



# Arrhythmias in Patients With Pulmonary Hypertension; A Narrative Review of the Current Literature

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## Abstract

Incidence and prognostic relevance of supraventricular arrhythmias were evaluated in nine studies. These studies investigated patients with different forms of pulmonary hypertension. Supraventricular arrhythmias were more often found in patients with group two pulmonary hypertension. Common findings in these patients were elevated right atrial pressure and diameters and reduced tricuspid annular plane systolic excursion (TAPSE). Elevations in other parameters like systolic pulmonary arterial pressure, mean pulmonary arterial pressure, and pulmonary vascular resistance (PVR) were inconsistent. Most of the patients with arrhythmias suffered symptoms and improved after sinus rhythm (SR) was restored. The prognostic relevance of non-sustained ventricular tachycardia was evaluated in only one study. Non-sustained ventricular tachycardia does not seem to be prognostically relevant. Extending Holter electrocardiogram (ECG) monitoring over 24 hours up to 72 hours raises the detection rate of arrhythmias. Ablation of arrhythmias, especially atrial flutter and atrioventricular node reentry tachycardia, is feasible and safe in these patients.

**Keywords:** Pulmonary Hypertension, Arrhythmias, Atrial Flutter, Atrial Fibrillation, Prognostic Relevance

## 1. Background

Pulmonary hypertension (PH) is defined as an increase in the mean pulmonary pressure (mPAP) >25 mm Hg at rest and capillary wedge pressure (PCWP) <15 mm Hg in precapillary (group 1, 3-5) or >15 mm Hg in postcapillary (group 2) forms.<sup>1</sup> Proliferation of pulmonary artery smooth muscle and endothelial cells, endothelial dysfunction, inflammation and excessive vasoconstriction lead to arteriolar obstruction, elevated pulmonary arterial pressure, and increased pulmonary vascular resistance (PVR).<sup>2,3</sup> Increased PVR causes elevated afterload of the right ventricle and cardiac remodelling.<sup>4</sup> Elevated right-sided filling pressure and cardiac remodelling could provide the substrate or trigger for arrhythmias.<sup>5,6</sup> Several studies have evaluated the incidence of supraventricular and ventricular arrhythmias and their prognostical relevance in patients with PH.<sup>7-15</sup>

It is already known that supraventricular arrhythmias are associated with clinical deterioration, but the incidence

of sudden cardiac death was not elevated in these patients.<sup>8,10,12,14,15</sup> The incidence and clinical/prognostical relevance of non-sustained ventricular tachycardia was analyzed in only three studies.<sup>16-18</sup>

## 2. Objective

The aim of this review is to give an actual and comprehensive overview of the current literature with respect to incidence and clinical and prognostical relevance of arrhythmias in patients with PH.

## 3. Methods

This review summarized the current evidence from the literature. Studies indexed (until 20/11/2017) in Medline and published in English or German that investigated patients in all PH groups (1-5) were considered. Medline searches included the following keywords: pulmonary hypertension, PH, incidence, arrhythmias, supraventricular arrhythmias, ventricular arrhythmias, ventricular

tachycardia, atrial fibrillation, atrial flutter, prognostic relevance, electrophysiological studies, ep-studies, EPS, and ablation. Studies fulfilling the search criteria were reviewed for incidence of arrhythmia, diagnostic tools, kinds of arrhythmia, patient characteristics, correlation of echocardiographic results/hemodynamic parameters and arrhythmias, clinical relevance of arrhythmias, and prognostic relevance of arrhythmias.

## 4. Results

### 4.1. Supraventricular Arrhythmias

Supraventricular arrhythmias in patients with PH were evaluated in nine studies (Table 1).

In a recent study by the current authors, 167 patients (mean age  $61.5 \pm 14.4$  years) with an initial diagnosis of PH (groups 1-5) were evaluated for incidence of arrhythmia during long-term follow up (FU), and the prognostic value of electrocardiography data was assessed.<sup>7</sup> Baseline electrocardiograms (ECGs) revealed a sinus rhythm (SR) in 137 patients and atrial fibrillation (AFib) in 30 patients, most of whom suffered from pulmonary venous hypertension (PVH, 53.3%). During follow up ( $n=137$  patients), AFib was detected in 13 patients (53.8% group 1 PH). At the timepoint of baseline ECG, patients were treated with beta-blockers ( $n=42$ ), calcium channel blockers ( $n=35$ ), and digitalis ( $n=13$ ), and a cardiac pacemaker was

