Title:

The role of pulmonary artery wedge pressure on the incidence of atrial fibrillation and atrial tachycardias in patients with isolated pre-capillary pulmonary hypertension

Short title:

Atrial fibrillation and pulmonary hypertension

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SUMMARY

Background: Atrial fibrillation and atrial tachycardias (AF / AT) have been reported as a common condition in patients with pulmonary hypertension (PH). As yet, limited data exists about the significance of the borderline post-capillary pressure component on the occurrence of AF / AT in patients with isolated pre-capillary PH.

Methods: We retrospectively studied the prevalence of AF / AT in 333 patients (mean age 61 ± 15 years; 44% males) with pre-capillary idiopathic / familiar pulmonary arterial hypertension, and inoperable chronic thromboembolic pulmonary hypertension. The prevalence of AF / AT was analyzed in different categories of pulmonary artery wedge pressure (PAWP).

Results: In the study population overall, the mean PAWP was 10.5 ± 3 mmHg; median of 11 mmHg, range 2-15 mmHg. AF / AT was diagnosed in 79 patients (24%). The proportion of AF / AT among patients with PAWP below the median (≤11 mmHg) was lower than in subjects with PAWP between 12 and 15 mmHg, 30 (16%) vs. 46 (35%), p = 0.0001. Compared to the patients with PAWP≤11 mmHg, subjects with PAWP between 12 and 15 mmHg were older (65 ± 13 years vs. 58 ± 16), with more prevalent arterial hypertension [100 (70%) vs. 106 (55%)] and diabetes mellitus [50 (35%) vs. 48 (25%)], showed larger size of the left atrium (42 ± 7 vs. 40 ± 6 mm), and higher values of right atrium pressure (12 ± 5 vs. 8 ± 5 mm Hg); $p < 0.05$ in all comparisons.

Conclusion: The prevalence of AF / AT in the group studied increased with the growing post-capillary component.

KEY WORDS: Pulmonary hypertension, Atrial fibrillation, Atrial tachycardia, Atrial flutter, Pulmonary artery wedge pressure

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiological disorder which is defined by the elevation of pulmonary artery mean pressure (PAMP) to above 25 mmHg. Pulmonary artery wedge pressure (PAWP) is crucial in distinguishing between pre-capillary (PAWP ≤15 mmHg) and post-capillary PH (PAWP >15 mmHg). Based on the hemodynamic characteristics, pathological findings, and a similar clinical presentation, PH can be categorized into 5 main groups (Galie *et al.* 2016; Simonneau *et al.* 2004). Despite the recent developments of various treatment strategies, which have improved the hemodynamics, exercise capacity, and the quality of life in patients with PH, the prognosis of PH is generally inauspicious. (Galie *et al.* 2016)

Supraventricular tachycardias (SVTs), including atrial fibrillation and atrial tachycardias (AF / AT), have been reported as a common condition in patients with PH of different aetiologies. The range of cumulative incidence of SVTs varies between 10-36%, including all types of pulmonary arterial hypertension (PAH) (Fingrova *et al.* 2021; Olsson *et al.* 2013; Rottlaender *et al.* 2012; Smith *et al.* 2018; Wen *et al.* 2014), Eisenmenger's syndrome (Cannillo *et al.* 2015), or inoperable chronic thromboembolic PH (CTEPH) (Rottlaender *et al.* 2012; Smith *et al.* 2018; Tongers *et al.* 2007). A high prevalence of AF / AT was also identified in CTEPH patients treated with pulmonary endarterectomy, with a high number of newly diagnosed AF / AT during long-term follow-up after surgery (Fingrova *et al.* 2019).

SVTs in patients with PH frequently lead to clinical deterioration (Fingrova *et al.* 2021; Olsson *et al.* 2013; Rottlaender *et al.* 2012; Smith *et al.* 2018; Tongers *et al.* 2007; Wen *et al.* 2014), and arrhythmia development has also been investigated as a predictor of mortality (Cannillo *et al.* 2015; Olsson *et al.* 2013; Smith *et al.* 2018; Wen *et al.* 2014). Sinus rhythm (SR) restoration appears to improve the clinical outcome at least in patients with idiopathic PAH (IPAH) and inoperable CTEPH (Olsson *et al.* 2013; Wen *et al.* 2014).

