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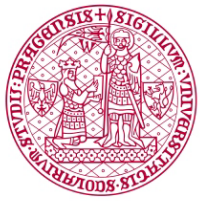

CHARLES UNIVERSITY
First Faculty of Medicine

MUDr. Milan Dusík

Arrhythmias in Pulmonary Hypertension

Poruchy srdečního rytmu u plicní hypertenze

Dissertation Thesis

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Prague, 2024

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Abbreviations

AF	atrial fibrillation
AFL	typical atrial flutter
AT	atrial tachycardia
AVNRT	AV nodal reentrant tachycardia
AVRT	atrioventricular reentrant tachycardia
BNP	B-type natriuretic peptide
Bpm	beats per minute
CO	cardiac output
CI	cardiac index
CTEPH	chronic thromboembolic pulmonary hypertension
DCCV	direct current cardioversion
ECG	electrocardiography
ESC	European Society of Cardiology
FAC	fractional area change
LA	left atrium
mPAP, **PAMP**	mean pulmonary arterial pressure
PAH	pulmonary arterial hypertension
PAWP	pulmonary arterial wedge pressure
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RA	right atrium
RHC	right heart catheterization
SVT	supraventricular arrhythmia
TAPSE	tricuspid annular plane systolic excursion

Acknowledgement

After finishing at the First Faculty of Medicine I decided to focus on cardiology, and I was looking for a place to gain both clinical and scientific skills. Fortunately, I found the opportunity to work at the 2nd Department of Medicine of the Charles University and General University Hospital in Prague. It has been almost 7 years since then and I appreciate every single day. The unique atmosphere makes it the right place to learn, improve, and grow. For which, I would like to thank to professor Linhart and professor Bělohlávek. I am also grateful to all my colleagues with whom I have had the opportunity to work, as they helped me to move further forward.

I would also like to express my thanks to Professor Jansa. He was the first who gave me the insight in pulmonary hypertension and who sparked my curiosity in the possible ways to improve the prognosis, or at least the quality of life, of those severely ill patients. The first months after graduation spent under his leadership in the Centre for Pulmonary Hypertension will always remain in my memory.

I feel very lucky in choosing my supervising tutor as I believe that none of my work would be possible without professor Havránek. He taught me the basic principles of scientific work and research, and helped me to understand the sometimes confusing world of statistics. He was the one who brought me to arrhythmology and showed me its' fascinating, complicated, but always strictly logical rules. Above all, he has always been extremely friendly, helpful, and kind and acted with calmness and understanding. For all of this, I would like to express my immense gratitude to him.

Last but not least, I would like to thank to my whole family, especially my wife Denisa, who has patiently supported me throughout my study. From the very beginning, she has often been in the role of the very first reviewer of my work. Her apt remarks and comments have helped me many times to improve and evolve my projects, but also kept my feet on the ground in case I was unduly enthusiastic. Finally, I want to mention both of my children, who acted as the strongest motivation for finishing this work.

Abstract

Pulmonary hypertension (PH) is defined by the elevation of the mean pulmonary artery pressure above 20 mmHg. PH affects about 1% of population. Based on the similar pathophysiological mechanisms, clinical and hemodynamic characteristics, and therapeutic possibilities, PH is classified into 5 groups. Right heart catheterization is a crucial assessment to establish the diagnosis. Supraventricular tachycardias (SVTs), including atrial fibrillation (AF) and other atrial tachycardias (AT), are frequently found in patients with PH with a reported cumulative incidence of 10-36 %. The presence of an SVT in a PH patient leads to further deterioration and worsens the prognosis. This thesis is based on four distinct analyses focused on the SVTs in PH.

The first analysis described the arrhythmias in patients with chronic thromboembolic pulmonary hypertension. The prevalence of AF/AT reached 29% and their presence was associated with reduced functional capacity. Despite the improved hemodynamics, the incidence of arrhythmias rose significantly after the pulmonary endarterectomy.

The second analysis retrospectively studied the SVT prevalence and its association with PAWP values in patients with pre-capillary PH. Patients with PAWP above 11mmHg had higher arrhythmia prevalence, possibly because of the involvement of the left-sided substrate.