**Table 1.** Studies Investigating Supraventricular Arrhythmias in Patients With Pulmonary Hypertension

First Author	Year	No. of Patients	PH Group(s)	Arrhythmias	Diagnostic Tool	Main Results
Bandorski <sup>7</sup>	2016	167	1-5	AFib	12-lead ECG	Retrospective study; elevated right atrial diameter/pressure in patients with AFib
Malaczynska-Rajpold <sup>8</sup>	2015	48	1	AFib, AFlu, AT, fVT	12-lead ECG	Retrospective study; elevated right atrial diameter/pressure/BNP and lower TAPSE in patients with arrhythmias, survival in patients with/without arrhythmias (41.9% vs. 66.3%; not statistically significant)
Cannillo <sup>9</sup>	2015	77	1,3,4	AFib, ectopic atrial tachycardia, right atrial flutter, AVNRT, paroxysmal supraventricular tachycardia	12-lead ECG	Retrospective study; elevated NT-proBNP in patients with arrhythmia, no differences in right atrial parameters, mortality higher in patients with arrhythmias (53% vs. 13%)
Wen <sup>10</sup>	2014	280	1	AFib, AFlu, AT	12-lead ECG	Prospective study; survival in patients with transient episodes of arrhythmia not statistically different from patients without arrhythmias, shorter survival in patients with permanent arrhythmias, elevated right atrial and ventricle diameter/pressure/BNP, and reduced CI, mixed venous saturation in patients with arrhythmias
Kamathreddy <sup>11</sup>	2014	311	1-5	AFib, AFlu	12-lead ECG	Retrospective study; many patients with group 2 PH (69.4%), no prognostic relevance of arrhythmias, high rate of recurrence after ablation and high rate of new onset (other) of arrhythmia
Olsson <sup>12</sup>	2014	239	1,4	AFib, AFlu	12-lead ECG	Prospective study; survival in patients with transient episodes of arrhythmias not statistically different from patients without arrhythmias, 6-MWD reduced+BNP elevated during arrhythmia and increased/decreased after restoration of SR, baseline values of RAP, mPAP and PVR higher in patients with arrhythmias
Rottlaender <sup>13</sup>	2012	225	1-5	AFib	12-lead ECG	Retrospective study; NT-proBNP elevated and 6-MWD reduced in patients with arrhythmias, right atrial pressure/ right atrial area elevated and TAPSE/cardiac output reduced in patients with arrhythmias
Ruiz-Cano <sup>14</sup>	2010				12-lead ECG, EPS	Retrospective study; arrhythmias led to clinical relevant restoration of SR, improved 6-MWD, ablation (AVNRT/Aflu) effective and safe
Tongers <sup>15</sup>	2007	231			12-lead ECG	Retrospective study, arrhythmias led to clinical deterioration, higher mortality in patients with arrhythmias

AFib=atrial fibrillation, AFlu=atrial flutter, AT=atrial tachycardia, ECG=electrocardiogram, EPS=electrophysiological study, fVT=fascicular ventricular tachycardia, mPAP=mean pulmonary arterial pressure, No=Number, PVR=pulmonary vascular resistance, PH=pulmonary hypertension, RAP=right atrial pressure, SR=sinus rhythm, 6-MWD=six minute walk distance.

implanted in 17 patients (indication: bradyarrhythmia). In patients developing AFib during follow up, P-wave duration was not different from that in patients with SR ( $0.11 \pm 0.02$  s vs.  $0.10 \pm 0.02$  seconds;  $P=0.193$ ). Patients with short P-waves ( $<0.1$  s) showed improved survival rates ( $88.1 \pm 6.7$  vs.  $49 \pm 5.8$  months) compared to patients with long P-waves ( $>0.11$  s), considering that this association was influenced by age (multivariate analysis). Other ECG parameters showed no correlation between duration of intervals and survival. Survival from diagnosis was  $79.4 \pm 5.4$  months in patients with SR,  $64.4 \pm 12.9$  months in patients with AFib during FU, and  $58.8 \pm 8.9$  months in patients with AFb in baseline ECG ( $P=0.565$ ). Patients with AFib had higher atrial diameter, atrial pressure and reduced tricuspid annular plane systolic excursion (TAPSE) without statistical significance.