It has been also shown that the prevalence of particular types of SVTs can differ according to the aetiology of PH. A high number of AF was reported in patients with post-capillary PH, leading to an overall higher arrhythmia prevalence in this group (Galie *et al.* 2004; Galie *et al.* 2009).

However, only a little is known about the significance of the borderline post-capillary pressure component on the occurrence of AF / AT in patients with pre-capillary PH. In a former work from our centre, it has been demonstrated that even in those patients left-sided substrate could play an important role in the arrhythmogenesis of complex atrial arrhythmia (Fingrova *et al.* 2019).

Therefore, we analysed data from a large single-centre database with the aim of identifying the impact of concrete PAWP values on AF / AT (common atrial flutter including) prevalence. The secondary objective was to describe the differences between patients with early and late onset of arrhythmia in terms of the predisposing factors and hemodynamics.

METHODS

We performed a retrospective analysis of a dedicated registry of consecutive patients who were diagnosed and treated for idiopathic or familiar PAH (IPAH / FPAH) or inoperable CTEPH, at a single centre between 2003 and 2017. The final follow-up was set for December 2018. The study was performed according to the principles of good clinical practice and in compliance with the Declaration of Helsinki. The whole study was approved by the local Ethics committee (Ethics Committee in General University Hospital in Prague, No. 1121/16-S-IV). All patients gave written informed consent agreeing to data collection and analysis for scientific purposes.

Detailed protocol of the study has been described previously (Fingrova *et al.* 2019). In brief, all involved patients underwent a routine baseline work-up, according to contemporary standards (Galie *et al.* 2004; Galie *et al.* 2009; Galie *et al.* 2016), including all indicated non-invasive and invasive methods, and right heart catheterization to confirm and classify PH. The diagnosis of PH required a confirmation of the PAMP ≥25 mmHg by the baseline right heart catheterization.

Patients with combined post- and pre-capillary PH [defined as PAMP ≥25 mmHg and simultaneous elevation of PAWP >15 mmHg and pulmonary vascular resistance (PVR) >3 Wood Units (WU)] or with

isolated post-capillary PH (defined as PAMP ≥ 25 mm Hg and PAWP >15 mm Hg, but having a PVR ≤3 WU) were excluded from the study (Galie *et al.* 2016).

All patients were evaluated regularly at 1 to 6 monthly intervals, or whenever clinically indicated. For further evaluation, the time of the PH diagnosis was set as the beginning of the study. Routine examinations and standard 12-lead ECGs were obtained as part of the regular follow-up program. A 24-hour, 48-hour or longer ECG monitoring was performed when indicated by a clinician based mainly on paroxysmal arrhythmia suspicion. The period of monitoring was dictated by the clinical situation. A prevalent AF or AT was defined as evidence of the presence of a documented arrhythmia on the standard 12-lead ECGs and / or ECG monitors in a patient's personal history, or at the time of diagnosis or during a follow-up. The diagnosis of an AF / AT was confirmed by an experienced cardiologist in each case. For the purpose of the study, common atrial flutter was included into the AT group. All types of AF (paroxysmal, persistent, permanent) were included.

Statistical analysis

The continuous variables were expressed as means with standard deviations. After testing for normality (Shapiro-Wilk's test) the data was compared using the 2-tailed t-test for independent samples or advanced ANOVA tests to compare more than two means. The categorical variables were expressed as percentages and compared by the $\chi 2$–test or the Kruskal-Wallis test when appropriate. A P-value of <0.05 was considered as significant. All analyses were performed using the STATISTICA vers.12 software (Statsoft, Inc., Tulsa, USA).

RESULTS

A total of 333 patients (mean age 61 ± 15 years; 44% males) were included in the analysis. AF / AT was diagnosed in 79 patients (24%). The baseline clinical and demographical characteristics of the total population and subgroups are shown in Table 1. In summary, patients who developed arrhythmia were of a slightly higher age, had higher prevalence of arterial hypertension and diabetes mellitus, had a reduced 6MWT distance, higher left atrium (LA) diameter, slightly bigger end-diastolic left ventricular diameter, and a more elevated right atrial pressure (RAP).

In the overall study population, the mean PAWP was 10.5 ± 3 mmHg; range 2-15 mmHg; mode of 11 mmHg; median of 11 mmHg; interquartile range (IQR) of 8-13 mmHg. Patients with manifest AF / AT had higher values of PAWP than those subjects without arrhythmia (12 ± 3 vs 10 ± 3 mmHg; p = 0.001). The proportion of patients with and without AF / AT in relation to their PAWP values is shown in the histogram in Figure 1.