The third analysis tested the acute effect of arrhythmia termination on the hemodynamic status. The sinus rhythm restoration led to only slight changes in hemodynamics, irrespective of the PH presence. Cardiac output rose significantly after the AF termination. The termination of an organized AT did not have an impact on the cardiac output value.

The fourth analysis compared the limited and extended approach to catheter ablation of SVTs in PH patients. There was not a significant difference in arrhythmia recurrence rate between the groups during the follow-up. Despite right atrial enlargement, the right-sided substrate was rare.

Further research is needed to gain deeper knowledge about the mechanisms of heart rhythm disorders in pulmonary hypertension to establish the best possible ways of their management.
Key words: Pulmonary hypertension, supraventricular arrhythmia, catheter ablation

Abstrakt v českém jazyce

Plicní hypertenze (PH) je definována zvýšením středního tlaku v plicnici nad 20 mmHg a postihuje asi 1 % celosvětové populace. Běžně se PH dělí na 5 skupin s ohledem na rozdílnou patofyziologii, klinické a hemodynamické charakteristiky a možnosti terapie. Klíčovým vyšetřením v rámci diagnostiky PH je pravostranná srdeční katetrizace. Supraventrikulární arytmie (SVT) včetně fibrilace síní (AF) a jiných síňových tachykardií (AT) jsou u pacientů s PH časté. Jejich kumulativní incidence se udává v rozmezí 10–36 %. Přítomnost SVT zhoršuje prognózu pacientů s PH a vede k jejich klinickému zhoršení. Tato disertace je založena na výsledcích čtyř prací zaměřených na téma SVT u plicní hypertenze.

První studie se zabývala analýzou výskytu arytmií u pacientů s chronickou tromboembolickou plicní hypertenzí. Celková prevalence SVT dosáhla 29 % a přítomnost arytmie vedla ke zhoršení funkční kapacity nemocných. Navzdory zlepšení hemodynamických parametrů po provedení endarterektomie plicnice incidence SVT po operaci významně narostla.

Druhá práce se zaměřila na souvislost mezi hodnotou tlaku v zaklínění (PAWP) a výskytem SVT u prekapilární PH. U pacientů s PAWP nad 11 mmHg byla prevalence arytmií významně vyšší. Možným vysvětlením je současný výskyt arytmogenního substrátu v levé síni.

V rámci třetího projektu jsme zkoumali efekt terminace arytmie na hemodynamický stav. Obnovení sinusového rytmu vedlo pouze k minimálním změnám hemodynamiky jak u pacientů s PH, tak i u dalších skupin nemocných. Srdeční výdej vzrostl významně jen po ukončení fibrilace síní. Ukončení organizované AT nemělo na hodnotu srdečního výdeje vliv.

Čtvrtá analýza porovnávala efekt limitovaného (cíleného) a extenzivního provedení katetrizační ablace SVT u nemocných s PH. V průběhu sledování nebyl zaznamenán významný rozdíl v četnosti recidivy arytmií. Přes významnou dilataci pravé síně byl pravostranný arytmogenní substrát u těchto nemocných nalezen jen zřídka.

K objasnění komplexních patofyziologických mechanismů vedoucích k výskytu poruch srdečního rytmu u PH budou potřebné ještě další projekty.

Klíčová slova: plicní hypertenze, supraventrikulární arytmie, katetrizační ablace

1. Introduction

The term "pulmonary hypertension" (PH) is commonly used to describe the presence of an elevated pulmonary arterial pressure. Therefore, PH is more of a hemodynamic state than a concrete diagnosis and it can be caused by a broad variety of pathophysiological processes. (Hoeper M.M. *et al.*, 2017) Irrespective of the concrete etiology, the worldwide prevalence of PH is estimated to be around 1%, which means that it is a common condition that is encountered in daily cardiological routine. (Hoeper M.M. *et al.*, 2016) Moreover, PH is generally associated with increased morbidity and mortality. Heart rhythm disorders, especially supraventricular arrhythmias (SVTs), represent common co-morbidity of patients with PH. In those patients, SVTs are often connected with further clinical deterioration and sinus rhythm (SR) restoration can relieve the patient's symptoms. (Daliento L. *et al.*, 1998; Ruiz-Cano M.J. *et al.*, 2011; Tongers J. *et al.*, 2007; Wen L. *et al.*, 2014). However, the concrete arrhythmogenic mechanisms in PH patients still remain unclear. Despite the high prevalence and clinical significance, the optimal treatment strategy for heart rhythm disorders in PH patients has not yet been established due to the lack of robust prospective data. (Galie N. *et al.*, 2016)

