

# Rhythm disorders and electrocardiographic abnormalities in adult patients with pulmonary arterial hypertension (RCD code: class II)

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## Abstract

Cardiac arrhythmias may occur in the course of pulmonary hypertension as a result of structural changes related to pressure overload, myocardial hypertrophy and chamber dilation. Arrhythmias compromise greatly to clinical course of disease as they are related to clinical decline, worse outcome and prognosis. Common supraventricular arrhythmias (as atrial fibrillation or atrial flutter) are related to clinical deteriorations (in more than 80% of cases) and worse survival. Therefore early recognition and successful treatment is a key to improve outcome. This objective may be achieved by terminating arrhythmias either by (in most of cases) electrical or pharmacological cardioversion. To prevent further recurrence, radiofrequency ablation is a safe and efficient procedure. Data concerning clinical significance of ventricular arrhythmias is not well described. Most common rhythm disorders that occur during cardiorespiratory arrest are as follows: bradycardia, pulseless electrical activity and asystole, while ventricular fibrillation is a rare finding. Chances for successful resuscitation are poor, and prognosis is unfavorable, as 80% of cardiopulmonary resuscitation are unsuccessful and only 6% of patients after cardiac arrest will end up without neurological defects. The article contains also data concerning usefulness of routine electrocardiography in establishing a diagnosis of pulmonary hypertension, assessment of right ventricular hypertrophy and right ventricular overload. JRCDD 2013; 1 (5): 4–7

**Key words:** arrhythmia, sudden cardiac death, cardiopulmonary resuscitation, atrial fibrillation, ECG

## Background

Cardiac arrhythmias may cause clinically significant problems in patients with structural heart disease. In pulmonary hypertension, structural changes are a result of pressure overload, which leads to right heart hypertrophy, dilation, and tricuspid regurgitation which increases the risk of arrhythmias. Supraventricular arrhythmias such as atrial flutter and atrial fibrillation, contribute greatly to increased prevalence of exacerbations of chronic heart failure, which may lead to serious complications and may worsen long term prognosis. Ventricular arrhythmias commonly lead to acute heart failure, while some of them are directly life-threatening conditions.

The number of studies concerning cardiac arrhythmias in patients with pulmonary arterial hypertension (PAH) is limited. The current evidence on the prevalence and clinical significance of rhythm abnormalities in this group of patients is based mostly on single center studies.

## Ventricular arrhythmias, sudden cardiac death and cardiopulmonary resuscitation in PAH

Despite major advances in the treatment during last two decades, PAH is still a condition, with a high mortality rate. Sudden cardiac death (SCD) has been reported to be responsible for approximately 30–40% of all deaths in PAH [1,2].

The following causes of SCDs has been proposed in PAH: rupture or dissection of pulmonary trunk [3], compression of left main coronary artery by dilated pulmonary artery, severe decompensation of heart failure and arrhythmias [4].

Hoeper M. et al aimed to assess the prevalence of cardiac arrest and outcomes after cardiopulmonary resuscitation, in a multi-center retrospective study involving 3130 patients with PAH from 17 different centres in Europe and United States [4]. During the observation period between 1997 and 2000, cardiorespiratory arrest

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occurred in 513 patients. Cardiopulmonary resuscitation (CPR) was initiated only in 132 subjects. Cardiorespiratory arrest was associated with significant concomitant illness in 54% of cases, most common respiratory tract infection (18%), followed by viral enteritis, inguinal hernia, thrombophlebitis and gastroenteritis. Electrocardiograms obtained at the time of collapse, showed severe bradycardia (45%), pulseless electrical activity (28%), and asystole (15%). Ventricular fibrillation and tachycardia were uncommon findings (8%), therefore defibrillation or cardioversion were rarely performed. The study also showed, that 90 days survival after cardiorespiratory arrest, without neurological deficits was only 6%. In as many as 80% of cases, an undertaken CPR were unsuccessful. Fourteen percent patients died within next 7–90 days, due to recurrent cardiac arrests and neurological complications.

Primary prevention of SCD in PAH is currently not recommended [1].

## Supraventricular arrhythmias

The most common clinically relevant supraventricular arrhythmias in pulmonary hypertension (PH) are atrial fibrillation (AF) and atrial flutter (AFL) [5].

