

# Atrial fibrillation and atrial tachycardia in patients with chronic thromboembolic pulmonary hypertension treated with pulmonary endarterectomy

Stepan Havranek<sup>1\*</sup>, Zdenka Fingrova<sup>1</sup>, David Ambroz<sup>1</sup>, Pavel Jansa<sup>1</sup>, Jan Kuchar<sup>2</sup>, Milan Dusik<sup>1</sup>, Jaroslav Lindner<sup>3</sup>, Jan Kunstyr<sup>4</sup>, Michael Aschermann<sup>1</sup>, and Ales Linhart<sup>1</sup>

<sup>1</sup>2nd Department of Medicine - Department of Cardiovascular Medicine, General University Hospital in Prague, 1st Faculty of Medicine, Charles University, U Nemocnice 2, Prague 128 08, Czech Republic;

<sup>2</sup>Regional Hospital in Tabor, Kpt. Jarose 2000, Tabor 390 03, Czech Republic;

<sup>3</sup>2nd Department of Surgery - Department of Cardiovascular Surgery, General University Hospital in Prague, 1st Faculty of Medicine, Charles University, U Nemocnice 2, Prague 128 08, Czech Republic; and

<sup>4</sup>Department of Anesthesiology, Resuscitation and Intensive Medicine, General University Hospital in Prague, 1st Faculty of Medicine, Charles University, U Nemocnice 2, Prague 128 08, Czech Republic

## KEYWORDS

Chronic thromboembolic pulmonary hypertension;  
Pulmonary endarterectomy;  
Atrial fibrillation;  
Atrial tachycardia;  
Atrial flutter;  
Clinical outcome

Atrial fibrillation (AF) and atrial tachycardia (AT) are frequently observed in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were treated with pulmonary endarterectomy (PEA). Their prevalence and impact on prognosis of patients are not known. We analysed the prevalence of AF/AT and the clinical outcome in 197 patients with CTEPH treated with PEA (median age 62; interquartile range 53-68 years; 62% males). The prevalence of AF/AT was 29% (57 patients). Compared to patients without arrhythmia, the subjects with AF/AT were older [60 (50-67) vs. 62 (57-70) years], manifested an increased size of the left atrium [39 (35-44) vs. 45 (40-50) mm], had a reduced 6-min walking distance [411 (321-506) vs. 340 (254-460) m], and higher pulmonary artery systolic pressure after PEA [38 (30-47) vs. 45 (38-71) mmHg], all results with  $P$ -value  $<0.05$ . During the follow-up with a median 4.2 (1.6-6.3) years, 45 (23%) patients died. In a multivariate Cox regression model only the male gender [hazard ratio (HR) 2.27, 95% confidence interval (CI) 1.15-4.50], a reduced 6-min walking distance (HR 3.67, 95% CI 1.74-7.73), and an increased New York Heart Association class (HR 8.56, 95% CI 4.17-17.60) were associated with mortality ( $P < 0.05$ ). The prevalence of AF/AT in patients with CTEPH treated with PEA is high. Arrhythmias are associated with reduced functional capacity but not with mortality.

## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by a persistent obstruction of the pulmonary arteries by organized thrombi, leading to flow

redistribution and secondary remodelling of the pulmonary microvascular bed.<sup>1,2</sup> The incidence of CTEPH has gradually increased in recent years.<sup>3</sup> Without treatment the prognosis of CTEPHs is unfavourable.<sup>4</sup> Although performing a balloon pulmonary angioplasty or using medical therapy may be suitable,<sup>3</sup> a surgical pulmonary endarterectomy (PEA) is the treatment of choice for operable CTEPH.<sup>1</sup> The majority of patients experience substantial relief from symptoms

\*Corresponding author. Tel: +420 224962605, Fax: +420 224912454, Email: stepan.havranek@lf1.cuni.cz

and near-normalization of haemodynamics after surgery.<sup>1,2,5</sup>

Supraventricular tachycardias have been frequently (range of cumulative incidence 10-25%) observed in patients with pulmonary hypertension (PH),<sup>6-11</sup> including inoperable CTEPH.<sup>7,10</sup> It has been shown that atrial tachyarrhythmias lead to clinical deterioration and may be associated with an increased risk of death in patients with PH.<sup>7,8,10,11</sup> Out of all types of supraventricular tachycardias in the PH population, atrial fibrillation (AF) and the related atrial tachyarrhythmias (AT), including Type I atrial flutter (AFL) are the most frequently observed ones.<sup>6,7,9-11</sup>

From the previously mentioned surveys, patients with CTEPH treated with PEA were not included. Up to date, epidemiological data and the clinical impact of AF/AT for this population remain unclear. This study has two objectives. The first is to evaluate the prevalence of arrhythmias and their clinical outcome in CTEPH patients treated with PEA. The second objective is to describe whether AF/AT epidemiology is influenced by surgical treatment. To accomplish these objectives, we designed the given retrospective analysis of the PH registry.

## Methods

Consecutive unselected patients, who were diagnosed and treated for CTEPH with PEA at a single centre between 2003 and 2017, were enrolled in the dedicated registry approved by the local ethics committee. The study was performed according to good clinical practice and in compliance with the Helsinki declaration. An individual written consent was obtained from each patient. The study was approved by the local ethics committee.