Pulmonary circulation has been at the center of interest since the founding of the 2nd Department of Medicine (Department of Cardiovascular Medicine, General University Hospital in Prague, 1st Faculty of Medicine, Charles University), and this resulted in the foundation of the first "Centre for Pulmonary Hypertension" in the Czech Republic in 1998, under the leadership of Professor Pavel Jansa. Nowadays, this center is one of the three specialized pulmonary hypertension centers in the Czech Republic, since 2017 it is also listed among the European Expert Centers focused on PH as part of the European Reference Network. As already stated above, arrhythmias are common among PH patients and, therefore, their pathophysiology, epidemiology, and management are continuously and thoroughly studied by the arrhythmogenic group at the 2nd Department of Medicine, currently lead by the Professor Štěpán Havránek.

2. Pulmonary hypertension

2.1 Pulmonary hypertension definition

PH is a pathophysiological disorder characterized by abnormally high pressures in the pulmonary artery. The first World Symposium on Pulmonary Hypertension in 1973 defined PH as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg measured at rest by right heart catheterization. This limit was set relatively high, mainly because of the former focus on pulmonary arterial hypertension (PAH), which is usually characterized by a more significantly increased mPAP. (Gelzinis T.A., 2022) At the 6th World Symposium on Pulmonary Hypertension in 2018, it was proposed to reconsider the hemodynamic definition of PH. (Simonneau G. *et al.*, 2019) This was based on a study conducted by Austrian authors which measured pulmonary arterial pressures in healthy individuals. The reported mPAP at rest was 14.0 ± 3 mmHg, with 20 mmHg being the upper limit of normal. These values were independent of age, sex, and ethnicity. (Kovacs G. *et al.*, 2009) On top of which, a different study focused on patients with systemic sclerosis concluded that patients with an mPAP between 21 and 24 mmHg had higher mortality and risk of disease progression, and were similarly symptomatic as patients with an mPAP over 25 mmHg. (Bae S. *et al.*, 2012; Valerio C.J. *et al.*, 2013) As a result, the PH definition was modified and in the recently released European Society of Cardiology (ESC) guidelines, the PH is defined by an mPAP >20 mmHg measured at rest by right heart catheterization. (Humbert M. *et al.*, 2022)

2.2 Pulmonary hypertension classifications

2.2.1 Hemodynamic classification

According to the latest ESC guidelines, several different types of PH can be defined by the concrete hemodynamical finding. (**Table 1**) As already stated, the mPAP value is crucial to diagnose the PH. Pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR, calculated by the formula: PVR = (mPAP – PAWP)/CO[1]) are then used to distinguish between pre-capillary and post-capillary. (Humbert M. *et al.*, 2022)

[1] CO – Cardiac output

Table 1. Hemodynamic definitions of pulmonary hypertension:

Pre-capillary PH	mPAP >20mmHg PAWP ≤15mmHg PVR >2WU
Isolated post-capillary PH	mPAP >20mmHg PAWP >15mmHg PVR ≤2WU
Combined post-capillary PH	mPAP >20mmHg PAWP >15mmHg PVR >2WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Adapted from the ESC guidelines 2022 (Humbert M. et al., 2022).

Abbreviations: CO – cardiac output; mPAP – mean pulmonary arterial pressure; PAWP – pulmonary arterial wedge pressure; PH – pulmonary hypertension; PVR – pulmonary vascular resistance.

2.2.2 Clinical classification of PH

The clinical classification was proposed by the World Health Organization to categorize PH into groups based on similar pathophysiological mechanisms, clinical and hemodynamic characteristics, and therapeutic possibilities. This classification is widely used in everyday practice. The latest update was published in the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (**Table 2**). Group 1 comprises PAH characterized by pre-capillary PH with elevated PVR, which usually leads to a progressive right ventricle failure. Group 2 is dedicated to PH as a consequence of left-sided heart disease (e.g., heart failure or valvular heart disease). Hemodynamically, this group is characterized by an elevated PAWP, i.e., PH is post-capillary or at least combined. PH due to chronic lung disease and/or hypoxia is labeled as group 3. It is typically pre-capillary and mild. (Humbert M. *et al.*, 2022) The most common cause is a chronic obstructive pulmonary disease, but it can also be caused by interstitial lung disease or sleep apnea. (Mandras S.A. *et al.*, 2020) Chronic thromboembolic PH (CTEPH, group 4) is usually a result of prior pulmonary embolism. It is characterized by the obstruction and remodeling of the pulmonary vessels leading to a pre-capillary PH. PH with unclear or multifactorial mechanisms is then encompassed in group 5. (Humbert M. *et al.*, 2022)