Malaczynska-Rajpold et al investigated the prevalence and type of arrhythmias and the efficiency/safety of antiarrhythmic treatment over a follow-up period of  $28.8 \pm 17.7$  months in 48 patients with group 1 PH.<sup>8</sup> Seventeen patients suffered from arrhythmias like AFib ( $n=8$ ), atrial tachycardia (AT,  $n=6$ ), and atrial flutter (AFlu,  $n=6$ ). Four patients had more than one type of tachyarrhythmia. One patient with a fascicular ventricular tachycardia was not included in the statistical analysis. Patients with arrhythmias were older ( $52.4 \pm 15.3$  vs.  $47.4 \pm 16.5$  years,  $P>0.05$ ), NT-proBNP was higher ( $2658.9 \pm 3020.3$  vs.  $1748.0 \pm 1646.5$  pg/mL), and hemodynamic measurement/echocardiography revealed higher right atrial pressure ( $11.6 \pm 3.8$  vs.  $7.1 \pm 3.6$  mm Hg;  $P>0.05$ ), right atrial area ( $33.4 \pm 12.3$  vs.  $25.8 \pm 6.3$  mm<sup>2</sup>;  $P=0.01$ ), pericardial effusion (53 vs. 16%;  $P=0.008$ ), and lower TAPSE ( $14.4 \pm 4.6$  vs.  $18.4 \pm 5.7$  mm;  $P=0.02$ ). More than half of the arrhythmic episodes (59%) led to clinical deterioration and/or right heart failure (functional class, edema of the lower extremities, ascites) with a recurrence of the same or another arrhythmia within  $5.3 \pm 3.4$  months. Treatment of arrhythmia included direct current cardioversion/overdrive pacing (AFlu, AFib, and AT), medical treatment with amiodarone, propafenone or verapamil (AFib) and radiofrequency ablation (AFlu, AT) in 10 of 17 patients. Six-year survival rates were 41.9% vs. 66.3% in patients with arrhythmias vs. patients without arrhythmias ( $P=0.64$ ).

Cannillo et al revealed Afib (paroxysmal:  $n=1$ , persistent:  $n=8$ , permanent:  $n=3$ ), ectopic atrial tachycardia ( $n=2$ ), right atrial flutter ( $n=2$ ), atrioventricular node reentry tachycardia (AVNRT,  $n=1$ ), and paroxysmal supraventricular tachycardia during a follow-up period of 35 months [IQR 21.5 to 53.5] in their patients (mean age = 66.7 years).<sup>9</sup> Detection of arrhythmias occurred during either routine follow up ( $n=4$ ) or symptom-related diagnostic treatment ( $n=13$ ) in mean 15.1 months [IQR 11.3 to 43.2] after the initial diagnosis of PH. Patients with/without arrhythmias showed no significant differences. The only difference was that NT-proBNP was lower in patients without arrhythmias (795 vs. 1370 pg/mL)

without statistical significance ( $P=0.48$ ). Treatment of arrhythmias involved rhythm control strategy ( $n=13$ , amiodarone, sotalolol, Ic antiarrhythmic drugs), electrical cardioversion ( $n=8$ ), and radiofrequency ablation ( $n=3$ , AVNRT/AFlu/AFib+AFlu). SR was initially restored in 11 patients. Recurrence of arrhythmia ( $n=9$ ) led to clinical deterioration associated with worsening of WHO functional class, reductions in the 6-minute walk and TAPSE, and higher levels of NT-proBNP. Mortality was higher in patients with arrhythmias (53% vs. 13%;  $p=0.001$ ). Mean time between occurrence of arrhythmia and death was 3.5 months [IQR 1.7 to 9.1].