The current study was part of a project on the epidemiology and clinical impact of supraventricular tachycardia in PH. The protocol used in this study has been previously described in detail.<sup>12</sup> In short, all patients underwent a routine baseline in-hospital work-up according to contemporary standards<sup>1</sup> including a complete assessment of their medical history, functional capacity, all indicated non-invasive and invasive methods, and right heart catheterization at the time of diagnosis. For patients with CTEPH, operability assessment included a perfusion scintigraphy and pulmonary angiography. All eligible patients were scheduled for surgery. The surgical technique developed by Daily and Jamieson<sup>13,14</sup> was used with some modifications.<sup>15</sup> Pulmonary endarterectomy surgery was performed in hypothermic circulatory arrest. An obstructive fibrous material from the pulmonary arteries was removed. Concomitant procedure: i.e. surgical revascularization, valve surgery, was performed during the same operation when indicated.

After PEA, all patients were regularly seen at 1-6 monthly intervals, or whenever clinically indicated, in an outpatient clinic. For all patients, the follow-up included an echocardiographically evaluated pulmonary artery systolic pressure (PASP). A standard 12-lead electrocardiography was obtained as part of the regular follow-up programme at each clinical visit.

Prevalent AF/AT (common, Type I AFL included) was defined as the presence of arrhythmia on the 12-lead surface

electrocardiography, 24-h electrocardiography monitors and/or during invasive electrophysiology testing and/or as indicated by a diagnosis found in the medical records, hospitalization, or ambulatory databases. The diagnosis of AF/AT was confirmed by an experienced cardiologist. Atrial fibrillation/AT documented in only the first 30 days after surgery was classified as early post-PEA arrhythmia. Patients with isolated early post-PEA arrhythmia were excluded from main analysis.

Based on clinical experiences and referred guidelines, rhythm control, i.e. the restoration of the sinus rhythm was usually attempted in all patients with a symptomatic or clinically significant tachycardia which was not previously classified as permanent. Patients with previously documented, known paroxysmal, or persistent AF/AT were scheduled for a concomitant MAZE procedure during PEA. In case of Type I AFL, the primary strategy was to restore the sinus rhythm with an early catheter ablation (CA). Atrial fibrillation patients or subjects with other AT than Type I AFL were treated with electrical cardioversion, if the sinus rhythm was not restored spontaneously or after initial antiarrhythmic therapy or in cases of heart failure symptoms. When the symptomatic recurrent AF/AT was manifested, a CA was scheduled.

## Statistical analysis

Continuous variables were expressed as means with standard deviations or by a median with an interquartile range (IQR) and compared with the two-tailed *t*-test for independent samples or by Mann-Whitney U test, respectively. Categorical variables were expressed as percentages and compared with the  $\chi^2$  test. The multivariate Cox regression model was used to identify independent predictors of mortality. A *P*-value <0.05 was considered significant. All analyses were performed using the STATISTICA version 12 software (StatSoft, Inc., Tulsa, OK, USA).

## Results

### Baseline characteristics of the cohort

A total of 197 patients (median age 62; IQR 53-68 years; 62% males) were included in the analysis. The prevalence of all types of AF/AT in the overall study population was 29% (57 patients). Twenty (10%) patients were excluded from main analysis due to manifestation of AF/AT only very early post-PEA. Baseline clinical and demographic characteristics of the total population and subgroups by the occurrence of AF or AT are shown in *Table 1*. Patients with prevalent AF/AT were older, more frequently had arterial hypertension, had bigger left atrial (LA) diameter, were in a worse New York Heart Association (NYHA) class, manifested shorter walking distance during the 6-min walking test (6MWT), and higher PASP after PEA (*Table 1*).

### Prevalence and clinical profile of arrhythmia manifestation before and prolonged after pulmonary endarterectomy

Out of all the patients with AF/AT (*n*=57), AF was detected in 30 (53%) and AT in 27 (47%) subjects, respectively. Type I AFL was diagnosed in 22 patients (39% of all