2.3 Pulmonary hypertension epidemiology

The estimated overall prevalence of PH is about 1% of global population and it is still growing. PH associated with the left heart disease (group 2) is the most common and it can typically be found in older patients. It has been proven that PH is present in at least 50% of patients with heart failure with preserved ejection fraction. The second most common is PH due to lung disease (group 3). (Hoeper M.M. *et al.*, 2016) PAH itself is a rare disease with a prevalence of 48 – 55 cases per million adults. (Leber L. *et al.*, 2021) According to current literature, CTEPH develops in 0.1% to 11.8% patients after an acute symptomatic pulmonary embolism. (Humbert M. *et al.*, 2022) Based on the recent data, the estimated prevalence of CTEPH is 26 – 38 cases per million adults. (Leber L. *et al.*, 2021)

Table 2. Clinical classification of pulmonary hypertension:

GROUP 1 – Pulmonary arterial hypertension (PAH) 1.1 Idiopathic: 1.1.1 Non-responders at vasoreactivity testing 1.1.2 Acute responders at vasoreactivity testing 1.2 Heritable 1.3 Associated with drugs and toxins 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
GROUP 2 – PH associated with left heart disease 2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fraction 2.2 Valvular heart disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 – PH associated with lung diseases and/or hypoxia 3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed restrictive/obstructive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease (e.g., high altitude) 3.6 Developmental lung disorders
GROUP 4 – PH associated with pulmonary artery obstructions 4.1 Chronic thromboembolic PH (CTEPH) 4.2 Other pulmonary artery obstructions
GROUP 5 – PH with unclear and/or multifactorial mechanisms 5.1 Hematological disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Chronic renal failure with or without hemodialysis 5.5 Pulmonary tumor thrombotic microangiopathy 5.6 Fibrosing mediastinitis

Adapted from the ESC guidelines 2022(Humbert M. et al., 2022).

Abbreviations: PH – pulmonary hypertension

2.4 Pulmonary hypertension diagnosis

2.4.1 Clinical presentation

The main symptoms of PH are progressive exercise dyspnea, fatigue, exhaustion, bendopnea, syncope and, in later phases, also signs of a right heart failure (lower extremities oedemas, ascites, increased venous pressure, etc.). Those unspecific symptoms and signs often lead to a late diagnosis of PH and delayed initiation of the treatment. (Oldroyd S.H. *et al.*, 2023)

2.4.2 Auxiliary assessments

PH patients can present with a normal electrocardiogram. However, typical electrocardiographic findings like P pulmonale, right axis deviation, right ventricular hypertrophy and strain pattern, or right bundle branch block may raise suspicion of PH and provide prognostic information. (Bonderman D. *et al.*, 2011) Chest radiography commonly reveals signs of right heart and pulmonary artery enlargement. Nevertheless, a normal chest X-ray cannot rule out PH. (Ascha M. *et al.*, 2017)

Echocardiography, which provides comprehensive information on the heart morphology and function, is a basic examination tool in modern cardiology. It is commonly used to estimate numerous hemodynamic variables including pulmonary artery and atrial pressures, and cardiac output. Currently, no single echo parameter alone can reliably inform about the PH presence and its etiology, and a thorough complete examination is therefore necessary. PH usually leads to the right ventricle overload resulting in its enlargement and dysfunction. Increased right ventricle pressure causes the flattening of the interventricular septum and D-shape of the left ventricle, which can be easily recognized using standard projections. Common echocardiographic parameters for right ventricular systolic function assessment are TAPSE (tricuspid annular plane systolic excursion), peak systolic velocity of tricuspid anulus, and FAC (fractional area change). Tricuspid and pulmonary regurgitation velocities are standardly used for an estimation of pulmonary artery pressure. Typical echocardiographic findings in PH also include a dilated right atrium as well as a distended inferior vena cava as a sign of an elevated central venous pressure. In PH associated with the left heart disease (group 2), echocardiography plays a special role as it can reveal the concrete pathology which led to increased pulmonary pressures. Especially in severe PH, a pericardial effusion can often be found. (Topyla-Putowska W. *et al.*, 2021)