Another study investigated 280 patients (mean age  $39 \pm 15$  years) with group 1 PH and SR.<sup>10</sup> ECGs revealed AFib ( $n=16$ ), AFlu ( $n=13$ ), and AT ( $n=11$ ) with an incidence of 6.4%, 12.4%, and 15.8% during the first, third, and sixth years of follow up ( $31 \pm 7$  months). Survival was lower in patients with arrhythmias (estimated survival at 1, 3, and 6 years was 85%, 64%, and 53% vs. 92%, 82%, and 75%,  $P=0.008$ ), whereas survival was better in patients with transient episodes of arrhythmia than in patients with permanent arrhythmias ( $P=0.011$ ) and statistically not different from patients without arrhythmias ( $P=0.850$ ). Arrhythmias led to clinical symptoms like dyspnea, palpitations, edema, or worsening of WHO functional class. Under therapy (electrical cardioversion,  $n=2$ ; radiofrequency ablation,  $n=1$ ; antiarrhythmic drugs,  $n=37$ ), all patients converted to SR leading to clinical improvement. Recurrence of arrhythmia was observed in 7 of 13 patients with and in 12 of 16 patients with AFib. In patients with arrhythmias, echocardiography revealed high rates of dilated right atria and ventricles and pericardial effusions. Right atrial pressure ( $13 \pm 5$  vs.  $8 \pm 5$  mm Hg) and PVR ( $18 \pm 7$  vs.  $15 \pm 7$  Wood units) were higher, and the cardiac index ( $2.3 \pm 0.9$  vs.  $2.6 \pm 1.5$  l/min/m<sup>2</sup>) and mixed venous saturation ( $59 \pm 9\%$  vs.  $62 \pm 11\%$ ) were lower in patients with arrhythmias. BNP was elevated ( $456 \pm 396$  vs.  $318 \pm 339$  pg/mL;  $P=0.007$ ) in these patients, too.

The study of Kanmanthareddy et al investigated the incidence of arrhythmias in 311 patients (mean age  $61 \pm 13$  years) with all groups of PH; most of them (69.4%) suffered group 2 PH.<sup>11</sup> ECGs revealed AFib or AFlu in 121 patients (39%). The authors did not give any information about the distribution of arrhythmias related to PH groups. Patients with arrhythmias were older ( $66 \pm 12$  vs.  $57 \pm 14$  years;  $P<0.001$ ) and suffered from arterial hypertension more often (74% vs. 67%;  $P=0.03$ ), diabetes (38% vs. 30%;  $P=0.015$ ), coronary artery disease (59% vs. 55%;  $P<0.001$ ), mitral regurgitation (79 vs. 57%);  $P=0.001$ ), and impaired left ventricular ejection fraction (LV-EF  $<50\%$ ) (28% vs. 17%;  $P=0.027$ ). Pulmonary capillary wedge pressure (PcWP) was higher ( $20.3 \pm 8$  vs.  $17 \pm 9$  mm Hg;  $P=0.022$ ) and left atrium was more dilated ( $4.7 \pm 0.9$  vs.  $4 \pm 0.7$  mm;  $P<0.001$ ) in patients with arrhythmias. Age (OR 1.04;  $P=0.04$ ) and left atrial size (2.57;  $P<0.001$ ) were independent predictors of mortality in multivariate regression analysis. During follow up ( $22 \pm 14$  months),

35 patients (12%) died; no significant difference was observed between patients with and without arrhythmias (10% and 13%, respectively;  $P=0.549$ ). Forty-three patients underwent ablation: 20 patients with cavo-tricuspid isthmus ablation for right atrial flutter, 10 patients pulmonary vein isolation for AFib (additional cavo-tricuspid isthmus ablation  $n=4$ ), and 13 patients atrioventricular node ablation. One year after ablation, 17/20 patients who underwent cavo-tricuspid isthmus ablation developed AFib, and all patients after pulmonary vein isolation had a recurrence of AFib.