**Table 1** Baseline demographic and clinical characteristics

	Overall population	AF/AT No	AF/AT Yes	$P_1$ -value	AF/AT Early post-PEA	$P_2$ -value
N	197	120	57	—	20	—
Age (years)	62 (53-68)	60 (50-67)	62 (57-70)	0.02	65 (60-70)	0.06
Males	123 (62)	71 (59)	41 (72)	0.09	11 (55)	0.74
Arterial hypertension	124 (63)	66 (55)	45 (79)	0.002	13 (65)	0.4
LA in PLAX (mm)	41 (36-46)	39 (35-44)	45 (40-50)	<0.001	37 (34-42)	0.35
RA in A4C (mm)	53 (44-62)	54 (44-61)	54 (46-65)	0.34	48 (38-55)	0.07
RV in A4C (mm)	50 (42-57)	50 (43-57)	51 (41-57)	0.77	48 (42-52)	0.2
EF LV (%)	65 (60-70)	65 (60-69)	65 (58-70)	0.39	67 (62-72)	0.22
TAPSE (mm)	16 (13-20)	16 (13-19)	16 (13-20)	0.80	19 (14-22)	0.08
PAMP (mmHg)	53 (47-60)	52 (47-61)	53 (47-60)	0.63	54 (47-59)	0.93
PAWP (mmHg)	12 (9-14)	12 (9-14)	13 (10-15)	0.08	11 (10-13)	0.6
RAP (mmHg)	11 (8-15)	11 (8-15)	11 (8-16)	0.61	11 (8-14)	0.69
PASP after PEA	40 (31-50)	38 (30-47)	45 (38-71)	0.003	38 (35-46)	0.68
NYHA III-IV	51 (26)	27 (23)	22 (39)	0.03	2 (10)	0.17
6MWT (m)	394 (301-485)	411 (321-506)	340 (254-460)	0.01	408 (319-476)	0.79
Mortality rate	45 (23)	27 (23)	16 (28)	0.47	2 (10)	0.19
Follow-up (years)	4.2 (1.6-6.3)	4.2 (1.3-6.4)	4.3 (1.9-6.0)	0.72	4.3 (2.9-6.0)	0.94

Values are expressed as median (interquartile range) or as  $n$  (%).  $P_1$ -value—comparison of patients without any documented AF/AT and those with AF/AT (patients with a manifestation of AF/AT only during the first 30 days after PEA are excluded).  $P_2$ -value—comparison of patients without any documented AF/AT and patients with only early post-PEA arrhythmia manifestation.

AF, atrial fibrillation; AT, atrial tachycardia; EF LV, ejection fraction of left ventricle; LA in PLAX, left atrial size in parasternal long-axis view; NYHA, New York Heart Association; PAMP, pulmonary arterial mean pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; RA in A4C, right atrial size in apical four-chamber view; RAP, right atrial pressure; RV in A4C, right ventricle in apical four-chamber view; TAPSE, tricuspid annular plane systolic excursion; 6MWT, 6-min walking test.

subjects with AF/AT). Out of all the patients with AF/AT ( $n=57$ ), 17 subjects (30%) the arrhythmia occurred prior to the PEA [AF: 12 (71%); AT: 5 (29%); AFL 4 (24%)]. In remaining 40 patients (70%) arrhythmia appeared during the long-term follow-up after PEA [AF: 18 (45%); AT: 22 (55%); AFL 18 (45%)]. The differences in the spectrum of diagnosed arrhythmias before and after PEA did not reach statistical significance ( $P=0.07$ ) (Figure 1).

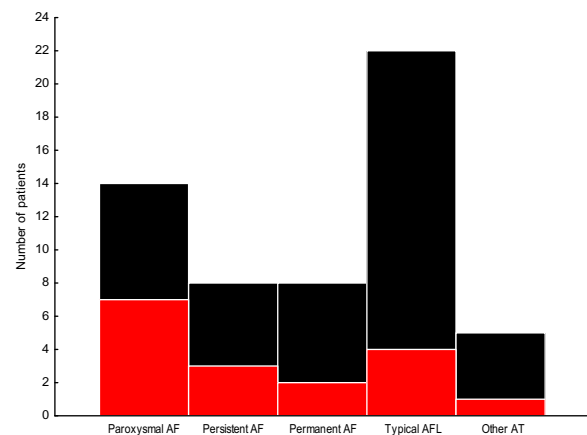
The clinical and demographic profile of patients with AF/AT manifestation before and after PEA is shown in Table 2. Patients with a known diagnosis of AF/AT before PEA ( $n=17$ ) differed significantly from those in whom arrhythmia developed after PEA ( $n=40$ ). These individuals had a reduced distance during the 6MWT, had more frequently symptoms ranging within NYHA III or IV class, and had higher mortality rate.

### Profile of patients with right atrial arrhythmia

When comparing patients with AF or AT, subjects with Type I AFL had a more dilated right atrium (RA) [median 62 (IQR 50-68) vs. 48 (42-61) mm;  $P<0.01$ ] and right ventricle (RV) [median 55 (IQR 49-60) vs. 47 (42-53) mm;  $P=0.047$ ]. In the rest of the tested parameters (including tricuspid annular plane systolic excursion and LA size), no significant differences were noted (Figure 2).

### Characteristics of patients with arrhythmia occurring only in the early post-pulmonary endarterectomy period

In addition to the 57 patients with AF/AT appearing either prior PEA or during the long-time follow-up after the



**Figure 1** The spectrum of detected arrhythmia. The red columns visualize patients with arrhythmia manifested before the pulmonary endarterectomy; black columns refer to patients with arrhythmia diagnosed during a long-term follow-up after the surgery. AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia.

procedure, a proportion of patients developed AF/AT in the early post-PEA period defined as <30 days after surgery. Overall this event occurred in 20 (10%) patients. In this group, an excessive prevalence of AF was noted [AF: 18 (90%), AT: 2 (10%), AFL: 1 (5% of all AF/AT)]. Majority of patients (16/80%) manifested AF/AT within first 7 days after surgery. Rest of subjects (4/20%) developed arrhythmia within second week post-PEA. No statistically significant difference was identified between patients with manifested arrhythmia in only the early post-PEA period and