Other diagnostic methods used in PH patients include laboratory testing and blood gas analyses, pulmonary function testing, ventilation/perfusion scanning, abdominal ultrasound, chest computed tomography, cardiac magnetic resonance imaging, exercise testing, genetic counselling, and others. (Oldroyd S.H. *et al.*, 2023)

2.4.3 Right heart catheterization

Right heart catheterization (RHC) using a dedicated Swan-Ganz catheter remains the gold standard for a PH confirmation. Several parameters are usually measured during the invasive hemodynamical examination and other auxiliary parameters can be calculated. (**Table 3**) RHC is necessary for measuring the pulmonary arterial wedge pressure (PAWP) which is crucial to distinguish between pre-capillary and post-capillary PH. (Vachiery J.L. and Gaine S., 2012) In patients with idiopathic, heritable, and drug-associated PAH, it is recommended to perform vasoreactivity testing during the RHC in order to detect those patients who can respond to treatment with calcium channel blockers. (Humbert M. *et al.*, 2022; Sitbon O. *et al.*, 2005)

Table 3: Selected hemodynamic parameters obtained (directly measured or calculated) by RHC and their suggested normal values.

Right atrial pressure, mean (RAP)	2 – 6 mmHg
Pulmonary artery pressure, systolic (sPAP)	15 – 30 mmHg
Pulmonary artery pressure, diastolic (dPAP)	4 – 12 mmHg
Pulmonary artery pressure, mean (mPAP)	8 – 20 mmHg
Pulmonary arterial wedge pressure, mean (PAWP)	≤15 mmHg
Cardiac output (CO)	4 – 8 L/min
Cardiac index (CI)	2.5 – 4.0 L/min·m2
Pulmonary vascular resistance (PVR)	0.3 – 2.0 WU
Stroke volume (SV)	60 – 100 mL

Adapted from the ESC guidelines 2022 (Humbert M. et al., 2022).

2.5 Pulmonary hypertension treatment

General recommendations for PH patients include exercise training within symptom limits (Ehlken N. *et al.*, 2016; Grunig E. *et al.*, 2021), psychosocial support, and prophylactic immunization against respiratory infections. (Humbert M. *et al.*, 2022) Oxygen therapy is advised in patients with proven low arterial blood oxygen level. (Ulrich S. *et al.*, 2019) Iron should be supplemented in the presence of an iron-deficiency anemia. (Ruiter G. *et al.*, 2015) In case of signs of right ventricular failure and fluid retention, diuretics are recommended. (Stickel S. *et al.*, 2019)

2.5.1 Group 1 – Pulmonary arterial hypertension (PAH)

The main approach to the PAH treatment is pharmacological. Nowadays, several types of specific vasodilatory drugs are available. The therapy is usually started with phosphodiesterase 5 inhibitors or an endothelin receptor antagonist taken perorally as a monotherapy or combination. (Humbert M. *et al.*, 2022) Patients who respond to the acute vasoreactivity testing may be treated with calcium channel blockers. (Rich S. *et al.*, 1992; Sitbon O. *et al.*, 2005) In case of an insufficient response to the initial therapy, prostacyclin receptor agonist or prostacyclin analogues can be added. (Humbert M. *et al.*, 2022)

2.5.2 Group 2 – PH associated with left heart disease

The primary approach in the treatment of a pulmonary hypertension associated with left heart disease is the treatment of the underlying heart pathology. (McDonagh T.A. *et al.*, 2021; Vahanian A. *et al.*, 2021) Specific drugs approved for PAH treatment are generally not recommended, as they may have potentially detrimental effects. (Humbert M. *et al.*, 2022)

2.5.3 Group 3 – PH associated with lung diseases and/or hypoxia

The cornerstone of the treatment is the optimalization of the underlying lung disease management including oxygen therapy. The specific vasodilatory treatment is generally not recommended. (Humbert M. *et al.*, 2022)