Olsson and colleagues study investigated 231 patients (mean age 55 years) with PH [group 1: 157 patients, group 4 (inoperable chronic thromboembolic PH): 82 patients].<sup>12</sup> Arrhythmias were detected in 48 patients, AFib and AFLu in 24 patients each. Patients who developed arrhythmias during follow up had higher baseline values for right atrial pressure (8 vs. 6 mm Hg;  $P=0.035$ ), mean pulmonary arterial pressure (52 vs. 45 mm Hg;  $P<0.001$ ), PVR (880 vs. 700 dyn s  $\text{cm}^{-5}$ ;  $P<0.001$ ), NT-proBNP (3340 vs. 2113 ng/L;  $P=0.394$ ), and lower values for cardiac index (2.3 vs. 2.5 l/min/m<sup>2</sup>;  $P=0.213$ ) and mixed venous saturation (60 vs. 64%;  $P=0.002$ ). Patients with group 1 PH seemed to be more at risk to develop arrhythmias. Incidence for new onset of an arrhythmia after 1, 2, 3 and 4 years was 13.4%, 9.2%, 23.6%, and 25.1%, respectively. Patients with arrhythmia presented with dyspnea on exertion, weight gain (>2 kg), palpitations, worsening of functional class, right heart failure, and increased heart rate with a mean of 112 beats/min, 33 beats/min higher than before onset of arrhythmia. Only 17% of patients were without symptoms and in clinical stable condition. Distance in 6-MW shortened during episodes of arrhythmia (before:  $362 \pm 114$  m; after detection of arrhythmia:  $258 \pm 147$  m; at follow up:  $345 \pm 137$  m;  $P<0.05$ ). BNP (baseline level  $2687 \pm 2260$  ng/L) significantly increased ( $P<0.05$ ) with onset of arrhythmia ( $5926 \pm 4648$  ng/L) and decreased after restoration of SR ( $3360 \pm 2804$  ng/L). SR was initially restored in all patients with AFLu (electrical cardioversion  $n=9$ , overdrive pacing  $n=1$ , radiofrequency ablation  $n=3$ , drug therapy  $n=11$ ) and in 16 patients with AFib (drug therapy: amiodarone  $n=2$ , dronedarone  $n=1$ ; electrical cardioversion  $n=18$ ). Survival in patients with arrhythmias was shortened in comparison to patients without arrhythmias (1/2/3 years: 87%/82%/76% vs. 91%/81%/55%;  $P=0.037$ ). Patients with AFib had a higher mortality than patients with AFLu (1/2/3 years: 82%/77%/69% vs. 89%/86%/79%;  $P=0.042$ ), whereas survival in patients with paroxysmal episodes of arrhythmias was not significantly different from patients without arrhythmias (1/2/3 years: 96%/90%/69% vs. 87%/82%/76%;  $P=0.039$ ). Restoration of SR was prognostically relevant. Patients who developed permanent AFib had a shorter survival period than patients in whom SR was restored (1/2/3 years: 64%/55%/27% vs. 95%/80%/57%;  $P=0.01$ ).

Rottlaender et al investigated the incidence of AFib in 225 patients (age: SR  $62.9 \pm 1.2$ , AFib  $71.2 \pm 1.1$ ) with PH

of all groups.<sup>13</sup> Many patients ( $n=52$ ) suffered from group 2 PH (42.9%). AFib was detected in 70 patients (31.1%), paroxysmal AFib in 29 patients (41.3%), and permanent/persistent AFib in 41 patients (58.7%). Most patients with AFib had either group 2 (42.9%) or group 4 (20%) PH and suffered from coronary heart disease (27.1%) and arterial hypertension (63.3%). NT-proBNP was elevated in patients (all PH groups) with AFib ( $2128.88 \pm 429.97$  vs.  $3252.79 \pm 401.76$ ;  $P<0.05$ ) and the 6-minute walk distance (6-MWD) was shorter ( $355.55 \pm 9.86$  vs.  $321.98 \pm 14.1$ ;  $P<0.05$ ). Excluding patients with group 2 PH showed similar trends related to NT-proBNP and 6-MWD. Hemodynamic and echocardiographic evaluation revealed elevated right atrial pressure and right atrial area and reduced values of TAPSE and cardiac output.

Ruiz-Cano et al evaluated the clinical implications of arrhythmias in patients with PH (group 1) and assessed the safety and efficacy of electrophysiological studies (EPS) in these patients ( $n=282$ , mean age  $47.3 \pm 14.3$  years).<sup>14</sup> Mean interval between diagnosis of PH and onset of arrhythmia was  $60.3 \pm 55.9$  months. Number of detected arrhythmias was 28 (AFib in 12 patients, AFLu in 12 patients and ANVRT in 4 patients). Most of the patients (AFib, AFLu, but not AVNRT) suffered from symptoms (82%), and 6-MWD decreased from  $423.7 \pm 74.6$  to  $252.1 \pm 145.8$  m ( $P<0.001$ ) after onset of arrhythmia. Conversion to SR led to an increased distance in the 6-MWD of  $196 \pm 163$  m. Approximately half (46.4%) of the patients needed an increase in PH-specific therapy independent from conversion to SR or rate control. Mean time from onset of arrhythmia to death or transplantation was 17.8 months. Five patients (AFib  $n=1$ , AFLu  $n=4$ ) died during follow up. Ablation was effective in all patients with AVNRT and in most patients with AFLu (95%).