**Table 2** Demographic and clinical characteristics in relation to manifestation of arrhythmia before and after pulmonary endarterectomy

	AF/AT Before PEA	AF/AT After PEA	P-value
N	17	40	—
Age (years)	62 (56-71)	62 (58-70)	0.58
Males	12 (71)	29 (73)	0.88
Arterial hypertension	15 (88)	30 (75)	0.27
LA in PLAX (mm)	45 (40-47)	45 (42-50)	0.34
RA in A4C (mm)	49 (40-64)	59 (48-66)	0.27
RV in A4C (mm)	49 (40-58)	52 (43-57)	0.38
EF LV (%)	65 (61-67)	65 (57-70)	0.67
TAPSE (mm)	16 (14-20)	16 (12-19)	0.34
PAMP (mmHg)	53 (41-62)	53 (48-60)	0.9
PAWP (mmHg)	13 (10-15)	13 (11-15)	0.95
RAP (mmHg)	10 (7-12)	13 (8-17)	0.2
PASP after PEA	46 (41-83)	43 (38-65)	0.32
NYHA III-IV	10 (59)	12 (30)	0.04
6MWT (m)	278 (235-365)	364 (298-473)	0.04
Mortality rate	8 (47)	8 (20)	0.04
Follow-up (years)	4.3 (1.9-6.0)	5.0 (2.9-6.8)	0.09

Values are expressed as median (interquartile range) or as *n* (%). *P*-value—comparison of patients with arrhythmia before and long term after pulmonary endarterectomy.

AF, atrial fibrillation; AT, atrial tachycardia; EF LV, ejection fraction of left ventricle; LA in PLAX, left atrial size in parasternal long-axis view; NYHA, New York Heart Association; PAMP, pulmonary arterial mean pressure; PASP, pulmonary artery systolic pressure; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; RA in A4C, right atrial size in apical four-chamber view; RAP, right atrial pressure; RV in A4C, right ventricle in apical four-chamber view; TAPSE, tricuspid annular plane systolic excursion; 6MWT, 6-min walking test.

without any arrhythmia (Table 1). When compared to the rest of the patients with AF/AT, the subjects with early post-PEA manifestation of AF/AT had a smaller LA size [IQR 37 (34-42) vs. 45 (IQR 40-50) mm;  $P=0.0002$ ] and were more frequently in the NYHA I class [10 (50%) vs. 15 (26%);  $P=0.048$ ]. The difference in post-operative PASP between patients with early post-PEA arrhythmia and remaining patients with the history of AF/AT was above the threshold for statistical significance 38 (IQR 35-46) vs. 45 (IQR 38-71) mmHg;  $P=0.06$ .

### Treatment strategies in patients with arrhythmia

Out of all the patients with AF/AT ( $n=57$ ) (excluding the early post-PEA events), initial rhythm control strategy (including both pharmacological and non-pharmacological methods) was used in 48 (84%) cases. In patients with AFL ( $n=22$ ), a CA/MAZE procedure during PEA was performed in 11 (50%) and 4 (18%) patients, respectively. In three patients with AFL (75% of all AFL diagnosed before PEA), CA was performed before surgery. At the final of follow-up, sinus rhythm persisted in 18 (82%) of all the subjects with AFL (3 patients had permanent AF and 1 had ongoing AFL). In AF and remaining cases of AT ( $n=35$ ), rhythm control was initially attempted in 33 (94%) patients. Non-pharmacological strategy (MAZE operation during PEA) was

applied in 7 (20%) patients, respectively. Other patients were treated by antiarrhythmic drugs only, predominantly with amiodarone. Despite rhythm control strategy (both pharmacological and non-pharmacological), the recurrence rate of AF and related AT was 20%. At the end follow-up, permanent arrhythmia was present in 12 patients (6% of the entire study population and 21% of all patients with AF/AT). The patients with permanent arrhythmia at the final follow-up, were in a more advanced NYHA class, had an increased PASP and larger LA diameter, as compared to patients with a stable sinus rhythm (Figure 3).

### Clinical outcomes in patients with and without atrial fibrillation/atrial tachycardia

During a follow-up with a median of 4.2 (IQR 1.6-6.3) years, 45 (23%) patients had died. According to univariate analysis, patients with a permanent AF/AT, with an arrhythmia manifestation before PEA, in a more advanced NYHA class or with a lower 6MWT distance were more likely to die (Table 3). In multivariate Cox regression model, the male gender, advanced NYHA classes, and a reduced 6MWT were associated with mortality (Table 3). Permanent arrhythmia at the end of study period was not identified as a mortality predictor in any model tested.