In a retrospective study of 109 adults with Eisenmenger's syndrome Cantor et al. showed that clinically relevant supraventricular arrhythmias, which required medical therapy, predicted increased mortality with a hazard ratio of 3.44 in a Cox multivariate survival analysis [6]. The most common cause of death in this group was congestive heart failure in 19 patients, followed by sudden cardiac death in 7 patients. Less common causes included endocarditis, cerebrovascular event and non-cardiac causes.

Tongers et al. [5] aimed to assess the prevalence and incidence rate of AF, AFL and their clinical significance. In a 6 year retrospective analysis they included 231 patients with PAH (204 patients) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH) (27 patients). Each patient was monitored and clinically assessed in time periods ranging from 1 to 6 months. During the observation period supraventricular tachycardia (SVT) occurred in 27 patients (31 episodes), most commonly represented by atrial fibrillation (13 episodes in 12 patients) and atrial flutter (15 episodes in 12 patients), followed by significantly less frequent atrioventricular nodal reentry tachycardia (AVNRT) (3 patients). New onset of these arrhythmias resulted in clinical deterioration and / or right heart failure in 84% cases. During episodes of supraventricular arrhythmias interventional approach was usually used as a first choice treatment. If unsuccessful it was followed by pharmacological treatment. AFL was terminated by electrical direct cardioversion in 6 patients, overdrive pacing in 2 patients, radiofrequency ablation in 3 patients, and pharmacological treatment in 1 patient. AFL recurred in only 2 patients, and in both of them a sinus rhythm was successfully restored with use of an overdrive pacing and radiofrequency ablation. In 3 patients with AVNRT use of a radiofrequency ablation (RFA) effectively terminated that arrhythmia. AF was successfully ceased by electrical cardioversion only in 2 out of 12 patients. Attempts to convert AF to sinus rhythm with drugs were unsuccessful in the remaining 10 patients. One patient after RFA for AVNRT developed persistent AF. Out of total of

11 patients with persistent AF 9 died during the observation period. Unfortunately AF was resistant to any attempted treatment. In contrast out of 16 patients with persistent sinus rhythm after at least 1 episode of SVT, only 1 patient died during observation period. In cases when sinus rhythm was re-established the risk of death was much lower (cumulative mortality 6.3% within follow-up time of  $26 \pm 23$  months), than in patients with persistent AF (cumulative mortality rate of 82% within follow-up time of  $11 \pm 8$  months). The global incidence of new onset of SVT was 2.8% annually per patient 5. Despite observed association between new onset of SVT and clinical deterioration, still there is no strong evidence whether SVTs are the cause of right heart failure, or just its consequence.

Olsson et al. [7] in their prospective study assessed a risk of a new-onset AFL and AF in patients with PH. They included 239 patients (157 with PAH, 82 with inoperable CTEPH) and observed them from 2005 till 2010. Each patient was assessed at the time of diagnosis and monitored in an out-patient department every 3–6 months. During the observation period at least one episode of AFL or AF occurred in 48 patients (24 cases of each AF and AFL). New onset AF or AFL was associated with clinical worsening, manifesting as a decreased 6-minute walk test distance ( $362 \pm 114$  m on a routine follow-up visit prior to event vs  $258 \pm 147$  m at onset of arrhythmia,  $p < 0.05$ ). After successful restoration of sinus rhythm 6-minute walk test distance increased to  $345 \pm 137$  m ( $p < 0.05$ ). Initial termination of SVT was successful in all cases of AFL and in 16 patients (67%) with AF. Most common initial treatment in AFL were drugs (11 patients) followed by electrical cardioversion (9 patients), RFA (3 patients) and overdrive pacing (1 patient). To prevent a recurrence of AFL, 16 patients underwent further RFA. Despite the efforts taken, five patients who initially had AFL developed AF during follow-up observation, and in 3 cases AF became permanent. In patients with AF the treatment of choice was electrical cardioversion if patient presented symptoms of heart failure, otherwise amiodarone was preferred. In case of AF (24 episodes), sinus rhythm was successfully restored in 16 patients with electrical cardioversion (within 18 attempts) and in 3 patients with a use of drugs. Although electrical cardioversion had high initial success rate, 5 of 16 patients had their sinus rhythm restored only temporarily and eventually developed a refractory AF. A stable sinus rhythm was sustained during the observation period in 21 (88%) of patients with AFL and 16 (67%) of patients with AF. Authors determined risk factors for a new onset of AF/AFL as follows: etiology of PH (AF/AFL were more frequent in PAH than in CTEPH), hemodynamic parameters (higher right atrial pressure and mean pulmonary arterial pressure, lower cardiac index), and laboratory tests (high bilirubin, high NT-proBNP). Patients without episodes AF/AFL had statistically significant better survival (5-year survival rate of 68%) as compared to for patients who developed at least 1 incident of AF/AFL (5-year survival rate of 47%). The incidence of AF/AFL during the observation time was associated with increased mortality risk with a hazard ratio of 1.75 [7]. Such observation gives some evidence of safety, feasibility and decent efficacy of ablation for atrial flutter or AVNRT in patients with PH despite structural alterations of the heart.

