, and an abdominal echo showed normal hepatopetal flow in the portal vein, essentially excluding presence of portal hypertension. The patient consented to a HIV test, which was negative. The echocardiogram showed no signs of left ventricular dysfunction or incompetence of the aortic and mitral valve, hence there was no indication that the pulmonary hypertension as secondary to left-sided heart disease. Pulmonary function tests showed a mild obstruction pattern with a diffusion capacity of 68%, corrected for alveolar volume. Arterial blood gas analysis rendered the following values: $O_2$ saturation 97% (94 to 99%), pH 7.47 (7.35 to 7.45), $pCO_2$ 4.2 kPa (4.5 to 6.0 kPa), $pO_2$ 10.9 kPa (10.6 to 13.3 kPa), base excess -0.4 mmol/l (-2 to 2 mmol/l) and bicarbonate concentration 22 mmol/l (22 to 29 mmol/l). Nocturnal oximetry showed no signs of desaturation or sleep apnoea. Additional CT imaging of the lungs and pulmonary arteries showed no signs of interstitial lung disease or thromboembolic disease, but dilatation of the right atrium, right ventricle, and central pulmonary arteries was striking (figure 3).

Since no satisfactory explanation could be found for the pulmonary arterial hypertension, the patient was classified as having idiopathic PAH. Despite the impressive level of PAH, treatment would not be reimbursed, given the relatively mild symptoms of the patient (NYHA functional class II). Since the severity of the disease led us to believe that refraining from treatment would lead to deterioration in the near future, we suggested that the patient should consider taking part in a clinical trial evaluating the benefit of an endothelin antagonist. The patient gave informed consent, and reported an improvement in her overall well-being during the first months of treatment. After one year of treatment pulmonary artery pressures

were virtually unchanged. However, systemic venous oxygen saturation had dramatically improved from 65 to 75%. Cardiac output calculated with the Fick method had increased from 5.5 l·m-2 to 7.9 l·m-2, meaning that PVR had dropped to approximately 600 dynes·s·cm-5. The ECG was unchanged compared with a year before. Since this pulmonary vascular resistance is still much higher than the upper limit of normal (≈240 dynes·s·cm-5), the patient received additional treatment with a phosphodiesterase inhibitor.

PAH is a rare disease, with an estimated incidence of 2 to 16 per million.[2] PAH often remains undetected until there are already advanced pulmonary vascular abnormalities.[1,3] In recent years, however, awareness for this orphan disease has increased, mainly due to the advent of new drug therapies.[4] Historically, the time interval from symptoms to diagnosis has been substantial for PAH patients, rendering most patients in NYHA class III or IV before treatment initiation.3 Although ECG abnormalities corresponding with right heart overload are present in the majority of PAH patients at diagnosis,[3,5] the scalar ECG has been considered inadequate for screening.1 Recent studies in rats and humans have illustrated, however, that even a mildly increased right ventricular pressure load is associated with substantial changes in myocardial electrical properties, detectable in a standard 12-lead ECG recording.[6,7] A possible explanation for the reportedly lower sensitivity for right ventricular pressure overload of the ECG by conventional assessment is the wide range of normal ECG values, i.e. the 'normal' heart axis ranges from -30° to +90° or even to +100°, depending on the criteria used.8 In contrast to the wide inter-individual heterogeneity in ECG characteristics, the ECG is a very reliable tool to detect intra-individual changes over time.

In this particular patient, there had been an extensive cardiac evaluation several years before. In the meantime, the patient developed PAH and the ECG changed markedly: the QRS axis turned rightward, changing from 36° to 90°, the R in lead V1 became >0.5mV and was more pronounced than the S, and there were diffuse repolarisation abnormalities. Together, these abnormalities correspond with increased right heart load and right ventricular hypertrophy.[8] This particular patient had relatively mild symptoms, given the severity of the PAH. The fairly stable cardiac situation was reflected by a sinus rhythm of 84 beats/min, indicating that stroke volume is adequate at rest.[9] The absence of a 'P pulmonale' (P wave >0.25 mV in lead II) signifies that PAH has not yet induced a significant retrograde atrial overload, which is otherwise an ominous sign of poor prognosis.[10,11] More specifically, P amplitude in lead II increases as a result of progressive RV hypertrophy-associated diastolic dysfunction, and RV dilatation-associated tricuspid regurgitation in PAH patients.[12] Karliner et al. documented an increase in P amplitude in lead II in healthy men who ascended from sea level to a height of 6300 meters above sea level on Mount Everest, and suffered from hypoxia-induced PAH.[12] Furthermore, QRS axis turned in a more rightward direction with increasing pulmonary vascular resistance at high altitude, a phenomenon also observed in our patient. Lastly, as QRS duration is related to ventricular size, function, and prognosis, here was no reason to believe that the right ventricle was performing poorly with a QRS duration of only 76 msec in this

patient.[13] There is fairly extensive knowledge on the ECG changes that can be observed with regression of right ventricular hypertrophy in developing newborns, as well as on the ECG abnormalities that remain present in people living at high altitudes.[10] Similarly, patients in whom PAH attenuating treatment is very effective – such as the rare patients who respond to calcium channel blockers – have shown dramatic ECG changes from a pattern corresponding with right ventricular hypertrophy to a (near)-normal pattern.[14] It is exceptionally rare that evolutionary ECG changes due to the development of PAH can be assessed. This is understandable, since PAH is an uncommon disease. Furthermore, PAH often presents relatively early in life, meaning patients lack cardiopulmonary comorbidity, and therefore prior ECG recordings. [2] Nevertheless, recording ECGs in patients at risk for developing PAH might be a cost-effective way of screening or longitudinal case-finding in selected groups of patients. Screening for PAH in patients at risk, such as patients with a genetic predisposition, HIV infection, portal hypertension, or systemic sclerosis, has been subject to debate for some time. [1] While results of clinical trials regarding earlier onset of treatment are awaited, critics claim that such screening is impracticable without properly validated tools. However, the results of improved ECG detection of increased right ventricular pressure load may well bring screening within reach.[7] Of course, pre-selecting patients at risk for pulmonary arterial hypertension will remain necessary, given the rarity of the disease. Now that the groups of patients at risk have been well identified,[1,2,15] there is ample opportunity to evaluate the diagnostic value of longitudinal ECG recordings in a clinical setting.

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