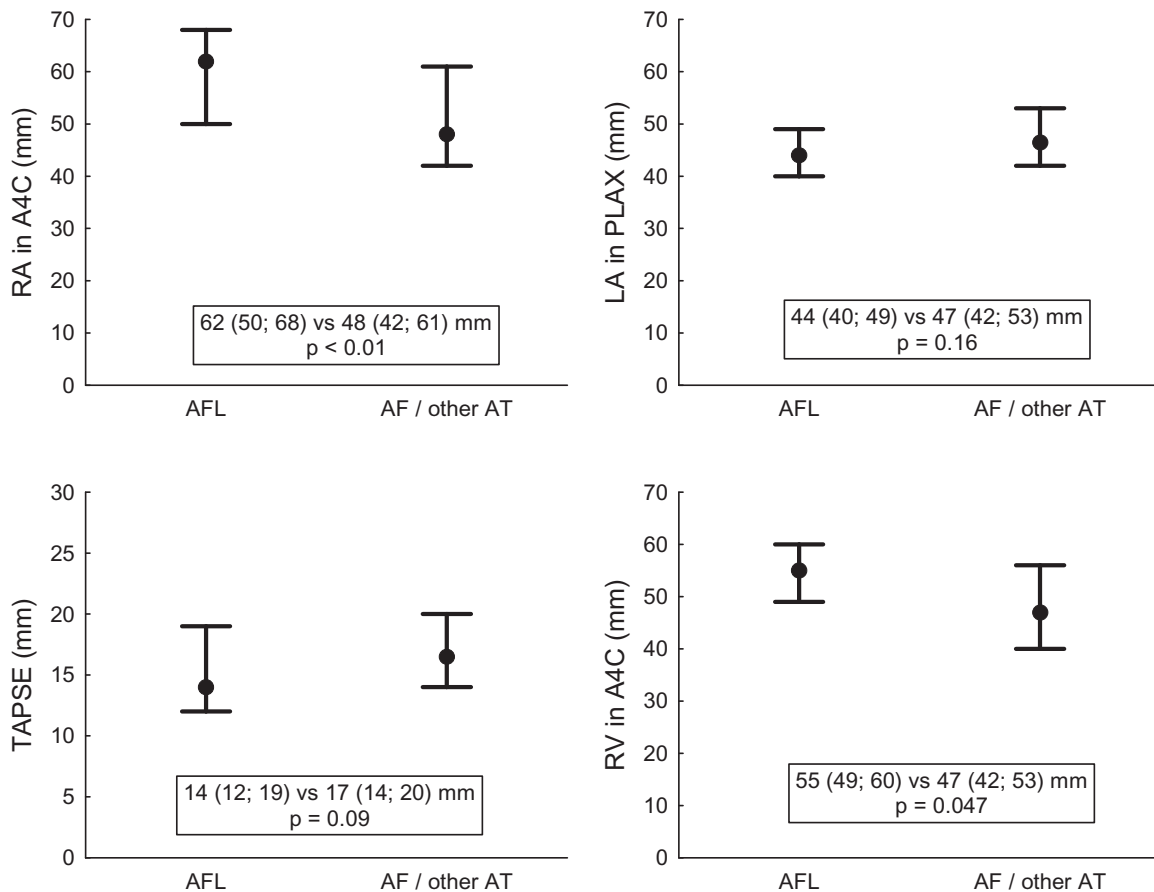
### Discussion

Our data show the prevalence and clinical outcome of AF or AT in a real-world population of patients with CTEPH treated with PEA. The occurrence of AF/AT is associated with advanced age, more prevalent arterial hypertension, larger LA size, higher post-operative PASP, and reduced functional capacity. Patients with AF/AT diagnosed prior to PEA manifested a worse clinical outcome after surgery. Although a permanent arrhythmia at the end of follow-up seemed to be associated with a worse clinical outcome in univariate pattern, only male gender, NYHA class, and 6MWT distance predicted mortality according to multivariate analysis.

### Epidemiology and pathophysiological mechanism of atrial fibrillation/atrial tachycardia in pulmonary endarterectomy patients

Most retrospective and prospective studies have reported a cumulative incidence of supraventricular arrhythmia ranging from 10% to 25% of patients with pulmonary arterial hypertension or inoperable CTEPH.<sup>8-10,16</sup> The most prevalent arrhythmias reported were AF and AFL.<sup>6,7,9-11</sup> To the best of our best knowledge, our analysis is the first to describe the epidemiology and clinical significance of AF/AT in CTEPH treated with PEA.

There is evidence supporting the RA substrate for AF/AT: PH leads to an enlargement of the RA as a consequence of the increased afterload of the RV and its progressively worsening filling.<sup>17</sup> A long-standing PH is associated with slowing conduction, reduced tissue voltage and regions of electrical silence in both the RA and the RV,<sup>18</sup> and modulations of the autonomic system may trigger and perpetuate arrhythmia.<sup>19,20</sup> In addition, the performed cardiac surgery



**Figure 2** Comparison of patients with Type I atrial flutter and atrial fibrillation or other atrial tachycardia. AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; LA in PLAX, left atrial size in parasternal long-axis view; RA in A4C, right atrium size in apical four-chamber view; RV in A4C, right ventricle in apical four-chamber view; TAPSE, tricuspid annular plane systolic excursion.

itself may increase the risk of post-incisional AF/AT after PEA resulting from RA cannulation and/or incision. Our data show substantial differences between patients with typical right-sided arrhythmia (i.e. Type I AFL) and AF or other AT in RA size. This finding supports role of advanced right atrial remodelling as consequence of the long-standing CTEPH in AFL arrhythmogenesis. Although the difference in the arrhythmia spectrum before and after PEA did not reach statistical significance, several Type I AFL seemed to increase after surgery and support the role of scarring related to surgical intervention.