The distribution of the prevalence of AF / AT in different intervals of PAWP is depicted in Figure 2. Those patients in the two lower PAWP groups (≤11 mmHg) had significantly reduced occurrence of arrhythmia, then patients in the upper two subgroups (30 (16%) vs. 46 (35%); p = 0.0001).

As shown in Table 2, patients with PAWP ≤11 mmHg were younger, with less prevalent arterial hypertension and diabetes mellitus, a lower size of LA, and lower values of RAP than those with PAWP between 12 and 15 mmHg.

Of all the patients with arrhythmia, 48 (61%) had no history of AF / AT at the time of diagnosis of PH. When compared to patients with a history of arrhythmia prior to the diagnosis of PH, those patients with arrhythmia manifestation during the follow-up were younger at the time of PH diagnosis (64 ± 10 vs. 72 ± 7 years; p = 0.0004). There were no statistically significant differences in the remaining variables. The spectrum of arrhythmias is shown in Table 3.

When only the patients with arrhythmia onset after the diagnosis of PH are analysed, the annual incidence of AF / AT is between 0.5 and 11 %, as shown in Figure 3.

DISCUSSION

SVTs are usually reported as common comorbidities in patients with PH, and the total prevalence of AF / AT was high in our registry as well (almost 24%). The main finding of our study is that in patients with invasively confirmed isolated pre-capillary PH the prevalence of AF / AT is very likely increasing with the growing post-capillary component. The group of patients with near to elevated PAWP (e.g. 11-

15 mmHg) had a significantly higher occurrence of arrhythmia than patients with lower PAWP (≤11 mmHg).

An exact arrhythmogenic substrate for complex atrial arrhythmias, including AF or AT in PH patients, remains unclear. There is emerging evidence indicating a significant role of right-sided substrate for complex atrial arrhythmia, based on the fact that PH leads to an increased afterload of the right ventricle (RV), resulting in RV hypertrophy and dilatation, as well as upstream enlargement of the right atrium (RA) (Pietra *et al.* 2004). Long-standing PH is frequently associated with decreased conduction and tissue voltage in some cases, with regions of "electrical silence" occurring in both the RA and RV (Medi *et al.* 2012). In addition, modulations of the autonomic system may trigger and perpetuate related arrhythmia (Folino *et al.* 2003; Schrier and Bansal 2008).

All patients in our study have been diagnosed as PH. Therefore, the role of right-sided proarrhythmogenic substrate is probable, which is supported by supranormal dimensions of RA and RAP elevation that could be found in our cohort. These findings also give us evidence about severity of PH and for example RA enlargement was already proven as an independent predictor of adverse outcome in PH patients (Cioffi *et al.* 2007). But it is necessary to mention, that even in an isolated pre-capillary PH could also the left-sided substrate play a particular role in the arrhythmogenesis of complex atrial arrhythmia. (Fingrova *et al.* 2019).

However, when a post-capillary component is present, the mechanisms of arrhythmia have been suggested as being more similar to a proarrhythmogenic substrate in left heart disease (Rottlaender *et al.* 2012). Elevated PAWP and end-diastolic left ventricular pressure represent a well-known mechanism leading to LA structural remodelling with a proarrhythmogenic effect. Left atrial remodelling, particularly LA dilatation, is a well-documented risk factor for the development of AF (Ausma *et al.* 1997; Spach and Josephson 1994).

According to our data, left atrium dimensions are abnormal in patients with nearly elevated PAWP and significantly bigger compared to patients with lower PAWP. By other words, there is a distinct echo finding of bi-atrial enlargement, that indicates possible combined left and right atrial substrate in this

group of patients. We believe that the increased prevalence of AF / AT in patients with higher values of PAWP is caused by simultaneous presence and additive effect of the LA substrate.

One factor which possibly explains the involvement of the left heart in the pathogenesis of AF / AT in PH patients may be due to the definition of pre-capillary PH itself. PH diagnosis is based uniquely on the resting invasive pulmonary pressure measurements. In addition, the PAWP limit is set relatively high above the limits of the presumed true physiological values. This may lead to a diagnosis of purely pre-capillary PH in a group of patients, in whom the PH is actually of the combined type (combined post-capillary and pre-capillary PH). It has been repeatedly shown (Borlaug *et al.* 2010; D'Alto *et al.* 2017) that a fluid challenge or exercise can unmask the post-capillary component in a large number of patients.