Tongers et al performed the first evaluation of incidence and clinical relevance of arrhythmias in patients with PH ( $n=231$ ) [group 1: 204 patients; group 4 (inoperable chronic thromboembolic PH): 27 patients].<sup>15</sup> Arrhythmias were observed in 27 patients (AFib  $n=12$ , AFLu  $n=12$ , AVNRT  $n=3$ ) in an average of 3.5 years ( $0 \pm 238$  months) after the initial diagnosis of PH. Most episodes (84%) led to clinical deterioration (worsening of functional class, edema, refractory ascites). Treatment of arrhythmias included cardioversion (AFib  $n=6$ , AFLu  $n=2$ ), overdrive pacing (AFLu  $n=3$ ), ablation (AFLu  $n=5$ , AVNRT  $n=4$ ), and medical treatment with amiodarone, verapamil, digoxin, and beta-blockers. Four patients suffered from a recurrence of arrhythmia: one patient after cavo-tricuspid isthmus ablation for AFLu, one patient after overdrive pacing for AFLu, and 2 patients after ablation of AVNRT. Restoration of SR improved clinical symptoms, and these patients had a markedly lower mortality than those without SR restoration (6.3% vs. 81%,  $P=0.01$ ).

#### 4.2. Ventricular Arrhythmias

Only a few studies have evaluated the incidence and clinical relevance of non-sustained ventricular tachycardia in



**Table 2.** Studies Investigating Ventricular Arrhythmias in Patients With Pulmonary Hypertension

First Author	Year	No. of Patients	PH-Group(s)	Arrhythmias	Diagnostic Tool	Main Results
Bandorski <sup>16</sup>	2016	78	1, 4	ns-VT	Holter-ECG 24-72h	Retrospective study; first evaluation of prognostic relevance of ns-VT, ns-VT not prognostically relevant, TAPSE reduced in patients with ns-VT, no difference in mean atrial pressure
Bandorski <sup>17</sup>	2015	92	1,3-5	AFlu, ns-VT, second-degree heart block, third-degree heart block, non-sustained atrial tachycardia	Holter-ECG for 72 h during daily activity	Prospective study; first time Holter-ECG during daily activity, ns-VT in 13%, reduced TAPSE/CI/venous saturation and elevated PVR in patients with ns-VT/AFlu/heart blocks
Folino <sup>18</sup>	2003	9	1	PVC	Holter-ECG for 24 h	PVC >700/24 h in 4 patients, SDNN+SDANN reduced in patients with higher RVSP

AFlu=atrial flutter, ECG=electrocardiogram, No=number, ns-VT=non-sustained ventricular tachycardia, PVC=premature ventricular complexes, RVSP=right ventricular systolic pressure, SDNN=standard deviation (SD) of all NN (N: normal) intervals, SDANN SD of the averages of NN intervals in 5-min segments.

patients with PH (Table 2).<sup>16-18</sup> Bandorski et al investigated 92 patients with PH (groups 1, 3-5) without a known history of preexisting arrhythmias.<sup>17</sup> Functional class was NYHA III/IV in 70.6%. Because of arterial hypertension, 13 patients were treated with beta-blockers. All 65 patients underwent Holter-ECG monitoring over 72 hours during daily activity, and mean recording time was 64 hours and 9 minutes. Heart rate ranged from 56 beats/min to 124 beats/min. Relevant arrhythmias were detected in 17 patients, non-sustained ventricular tachycardia (ns-VT, length 3-20 beats, cycle length: 260-600 ms, n=12), intermittent second-degree heart block, and intermittent third-degree heart block (n=3) and AFlu (n=1). Most cases of ns-VT (58.3%) were observed between 24 hours and 48 hours of Holter-ECG monitoring, and 25% was seen within the first 24 hours of monitoring. The other arrhythmias were also detected during the first 24 hours. Underlying etiologies were PH of groups 1, 4, and 5 (53%, 41%, and 16%) in patients with ns-VT, group 1 PH in AFlu, group 4 PH in intermittent second-degree heart block, and PH of groups 1 and 4 in intermittent third-degree heart block. None of the patients suffered from an LV-EF <50%, and coronary heart disease was known in 3 patients (AFlu: n=1, ns-VT: n=2). Two patients with third-degree heart block underwent cardiac pacemaker implantation. In one patient, the beta-blocker application was interrupted, and Holter-ECG did not show heart blocks anymore. One patient with second-degree heart block declined cardiac pacemaker implantation. Holter ECG revealed non-sustained atrial tachycardia. SDNN was lower in patients with AFlu, heart blocks, and ns-VT (129.29 ms vs 139.39 ms;  $P=0.008$ ). Holter ECG revealed 70 VES/72 h (0-15 946) on average and 85 SEVS/72 h (0-13,622). BNP levels were higher in patients with AFlu, heart blocks, and ns-VT (198.47 vs. 91.73 pg/mL;  $P=0.04$ ). Echocardiography and hemodynamic monitoring showed reduced TAPSE (19.2 vs. 21.4 mm;  $P=0.95$ ), CI (2.46 vs. 2.82 L/min/m<sup>2</sup>;  $P=0.158$ ), venous oxygen saturation (64.67% vs. 68.41%;  $P=0.158$ ), and elevated PVR (542 vs. 672 dyn.s.cm<sup>-5</sup>;  $P=0.247$ ) in patients with AFlu, heart blocks, and ns-VT.