2.5.4 Group 4 – PH associated with pulmonary artery obstructions

In contrast to the previous groups, surgical treatment (pulmonary endarterectomy) is a first line approach for operable patients. Other possibilities include percutaneous balloon pulmonary

angioplasty and pharmacological therapy. (Humbert M. *et al.*, 2022) In selected patients, all the mentioned modalities can be successfully combined. (Kim N.H. *et al.*, 2019) Lifelong anticoagulation is necessary in all patients with chronic thromboembolic pulmonary hypertension (CTEPH). (Bunclark K. *et al.*, 2020)

3. Heart rhythm disorders

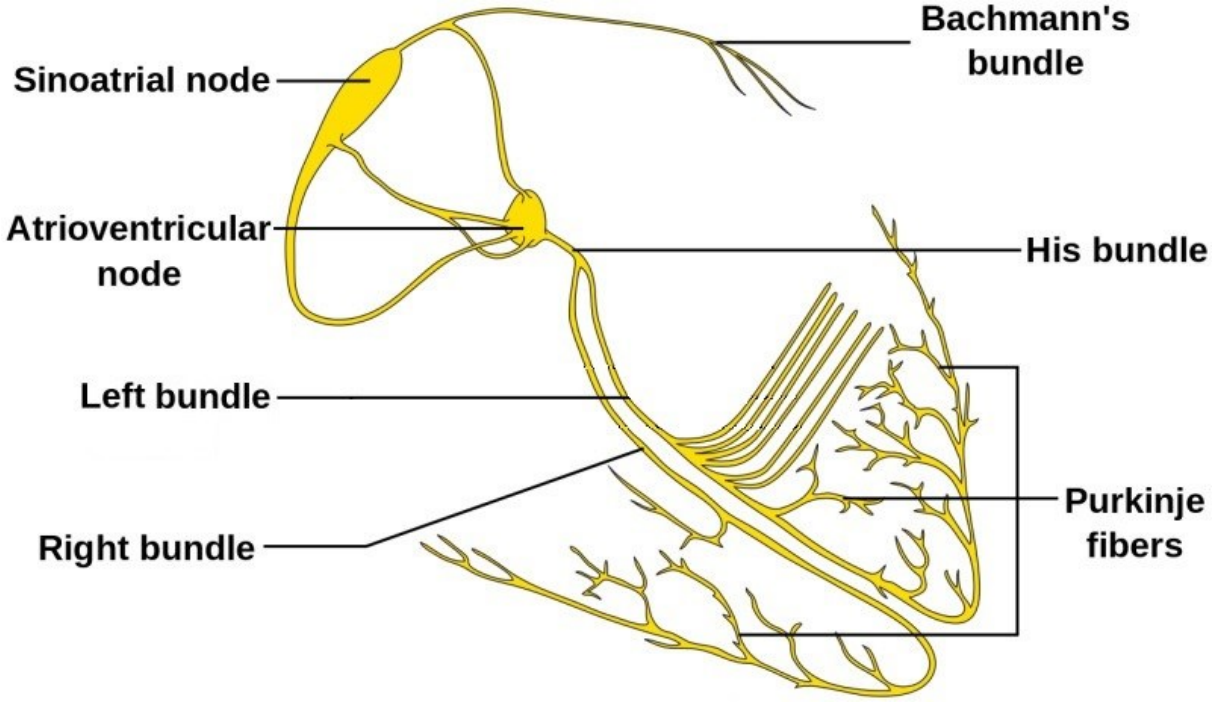
"Heart rhythm disorders" or "arrhythmias" are terms used to describe an abnormal heart rhythm. Contrary to which, "normal heart rhythm" is understood as a "sinus rhythm" (SR). In SR, electric signals are periodically produced in a sinus node located in the upper right atrium and conducted via atrial tissue to the atrioventricular (AV) node and then further through the His-bundle, left and right bundle branches, and Purkinje fibers to both ventricles. The overall prevalence of arrhythmias in the general population is usually reported between 1.5 – 5%. Because of the possibly clinically silent and paroxysmal occurrence the precise number is, however, hard to define. (Desai D.S. and Hajouli S., 2022) According to a trial which assessed the frequency of heart rhythm abnormalities in the national prospective cohort UK Biobank, containing about half a million adults, the reported overall prevalence of arrhythmias was >2% with an incidence of 0.5% per year. (Khurshid S. *et al.*, 2018) In a selected population of patients seen in a cardiology outpatient clinic, almost 40% presented with a heart rhythm disorder. (Vazquez Ruiz de Castroviejo E. *et al.*, 2005)