This hypothesis could be supported by the fact that in our study the parameters of age, diabetes mellitus, and arterial hypertension – frequent risk factors for left heart involvement with diastolic dysfunction – were associated with the development of arrhythmias. As suggested by Opitz (Opitz *et al.* 2016), these cases represent a borderline category of patients with “atypical IPAH” in whom the left heart involvement remains silent under resting conditions. Finally, in borderline PAWP cases the measurement method of PAWP may lead to an underestimation (using a digitized mean value) or overestimation (using end-expiratory values) of PAWP (Rosenkranz *et al.* 2016). Our data supports the hypothesis that truly elevated LA pressure could participate in the development of LA substrate and its arrhythmogenicity.

On the other hand, the high burden of paroxysmal, persistent, or permanent arrhythmia may be a cause of the LA remodelling itself (Ausma *et al.* 1997; Spach and Josephson 1994). Decreased atrial contraction, atrio-ventricular asynchrony, and a rapid heart rate with a reduction of diastolic filling are potential factors of left atrial remodelling. Moreover, it has been found that AF itself causes electrophysiological changes of the atrial myocardium which explains the progressive character of the arrhythmia (Wijffels *et al.* 1995; Aldhoon *et al.* 2010*).* Since in our cohort the LA diameter did not differ significantly according to the type of arrhythmia and was not dependent on the time of onset of AF / AT, the impact of pure arrhythmia’s burden on atrial remodelling does not lie in simply increasing the PAWP in our study. However, aging and external stressors such as arterial hypertension or diabetes were associated with the presence of AF / AT. All these conditions are also well known factors influencing

atrial electrophysiological and structural remodelling of the LA, which can be associated with the initiation of AF in the general population (Chimenti *et al.* 2010; Nguyen *et al.* 2009) as well as in the PH population (Medi *et al.* 2012). These facts are closely in accordance with our data and suggest the existence of some left-sided proarrhythmogenic substrate among patients with arrhythmia and pre-capillary PH.

As already mentioned, the mean RAP in studied population was elevated generally. Nevertheless, there was a difference in mean RAP values between groups with low and near to elevated PAWP - patients with higher values of PAWP had also slightly higher RAP. In general, this is the most likely caused by a backward propagation of elevated PAWP through pulmonary circulation to the right ventricle and atrium. We can see that this difference in RAP between our groups did not affect the RA sizes. We speculate, that structural changes of RA are so pronounced in studied population of PH patients, that this small further RAP elevation simply could not affect the RA architecture.

Nearly one third of patients in the group with AF / AT were diagnosed with arrhythmia during the follow-up. Those patients were significantly younger than patients with a history of arrhythmia prior to the diagnosis of PH. This can be further proof of the pro-arrhythmogenic effect of complex PH-related changes to the heart's structure, leading to arrhythmia onset in a younger age. The annual incidence of AF / AT during follow-up was around 4.5% of patients a year. However, the fluctuation of the annual incidence is considerable, being very probably caused by small number error, which is certainly more pronounced in the later years of follow-up, when the total number of patients at risk of arrhythmia is low. Nevertheless, we must keep in mind that for some patients the time of their diagnosis of PH was the real beginning of their regular follow-ups by a cardiologist. This could lead to the identification of arrhythmias (mainly paroxysmal) which had already been present for a longer time but remained silent.

Limitations

There were several limitations of our study, of which the most limiting is its retrospective and single-centre design. Despite a meticulous and systematic follow-up, some arrhythmias may have been missed. Our data was mainly based on standard electrocardiograms and carefully gathered patient histories. However, due to a lack of other routinely used means of rhythm monitoring, it is likely that

some self-terminating, clinically silent AF episodes may have been missed. Moreover, our hemodynamic investigation was based on a standard resting right heart catheterization, which is unable to detect cases of atypical forms of PH in which the PAWP may rise steeply during exertion or after a fluid challenge, unmasking the post-capillary component.