We have recently shown that the LA substrate could play a role in arrhythmogenesis of complex atrial arrhythmia, even in precapillary PH patients.<sup>12</sup> The increased LA size in AF/AT patients with CTEPH treated with PEA seems to be in line with our hypothesis suggesting the role of classical risk factors for AF contributing to its pathogenesis. This hypothesis is also supported by observation that RA enlargement was not excessive in AF patients. However, we hypothesize that increased residual PASP after PEA in patients with AF/AT is more likely due to a combination of advanced CTEPH, less effective surgical treatment, and by the existence of a subtle post-capillary component. The possible role of the post-capillary component is supported by an increase of post-operative PASP in patients with AF/AT onset before

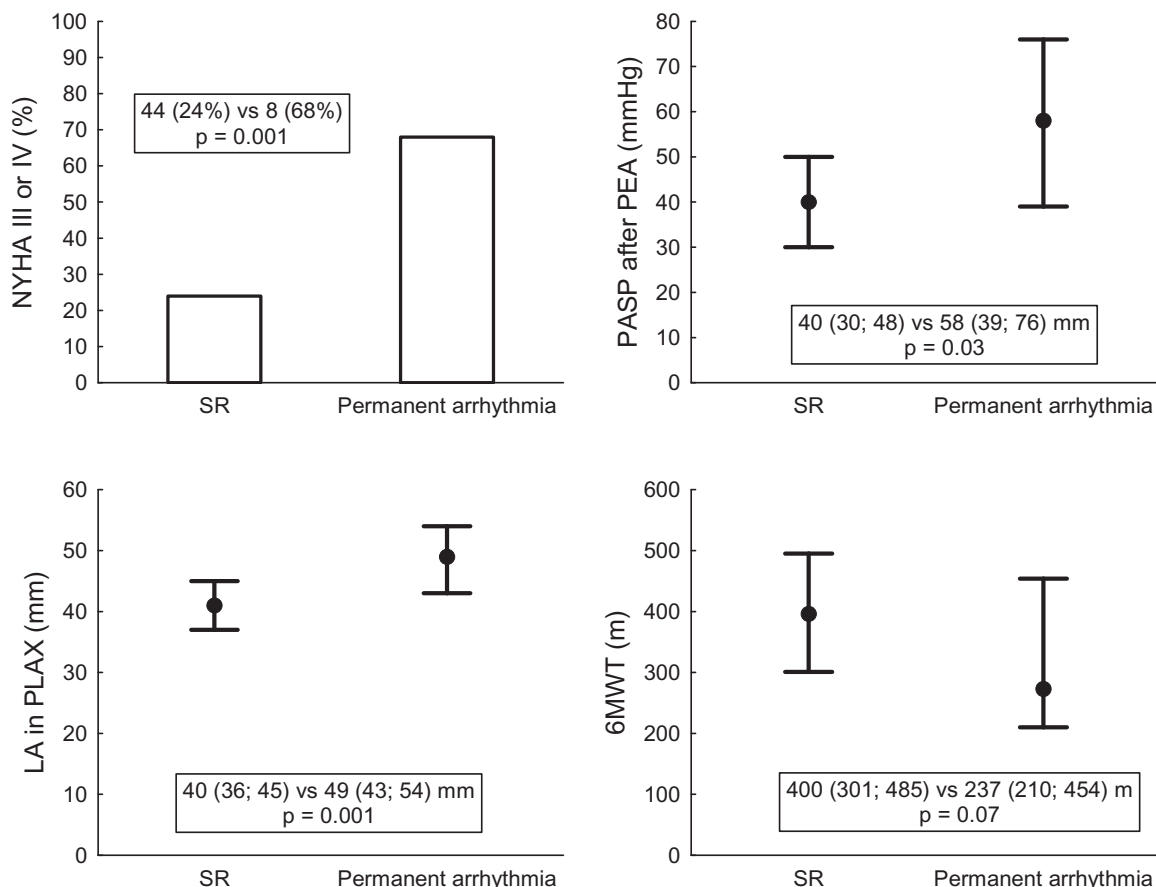
surgery. Actually the diagnosis of PH or CTEPH does not exclude a manifest or latent post-capillary component. First, because pulmonary artery wedge pressure limit is set relatively high above the limits of presumed physiological values. Second, PH diagnosis is uniquely based on resting invasive pulmonary pressure measurements. It has been repeatedly shown<sup>21,22</sup> that a fluid challenge or exercise can unmask a post-capillary component in a large number of patients.