Electrocardiography (ECG) is a basic diagnostic tool for arrhythmia assessment. As stated before, paroxysmal presence is a typical feature of numerous arrhythmias. In such cases, the standard 12-lead ECG with a 10 second long recording often does not capture the arrhythmia and longer monitoring is needed. Nowadays, various technical modalities such as ambulatory ECG monitoring, loop recorders, event recorders, and others can be used. (Desai D.S. and Hajouli S., 2022)

3.1 Heart rhythm disorders basic classification

Arrhythmias represent a vast and heterogenous group of disorders with a various range of clinical presentations and can be divided using several different parameters. Heart rate during an arrhythmia is commonly used as the very first variable for the closer characterization of a disorder. Arrhythmias with a heart rate of less than 60 beats per minute (bpm) are referred to as "bradycardias" and arrhythmias with the heart rate above 100 bpm are called "tachycardias". (Desai D.S. and Hajouli S., 2022) Tachycardias can then be further divided according to the site of origin. Supraventricular arrhythmias involve cardiac tissue at the level of the bundle of His or above, on the other hand, ventricular arrhythmias arise from the ventricular tissue. (Katritsis D.G. *et al.*, 2018)

Figure 1: Conduction system of the heart.



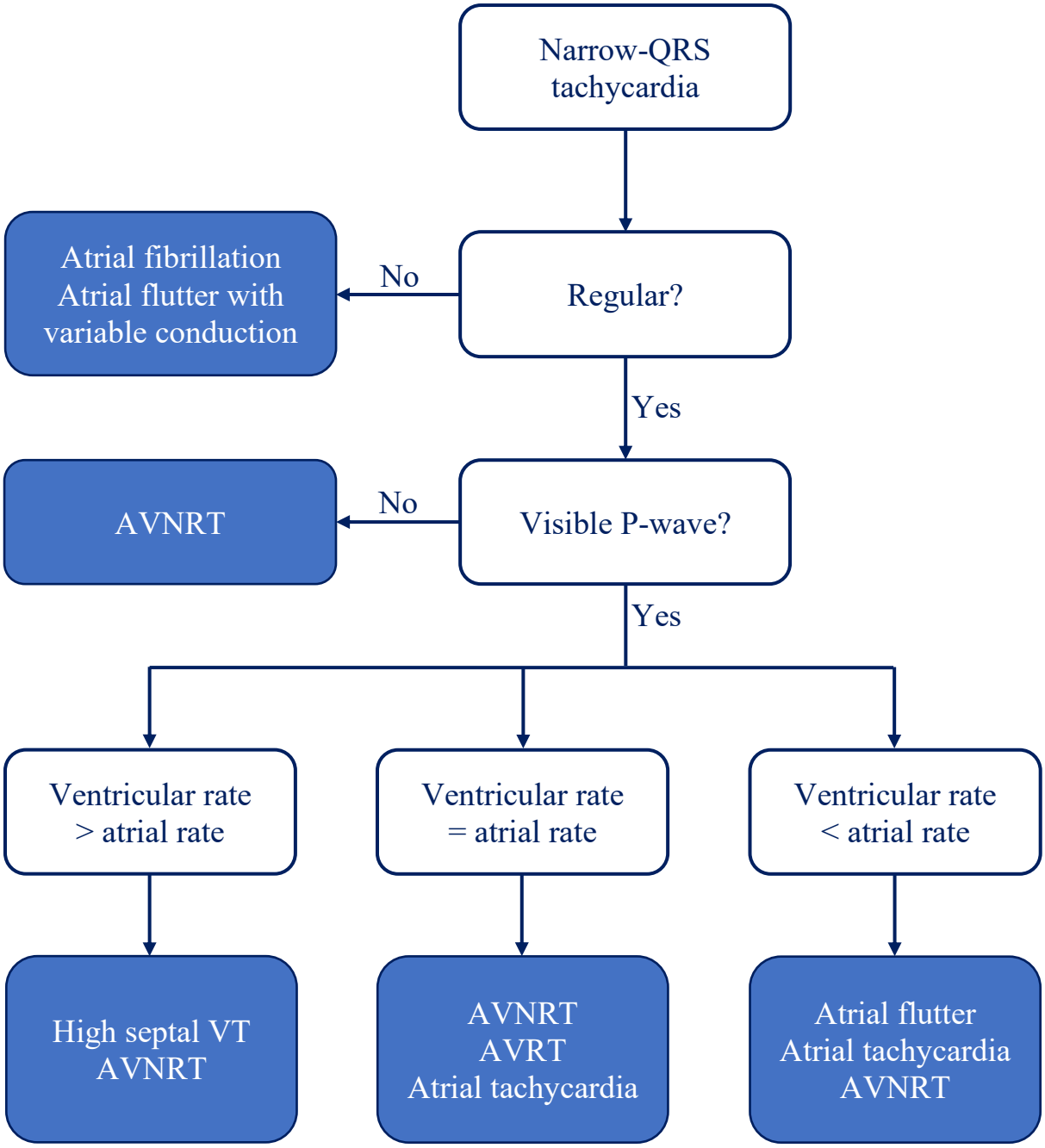
Adapted from Desai and Hajouli, Arrhytmias (Desai D.S. and Hajouli S., 2022).