CONCLUSION

The overall prevalence of AF / AT in the studied group of patients with isolated pre-capillary PH (IPAH / FPAH or inoperable CTEPH) was almost 24% (79 of 333 patients). The prevalence of AF / AT increased with a growing post-capillary component. Patients with near to elevated PAWP had significantly higher occurrences of arrhythmia. Those patients were older, with more prevalent arterial hypertension and diabetes mellitus, and larger size of LA, which points to the probable coexistence of left-sided proarrhythmogenic substrate even in patients with pre-capillary PH. Nearly one third of patients were diagnosed with AF / AT later during follow-up. These patients were significantly younger compared to those patients with a history of arrhythmia prior to the diagnosis of PH. This could be further proof of the pro-arrhythmogenic effect of complex PH-related changes in the heart's structure, leading to arrhythmia onset at a younger age.

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TABLES

Table 1: Baseline clinical and demographical characteristics.

	Total n = 333	**ARRHYTHMIA NO n = 254**	**ARRHYTHMIA YES n = 79**	**p value**
Age at diagnosis of PH (years)	61 ± 15	58 ± 16	69 ± 9	<0.0001
Male gender	145 (44%)	109 (43%)	36 (46%)	NS
Arterial hypertension	206 (62%)	140 (55%)	66 (84%)	0.0001
Diabetes mellitus	98 (29%)	60 (24%)	38 (48%)	0.0001
IPAH / FPAH	214 (64%)	165 (65%)	49 (62%)	NS
Inoperable CTEPH	119 (36%)	89 (35%)	30 (38%)	NS
Specific therapy	235 (71%)	179 (70%)	56 (71%)	NS
NYHA (class)				
- **I**	4 (1%)	3 (1%)	1 (1%)	NS
- **II**	62 (19%)	51 (20%)	11 (14%)	NS
- **III**	219 (66%)	162 (64%)	57 (72%)	NS
- **IV**	48 (14%)	38 (15%)	10 (13%)	NS
6MWT (meters)	326 ± 129	334 ± 131	298 ± 120	0.036
LA in PLAX (mm)	41 ± 7	39 ± 6	45 ± 7	<0.0001
LV EF (%)	63 ± 8	63 ± 8	62 ± 8	NS
LVEDD in PLAX (mm)	45 ± 8	44 ± 10	48 ± 7	0.001
RA in A4C (mm)	48 ± 10	47 ± 10	49 ± 11	NS
RV in A4C (mm)	45 ± 10	45 ± 10	44 ± 9	NS
TAPSE (mm)	18 ± 5	19 ± 5	17 ± 5	NS
PAMP (mmHg)	47 ± 13	48 ± 14	45 ± 12	NS
RAP (mmHg)	10 ± 5	9 ± 5	11 ± 5	0.033
Follow-up duration (years)	4.1 ± 2.7	4.1 ± 2.8	4.1 ± 2.5	NS

Legend: Values are expressed as mean ± SD or n (%). NS – non-significant; PH – pulmonary hypertension; IPAH / FPAH – idiopathic / familiar pulmonary arterial hypertension; CTEPH – chronic thromboembolic pulmonary hypertension; 6MWT – six minute walking test; LA – left atrium; LV – left ventricle; EF – ejection fraction; LVEDD – left ventricular end-diastolic diameter; RA – right atrium; RV – right ventricle; TAPSE – tricuspid annular plane systolic excursion; PAMP – pulmonary arterial mean pressure; RAP – right atrial pressure; PLAX – parasternal long axis view; A4C – apical four chamber view.

Table 2: Clinical parameters in patients with low and higher pulmonary artery wedge pressure.

Category (PAWP)	≤11 mmHg N = 191	12 – 15 mmHg N = 142	p value
Age at diagnosis of PH (years)	58 ± 16	65 ± 13	0.0002
Male gender	85 (45%)	60 (42%)	NS
Art. hypertension	106 (55%)	100 (70%)	0.005
Diabetes mellitus	48 (25%)	50 (35%)	0.047
IPAH / FPAH	129 (68%)	85 (60%)	NS
CTEPH	62 (32%)	57 (40%)	NS
Specific therapy	135 (71%)	100 (70%)	NS
NYHA (class)			
- **I**	2 (1%)	2 (1%)	NS
- **II**	36 (19%)	26 (18%)	NS
- **III**	130 (68%)	89 (63%)	NS
- **IV**	23 (12%)	25 (18%)	NS
6MWT (meters)	329 ± 129	320 ± 130	NS
LA in PLAX (mm)	40 ± 6	42 ± 7	0.03
LV EF (%)	63 ± 8	63 ± 8	NS
LVEDD in PLAX (mm)	44 ± 7	46 ± 8	NS
RA in A4C (mm)	48 ± 10	47 ± 10	NS
RV in A4C (mm)	46 ± 9	43 ± 10	NS
TAPSE (mm)	18 ± 5	19 ± 6	NS
PAMP (mmHg)	47 ± 13	48 ± 13	NS
RAP (mmHg)	8 ± 5	12 ± 5	0.0001
Follow-up duration (years)	4.3 ± 2.9	3.9 ± 2.4	NS