The prognostic relevance of ns-VT was not evaluated in this study. The survival of patients with ns-VT from 2 of the authors' studies was investigated retrospectively.<sup>16</sup> To match the results with other studies, only patients (n=78) with PH of groups 1 and 4 were included. Holter-ECG revealed ns-VT in 12 patients (PH group 1: n=8, group 4: n=4). Mean time from first diagnosis of PH to Holter ECG was  $6.2 \pm 4.1$  years in patients with ns-VT vs.  $5.4 \pm 3.9$  years in patients without ns-VT ( $P=0.736$ ). Patients with ns-VT were older ( $66.6 \pm 12.4$  vs.  $60 \pm 14.7$  years;  $p=0.112$ ) and had shorter 6-MWD ( $283 \pm 109$  vs.  $387 \pm 281$ ;  $P=0.941$ ). Echocardiography revealed reduced TAPSE (15.7 vs. 20.9 mm;  $p=0.001$ ) and elevated systolic pulmonary arterial pressure (sPAP, 72.7 vs. 61.6 mm Hg;  $P=0.163$ ) in patients with ns-VT. Results of right heart catheterization showed higher mean pulmonary arterial pressure (mPAP, 47.7 vs. 40.2 mm Hg;  $P=0.865$ ), PVR (835 vs. 532 dyn.s.cm<sup>-5</sup>;  $P=0.353$ ), and reduced cardiac index (2.42 vs. 2.81 l/min/m<sup>2</sup>;  $P=0.390$ ) and venous saturation (64 vs 685;  $P=0.700$ ) in patients with ns-VT. Interval from first diagnosis to death was not significantly different ( $P=0.855$ ) between patients with and without ns-VT ( $7.9 \pm 3.5$  vs.  $8.4 \pm 3.9$  years). Mean atrial pressure was not different in patients with and without ns-VT (4.3 vs. 4.4 mm Hg;  $P=0.865$ ).

Folino and colleagues' study evaluated ventricular arrhythmias and autonomic profiles in patients (n=9) with group 1 PH using 24 h Holter ECG monitoring.<sup>18</sup> In all patients, LV-EF was >50% (mean  $65.2 \pm 6$ ), values of RV-EF were between 44%-55% (mean  $49.3 \pm 5$ ), and right ventricular systolic pressure (RVSP) of  $91.2 \pm 25$  mm Hg. Three patients had an anamnesis of syncope. Holter ECG showed premature ventricular complexes (PVC, >700/24 h) in 4 patients and couplets in 2 patients. SDNN and SDANN were reduced in comparison to a control group of twenty healthy subjects (age  $39 \pm 18$  years) and in patients with PVC >700/24 h. Cardiopulmonary exercise tests revealed reduced workloads in all patients. Reasons for discontinuation were dyspnea and physical exhaustion; ventricular arrhythmias were recorded in none of the patients. Patients with the lowest SDNN (<90 ms) showed

higher RVSP ( $115 \pm 22.9$  vs.  $79.2 \pm 17.8$  mm Hg;  $P < 0.05$ ). SDNN was elevated in patients with syncope ( $131.7 \pm 36.5$  vs.  $88.4 \pm 20.0$ ).

## 5. Discussion

Incidence of supraventricular arrhythmias varied between 7.8% and 35%<sup>7-15</sup>; reasons for this difference remain unclear. Age does not seem to be a reason, because in the authors' study,<sup>7</sup> patients were older and had lower incidence of arrhythmias than in other studies,<sup>8-15</sup> despite it being well-known that prevalence of AFib increases with age.<sup>19</sup> Patients underwent (only) repeated twelve-lead ECGs in all studies during follow up. Self limiting episodes of arrhythmias may have been missed.