Current guidelines for the diagnosis and treatment of pulmonary hypertension emphasize that sustaining a stable sinus rhythm

is an important goal of treatment in patients with PAH. They also mention that some prophylaxis can be considered in order to achieve that goal by use of drugs that lack in negative inotropic effects (i.e. amiodarone) [8]. Use of other drugs in patients with pulmonary hypertension is currently not supported by reliable data. Electrical cardioversion seems to be effective and safe in this group, despite right heart failure and systemic hypotension [5].

Showkathali et al. [9] in their study aimed to evaluate efficacy, safety and feasibility of RFA in patients with pre-capillary PH. They included in their study 22 patients with the following diagnosis: 10 patients with IPAH, 1 patient with associated PAH and 11 patients with CTEPH. All patients had previously confirmed isthmus dependent AFL. Radiofrequency isthmus ablation was successful without complications in all cases. The success rate was high and only 3 patients have recurrence of arrhythmia within a follow-up period of 3 months. Two patients died within the follow up time due to procedure independent causes, namely pneumonia and pulmonary embolism. In 3 months following a procedure, patient underwent clinical assessment. Nine out of 20 patients improved their functional class, whereas in 11 functional class did not change. There was also a significant improvement in the functional class and 6 minute walk test distance from  $275 \pm 141$  prior ablation to  $293 \pm 146$  m afterwards. Parameters of right ventricle function measured with an echocardiography, remained unchanged [9]. The study confirms a short-term safety and efficiency, however data concerning a distant clinical benefits is missing.

## Electrocardiography in PAH

Typical changes in ECG found in PH are the signs of right ventricular and right atrial enlargement and hypertrophy.

Currently 24 criteria for diagnosis of right ventricular hypertrophy (RVH) are proposed by the American College of Cardiology, American Heart Association Task Force and the European Society of Cardiology Committee [10]. Table 1 presents current criteria for RVH with their estimated prevalence in IPAH population [10,11]. Majority of data that were used to establish ECG signs of RVH, come from surgical or post-mortem studies on inhomogeneous group of patients [12–19].

We recently assessed the accuracy of the recommended ECG criteria for predicting RVH and dilation in patients with IPAH. We referred the ECG criteria to the RV mas and volume as assessed by cardiac magnetic resonance.

In patients with IPAH, only the ECG voltage criteria based on R wave amplitude in V1 ( $RV1 > 6$  mm,  $R:SV1 > 1$ ,  $R:SV5$  to  $R:SV1 < 0.04$ ,  $\max RV_{1,2} + \max SI, aVL - SV1 > 6$  mm,  $RV1 + SV_{5,6} > 10.5$  mm,  $R:SV1 > R:SV3$ ,  $R:SV1 > R:SV4$ ), R wave amplitude in aVR, P wave amplitude in II and ventricular activation time in V1 were useful for differentiating between patients with and without RVH. A ventricular activation time in V1  $< 0.01$  s excluded RVH, whereas  $RV1 > 6$  mm,  $R:SV1 > 1$ ,  $RaVR > 4$  mm,  $R:SV5$  to  $R:SV1 < 0.04$  and PII  $> 2.5$  mm confirmed the diagnosis of RVH with 100% positive predictive value. Dilation of the RV could be diagnosed when the ventricular activation time was more than 0.045 s. [11].