Legend: Values are expressed as mean ± SD or n (%). NS – non-significant; PAWP – pulmonary artery wedge pressure; PH – pulmonary hypertension; IPAH / FPAH – idiopathic / familiar pulmonary arterial hypertension; CTEPH – chronic thromboembolic pulmonary hypertension; 6MWT – six minute

walking test; LA – left atrium; LV – left ventricle; EF – ejection fraction; LVEDD – left ventricular end-diastolic diameter; RA – right atrium; RV – right ventricle; TAPSE – tricuspid annular plane systolic excursion; PAMP – pulmonary arterial mean pressure; RAP – right atrial pressure; PLAX – parasternal long axis view; A4C – apical four chamber view.

Table 3: Spectrum of arrhythmia in relation to the time of its diagnosis and the diagnosis of pulmonary hypertension.

Diagnosis of arrhythmia	Total number of diagnosed patients N = 79	Prior to the diagnosis of PH N = 31	At the diagnosis of PH N = 26	After the diagnosis of PH N = 22	p value
Atrial tachycardia	16	8 (26%)	4 (15%)	4 (18%)	-
Atrial fibrillation	63	23 (74%)	22 (85%)	18 (82%)	-
- **Paroxysmal**	21	6 (19%)	9 (35%)	6 (27%)	-
- **Persistent**	21	11 (35%)	5 (19%)	5 (23%)	-
- **Permanent**	21	6 (19%)	8 (31%)	7 (32%)	-

Legend: Values are expressed as n (%). PH – pulmonary hypertension.

FIGURE LEGENDS:

Figure 1: Proportions of pulmonary artery wedge pressures in patients with and without atrial fibrillation or atrial tachycardia.

Legend: PAWP – pulmonary artery wedge pressure.

Figure 2: Proportion of patients with and without atrial fibrillation or atrial tachycardia according to the values of pulmonary artery wedge pressure.

Legend: PAWP – pulmonary artery wedge pressure.

Figure 3: Annual incidence of arrhythmia during follow-up.

Legend: AF / AT – atrial fibrillation / atrial tachycardia.