It is noteworthy that TAPSE was reduced,<sup>7,8,13</sup> and BNP,<sup>12,13</sup> right atrial area,<sup>7,8,10,13</sup> and mean right atrial pressure<sup>7,8,10,13</sup> were elevated in patients with arrhythmias. In Olsson and colleagues' study, all patients had normal left atrial dimensions<sup>12</sup>; in Rottlaender and colleagues' study, in patients without group 2 PH, elevated right atrial pressure and right atrial dilatation were associated with Afib<sup>13</sup> and seemed to be responsible for it.

Studies have revealed that supraventricular arrhythmias are prognostically relevant.<sup>7-9,12</sup> Interestingly, in the studies of Wen and Olsson, survival in patients with transient episodes of arrhythmias was not statistically different from patients without arrhythmias.<sup>10,12</sup> Most patients with arrhythmias suffered from symptoms<sup>8-10,14</sup> and improved after restoration of SR.<sup>8,12</sup> In Olsson and colleagues' study, restoration of SR was associated with improved 6-MWD and decreased NT-proBNP.<sup>12</sup> Interestingly, in Ruiz-Cano and colleagues' study, 46.4% of the patients needed more specific treatment of PH despite the restoration of SR or control of ventricular rate.<sup>14</sup>

Few studies have evaluated the prognostic relevance of ECG parameters. P-wave duration was associated with shorter survival, but in multivariate analysis this association was only borderline significant when age was included as a covariate ( $P = 0.06$ ).<sup>7</sup> QRS-width<sup>19</sup> and duration of QT-interval<sup>20,21</sup> were assessed in patients with PH and showed correlations with mortality. The results of these studies were not reported in other studies.

Ventricular tachycardias in patients with PH were revealed during continuous monitoring with Holter-ECG.<sup>16,17</sup> In accordance with the results of studies evaluating supraventricular arrhythmias, TAPSE was reduced in patients with nsVT<sup>16,17</sup> and cardiac index was reduced, whereas PVR, sPAP, and mPAP were elevated.<sup>16,17</sup> The authors' study showed that extending Holter ECG monitoring to longer than 24 hours raised the detection rate of arrhythmias.<sup>17</sup> The main result of the study was that the prognostical relevance of nsVT was missing. Because of the moderate sample size, the prognostic relevance and risk factors for nsVTs need to be obtained in larger series.

Electrophysiological studies showed that ablation in patients with AFlu is feasible and safe.<sup>21-27</sup> In Medi and colleagues' study, patients with right atria showing

## Review Highlights

### What Is Already Known?

Supraventricular arrhythmias are common in patients with pulmonary hypertension and lead in most cases to clinical deterioration. If possible cardioversion should be obtained. Permanent arrhythmias are associated with a worse prognosis.

### What This Study Adds?

This review highlights the frequency of (non-sustained) ventricular arrhythmias in patients with pulmonary hypertension and their prognostical relevance. Rhythm control should be sought in patients with supraventricular arrhythmias. Another important information is extending of Holter ECG monitoring (>24 hours) to raise the detection rate of arrhythmias. In patients with atrial flutter, focal atrial tachycardia and atrioventricular nodal reentrant tachycardia ablation is feasible and safe.

reduction of conduction velocity and an increase of areas of low voltage or electrical silence due to interstitial fibrosis were found.<sup>24</sup> The authors discussed these findings as a reason for lower pharmacologic or catheter-based success to restore SR.<sup>24</sup>

## 6. Conclusion

Supraventricular arrhythmias are common and, except transient forms, prognostically relevant in patients with PH. Most patients suffer from clinical symptoms. Restoration of SR should be targeted to improve patients' clinical presentation. Elevated RAP and right atrial diameters and reduced TAPSE are risk factors. The relevance of ECG parameters has to be evaluated in further studies. Non-sustained ventricular tachycardias showed no prognostical relevance in one study. Ablation of arrhythmias is feasible and safe.

## Authors' Contributions

Both authors fulfill the following International Committee of Medical Journal Editors (ICMJE) criteria for authorship:

1. Substantial contributions to the conception and design of the study or the acquisition, analysis, or interpretation of the data;
2. Drafting of the article or critical revision for important intellectual content;
3. Final approval of the version to be published;
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

## Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

## Ethical Approval

Not applicable.

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