Since in our study several well-known risk factors, such as ageing and arterial hypertension were associated with an increased risk of AF/AT, we assume that a proportion of CTEPH patients develop these arrhythmias due to the same reasons as in the general population.<sup>23,24</sup>

### Early post-operative arrhythmia

The incidence of AF/AT within first 30 days after PEA is not surprising. It is well known that AF is common after cardiac surgery, occurring in 15-45% of patients after surgical revascularization or valve surgery.<sup>25,26</sup> Despite post-operative AF being associated with an increased length of hospital stay and higher rates of complications including mortality,<sup>25,26</sup> the clinical profile of patients with perioperative AT/AF after PEA in our study is similar to patients





**Figure 3** Comparison between patients with permanent arrhythmia and those with sinus rhythm at the end of the follow-up. NYHA, New York Heart Association; LA in PLAX, left atrium in parasternal long-axis view; PASP, pulmonary artery systolic pressure; PEA, pulmonary endarterectomy; SR, sinus rhythm; 6MWT, 6-min walking test.

**Table 3** Mortality

	Univariate analysis			Multivariate Cox regression analysis		
	Dead no (N = 152)	Dead yes (N = 45)	P-value	HR	95% CI	P-value
Prevalent AF/AT	41 (27)	16 (36)	0.30	—	—	—
AF/AT before PEA	9 (6)	8 (18)	0.01	1.9	0.63-5.57	0.26
Permanent arrhythmia at the final follow-up	5 (3)	7 (16)	0.001	2.1	0.87-5.09	0.09
Age < 60 years	66 (43)	20 (44)	0.91	—	—	—
Male gender	91 (60)	32 (71)	0.18	2.27	1.15-4.50	0.02
Arterial hypertension	97 (64)	27 (60)	0.63	—	—	—
NYHA III or IV classes	21 (14)	31 (69)	<0.001	8.56	4.17-17.60	<0.001
6MWT < 350 m	31 (20)	30 (67)	<0.001	3.67	1.74-7.73	<0.001
PASP > 40 mmHg	66 (43)	24 (53)	0.24	—	—	—
PAMP > 50 mmHg	50 (33)	13 (29)	0.61	—	—	—

Values are expressed as n (%).

CI, confidence interval; AF, atrial fibrillation; AT, atrial tachycardia; NYHA, New York Heart Association; PAMP, pulmonary arterial mean pressure; PASP, pulmonary artery systolic pressure; PEA, pulmonary endarterectomy; HR, hazard ratio; 6MWT, 6-min walking test.

without any arrhythmia. Of note, our data show lower incidence of AF/AT in early post-PEA period. This incidence is more likely as result of protocol applied. The data says that arrhythmogenic complications occur usually within several days after surgery.

**Clinical outcome**

The presented data is in line with previous studies reporting that AF/AT in PH patients are associated with functional deterioration.<sup>6,7,9-11,17</sup> Olsson *et al.*<sup>7</sup> identified that the estimated survival rate after the diagnosis of PH was reduced

in patients with permanent AF compared to patients with transient episodes or without arrhythmia. Another study confirmed that supraventricular arrhythmia in patients with idiopathic pulmonary arterial hypertension presage substantial morbidity and mortality.<sup>11</sup> However, our data show that rather than the absence of a stable sinus rhythm, the male gender and a deterioration of functional parameters were stronger predictors of mortality in the multivariate analysis in our study. One of explanations of different observations of our study as compared to previously published data may be due to the fact that most patients treated with PEA in our cohort had excellent prognosis and near-normalization of haemodynamics after surgery.<sup>1,27</sup>

According to our data, a worse clinical outcome is more likely in patients with an onset of AF/AT before PEA than in patients where AF/AT was diagnosed during a long-term follow-up after the surgical procedure. Patients with a known arrhythmia before PEA manifested a lower tolerance to physical activity and manifested a higher mortality rate. We speculate that this finding may correspond with the longer duration of underlining conditions leading to the onset of AF/AT. As mentioned above, arrhythmia itself could participate in atrial electrophysiological and structural remodelling and may influence adverse clinical outcome. Based on our data, the presence of arrhythmia warrants more a cautious indication of PEA in an individual patient. On the other hand, the study did not evaluate the efficacy of AF/AT treatment on morbidity and mortality. Some patients were treated by MAZE as concomitant procedure during PEA. The role of this treatment as well as the role of CA is not known in CTEPH patients.

### Limitations

Our study has several limitations including the use of information from a single centre and its retrospective design. The data were based on standard electrocardiograms and by carefully analysing a patient's history. Because of the lack of other means to do rhythm monitoring, it is likely that some self-terminating, clinically silent AF/AT episodes might have been missed. Regular follow-up procedures were present in the post-PEA follow-up. Before an indication for PEA, arrhythmias were documented more randomly during preoperative work-up or were known from patient's history.

### Conclusions

The study confirmed a significant prevalence of AF/AT in an unselected population of CTEPH patients treated with PEA. An excessive number of new AF/AT was diagnosed during a long-term follow-up after PEA. The existence of AF/AT diagnosis before PEA is associated with a worse clinical outcome. In the overall CTEPH population treated with PEA, a history of any variant of tachycardia and final heart rhythm were not independently associated with mortality.

### Acknowledgements

We would like to thank Valerie Reeves for language correction.

### Funding

This study was supported by research grant from the Ministry of Health, Czech Republic (NV18-02-00027). This paper was published as part of a supplement financially supported by the Cardiovascular Research Program of the Charles University 'Progres Q38'.