FIGURES

Figure 1

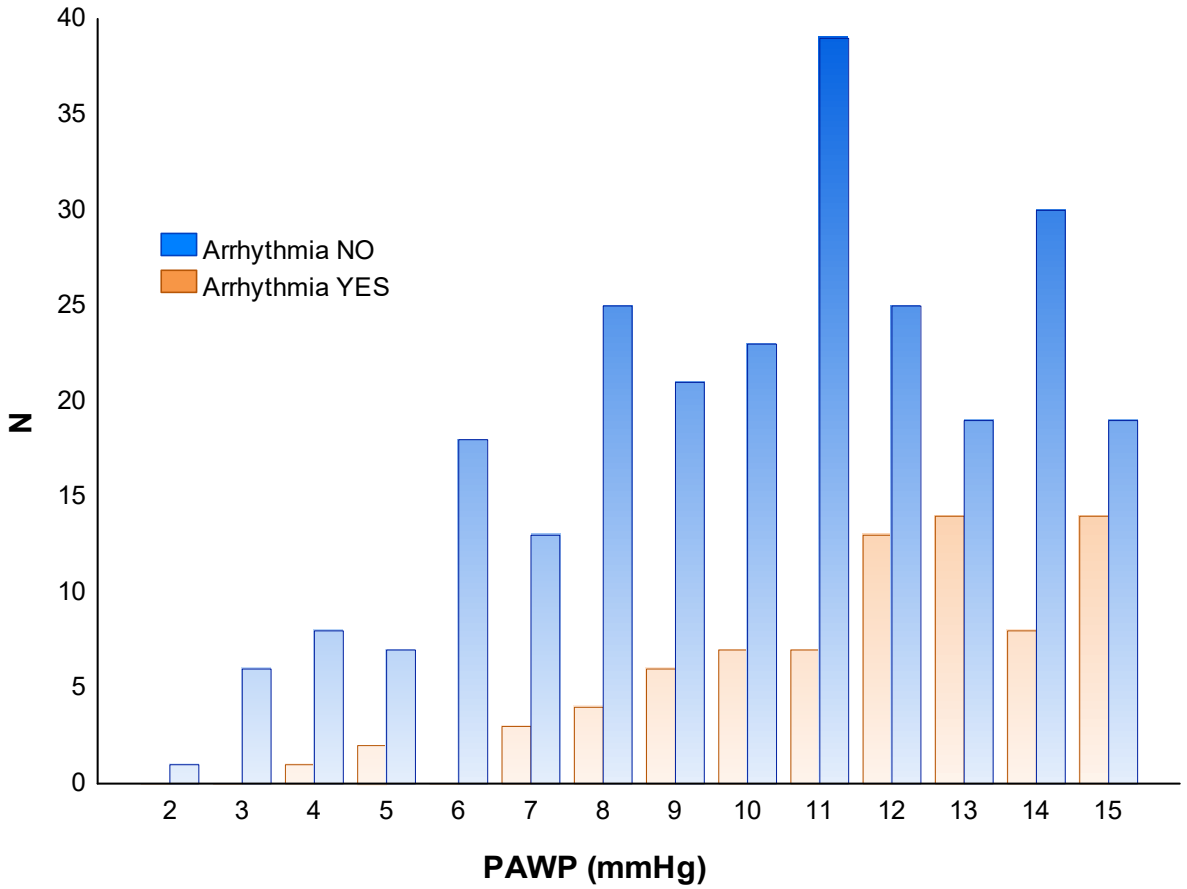


Figure 2

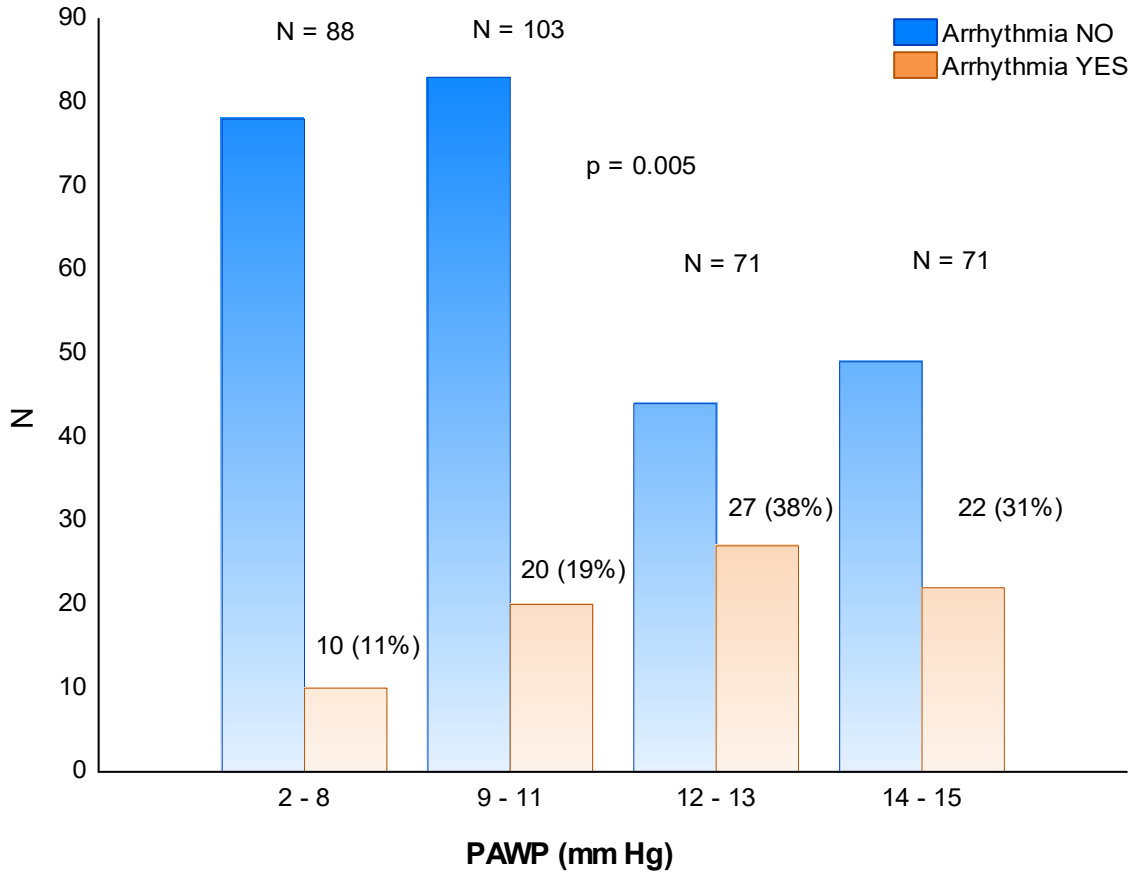
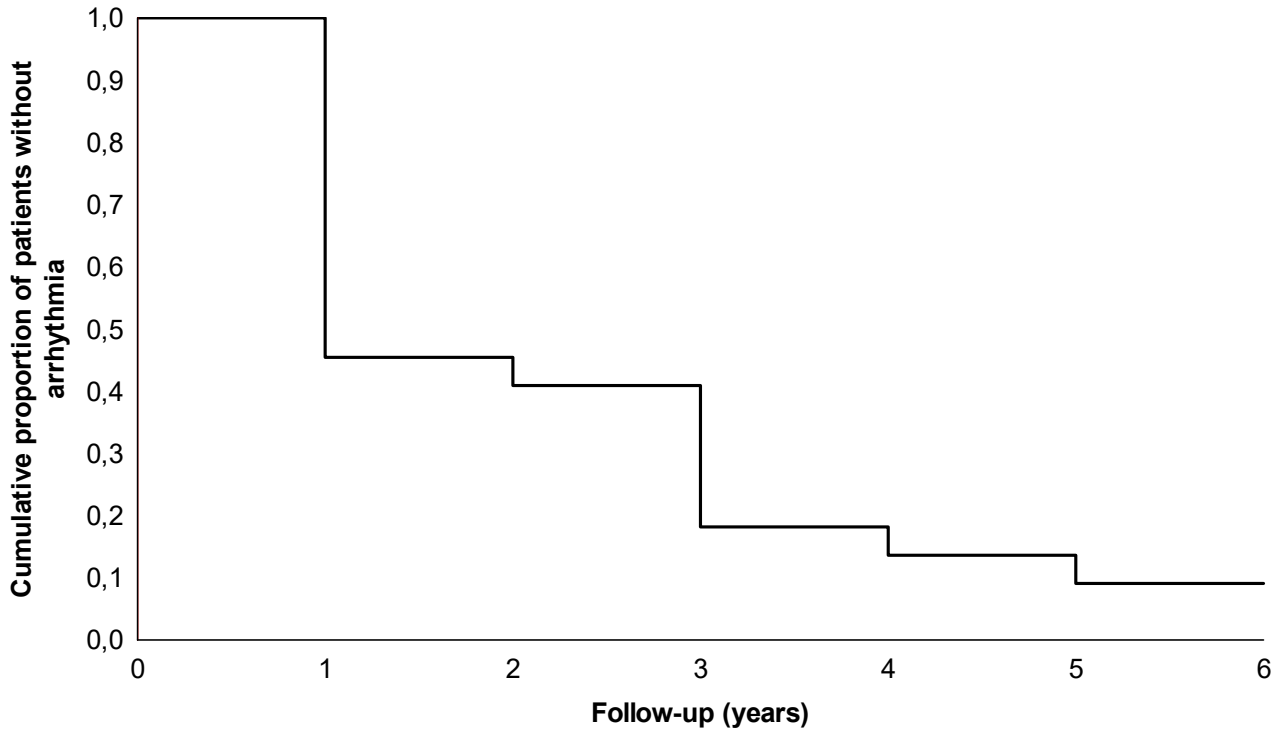

Arrhythmia NO
Arrhythmia YES
N = 88
N = 103
p = 0.005
N = 71
N = 71
10 (11%)
20 (19%)
27 (38%)
22 (31%)
N
0
10
20
30
40
50
60
70
80
90
2 - 8
9 - 11
12 - 13
14 - 15
PAWP (mm Hg)

Figure 3



Patients at risk:	231	183	127	85	42	9
Incidence of AF / AT:	12 (5%)	1 (0.5%)	5 (4%)	1 (1%)	2 (5%)	1 (11%)