**Table 1. Criteria for right ventricular hypertrophy according to the AHA/ACCF/HRS recommendations. Amplitudes are given in millimeters, where 1 mm = 0.1 mV [1]**

Criterion		Prevalence in IPAH [11]
Tall R in V <sub>1</sub>	>6 mm	35%
Deep S in V <sub>5</sub>	>10 mm	26%
Deep S in V <sub>6</sub>	>3 mm	74%
Tall R in aVR	>4 mm	17%
Small S in V <sub>1</sub>	<2 mm	61%
Small R in V <sub>5,6</sub>	<3 mm	8.7%
$(R_1 + S_{III}) - (S_1 + R_{III})$	<15 mm	96%
$(\max R \text{ in } V_{1,2}) + (\max S \text{ in I or aVL}) - (S \text{ in } V_1)$	>6 mm	83%
$R \text{ in } V_1 + S \text{ in } V_{5,6}$	>10.5 mm	74%
Increased R:S ratio in V <sub>1</sub>	>1	67%
Reduced R:S ratio in V <sub>5</sub>	<0.75	39%
Reduced R:S ratio in V <sub>6</sub>	<0.4	4%
Reduced (R:S in V <sub>5</sub> ) to (R:S in V <sub>1</sub> ) ratio	<0.04	6.7%
R peak in V <sub>1</sub> (QRS duration <0.12 s)	>0.035 sec	75%
QR in V <sub>1</sub>	present	61%
<b>Supporting criteria</b>		
RSR V <sub>1</sub> (QRS duration > 0.12s)	present	0%
S > R in I	present	78%
S > R in II	present	22%
S > R in III	present	8.7%
S I and Q in III ( $SQ_{III}$ )	present	78%
R:S in V <sub>1</sub> > R:S in V <sub>3</sub>	present	67%
R:S in V <sub>1</sub> > R:S in V <sub>4</sub>	present	67%
Negative T-wave V1 through V <sub>3</sub>	present	57%
P amplitude in II ( $P_{II}$ )	2.5 mm	26%
IPAH – idiopathic pulmonary arterial hypertension		

Although ECG can be useful in predicting RVH in patients with IPAH, generally ECG is not useful as a screening tool in PH, as it lacks sensitivity and specificity [8].

Bonderman et al. [20] have shown recently that ECG might be clinically useful to exclude the presence of pre-capillary PH. They proposed a two-step algorithm based on the assessment of right ventricular strain (defined as ST-segment deviation and T-wave inversion in leads V1–V3) and the level of NTproBNP. If a patient

did not have right ventricular strain and had NTproBNP <80 pg/ml the precapillary PH was excluded.

Right ventricular systolic dysfunction (RVSD) is a major complication of PH and a main predictor of death in patients with PAH [21,23].

Nagai et al. [23] aimed to assess usefulness of ECG to determine presence of RVSD in patients with PAH and inoperable CTEPH. The cardiac magnetic resonance imaging was used as a reference test for measurement of right ventricular ejection fraction. The cut-off point for presence of RVSD was at level of 35%. The prevalence of RVSD was high and almost half of the recruited group met the assumed criteria. Presence of R/S ratio > 1 in  $V_1$  or presence of qR pattern in  $V_1$  were found as predictors of RVSD for the whole group.

Interestingly, when an analysis was performed in patients with IPAH only, the combination of these two criteria provided very strong evidence for the presence of RVSD (with positive predictive values of 100%) [23].

The role and utility of ECG in monitoring response to the PAH specific treatment was performed in a study of Henkens et al. [24] They included 81 patients with PAH who were treated with endothelin receptor antagonists, sildenafil, prostacyclin or calcium channel blockers. For the purpose of the study the ECGs and hemodynamic data were collected and evaluated at baseline and within 1 year of follow-up. Positive response to treatment was defined as > 25% decrease in PVR to an absolute PVR of <500 dyne-s-cm<sup>-5</sup>. A couple of associations were identified between T wave axis, P wave amplitude, QRS axis and pulmonary vascular resistance (PVR). Interestingly P wave amplitude in lead II correlated linearly with a PVR. The authors concluded that patients with a T wave axis of < 25°, or patients with a T wave axis ≥ 25° and P wave amplitude in II lead ≤ 0.175 mV, can be expected to respond positively to the treatment.

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