**Conflict of interest:** none declared.

### References

- Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;**37**:67-119.
- Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2019;**40**:3453-3455.
- Amsallem M, Guihaire J, Arthur Ataam J, Lamrani L, Boulate D, Mussot S, Fabre D, Taniguchi Y, Haddad F, Sitbon O, Jais X, Humbert M, Simonneau G, Mercier O, Brenot P, Fadel E. Impact of the initiation of balloon pulmonary angioplasty program on referral of patients with chronic thromboembolic pulmonary hypertension to surgery. *J Heart Lung Transplant* 2018;**37**:1102-1110.
- Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. *Circulation* 2014;**130**:508-518.
- Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jais X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevielle P, Mayer E, Simonneau G. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an International Prospective Registry. *Circulation* 2016;**133**:859-871.
- Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;**19**:1845-1855.
- Olsson KM, Nickel NP, Tongers J, Hoeper MM. Atrial flutter and fibrillation in patients with pulmonary hypertension. *Int J Cardiol* 2013;**167**:2300-2305.
- Rottlaender D, Motloch LJ, Schmidt D, Reda S, Larbig R, Wolny M, Dumitrescu D, Rosenkranz S, Erdmann E, Hoppe UC. Clinical impact of atrial fibrillation in patients with pulmonary hypertension. *PLoS One* 2012;**7**:e33902.
- Ruiz-Cano MJ, Gonzalez-Mansilla A, Escibano P, Delgado J, Arribas F, Torres J, Flox A, Riva M, Gomez MA, Saenz C. Clinical implications of supraventricular arrhythmias in patients with severe pulmonary arterial hypertension. *Int J Cardiol* 2011;**146**:105-106.
- Tongers J, Schwerdtfeger B, Klein G, Kempf T, Schaefer A, Knapp J-M, Niehaus M, Korte T, Hoeper MM. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. *Am Heart J* 2007;**153**:127-132.
- Wen L, Sun M-L, An P, Jiang X, Sun K, Zheng L, Liu Q-Q, Wang L, Zhao Q-H, He J, Jing Z-C. Frequency of supraventricular arrhythmias in patients with idiopathic pulmonary arterial hypertension. *Am J Cardiol* 2014;**114**:1420-1425.
- Fingrova Z, Havranek S, Ambroz D, Jansa P, Linhart A. The left atrial substrate plays a significant role in the development of complex atrial tachycardia in patients with precapillary pulmonary hypertension. *BMC Cardiovasc Disord* 2019;**19**:157.
- Daily PO, Dembitsky WP, Peterson KL, Moser KM. Modifications of techniques and early results of pulmonary thromboendarterectomy for chronic pulmonary embolism. *J Thorac Cardiovasc Surg* 1987;**93**:221-233.

14. Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. *Curr Probl Surg* 2000;**37**:165-252.
15. Lindner J, Jansa P, Kunstyr J, Mayer E, Blaha J, Palecek T, Aschermann M, Grus T, Ambroz D, Tosovský J, Vitkova I. Implementation of a new programme for the surgical treatment of CTEPH in the Czech Republic—pulmonary endarterectomy. *Thorac Cardiovasc Surg* 2006;**54**:528-531.
16. Cannillo M, Grosso Marra W, Gili S, D'Ascenzo F, Morello M, Mercante L, Mistretta E, Salera D, Zema D, Bissolino A, Fusaro E, Marra S, Libertucci D, Gaita F. Supraventricular arrhythmias in patients with pulmonary arterial hypertension. *Am J Cardiol* 2015;**116**:1883-1889.
17. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, Reid LM, Tuder RM. Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol* 2004;**43**(12 Suppl S): 25S-32S.
18. Medi C, Kalman JM, Ling L-H, Teh AW, Lee G, Lee G, Spence SJ, Kaye DM, Kistler PM. Atrial electrical and structural remodeling associated with longstanding pulmonary hypertension and right ventricular hypertrophy in humans. *J Cardiovasc Electr* 2012;**23**:614-620.
19. Folino AF, Bobbo F, Schiraldi C, Tona F, Romano S, Buja G, Bellotto F. Ventricular arrhythmias and autonomic profile in patients with primary pulmonary hypertension. *Lung* 2003;**181**:321-328.
20. Schrier RW, Bansal S. Pulmonary hypertension, right ventricular failure, and kidney: different from left ventricular failure? *Clin J Am Soc Nephrol* 2008;**3**:1232-1237.
21. Bortlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;**3**:588-595.
22. D'Alto M, Romeo E, Argiento P, Motoji Y, Corra A, Di Marco GM, Iacono AM, Barracano R, D'Andrea A, Rea G, Sarubbi B, Russo MG, Naeije R. Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. *Chest* 2017;**151**:119-126.
23. Nguyen BL, Fishbein MC, Chen LS, Chen PS, Masroor S. Histopathological substrate for chronic atrial fibrillation in humans. *Heart Rhythm* 2009;**6**:454-460.
24. Chimenti C, Russo MA, Carpi A, Frustaci A. Histological substrate of human atrial fibrillation. *Biomed Pharmacother* 2010;**64**: 177-183.
25. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev* 2013;**1**:CD003611.
26. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT; Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720-1729.
27. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ni Ainle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;**41**:543-603.