3.2 Supraventricular tachycardias (SVTs)

Within my postgraduate study, I focused mainly on the topic of supraventricular tachycardias. Therefore, this overview will be predominantly concerned with this area as well.

On a 12-lead ECG, SVTs usually appear as a narrow-QRS tachycardia, which means a QRS duration ≤120 milliseconds. However, under specific circumstances, with pre-existing left or right bundle branch block being the most common, SVTs can present as a wide QRS arrhythmia. The differential diagnosis of narrow-QRS tachycardias is summed up in Figure 2. (Desai D.S. and Hajouli S., 2022)

Figure 2: Narrow-QRS tachycardia differential diagnosis.



Adapted from Kotadia (Kotadia I.D. et al., 2020).
Abbreviations: AVNRT: atrioventricular nodal reentrant tachycardia, AVRT: atrioventricular reentrant tachycardia, VT: ventricular tachycardia.

3.2.1 The presentation of SVTs

The clinical presentation and impact of atrial arrhythmias can vary significantly. Commonly reported symptoms are palpitations, fatigue, light-headedness, dyspnea, and altered consciousness. (Zimetbaum P. and Josephson M.E., 1998) More severe symptoms like dizziness, presyncope, or even syncope are more frequently reported in older patients and usually attributed to the immediate drop of the blood pressure after the onset of arrhythmia. (Razavi M. *et al.*, 2005) The development of tachycardia induced cardiomyopathy is represented by the classic signs of heart failure. (Zimetbaum P. and Josephson M.E., 1998) Some patients can report polyuria during the arrhythmia, perhaps as an effect of an increased atrial natriuretic peptide activity. (Abe H. *et al.*, 1997) A diagnosis based on the clinical features can be challenging, as symptoms of SVTs are generally not specific and the patient can even be misdiagnosed with a panic disorder. (Lessmeier T.J. *et al.*, 1997) On the other hand, pounding in the neck (also called "frog sign") is believed to be a typical sign of an AV nodal reentrant tachycardia (AVNRT) caused by the concomitant atrial and ventricular contraction. (Gursoy S. *et al.*, 1992)

3.2.2 Epidemiology of SVTs

Atrial arrhythmias are common in the general population. The paroxysmal SVTs' prevalence is usually referred to as 2.25/1000 persons and the incidence is 35/100 000 person-years. (Orejarena L.A. *et al.*, 1998) According to the famous Framingham study, the overall lifetime risk of developing atrial fibrillation (AF) or typical atrial flutter (AFL) is estimated at 16% for people without a history of heart failure or myocardial infarction. (Lloyd-Jones D.M. *et al.*, 2004) The most commonly stated risk factor for SVTs is age, as both the incidence and prevalence of atrial arrhythmias grow with aging. (Benjamin E.J. *et al.*, 1994) To illustrate, the estimated incidence of AF or AFL is 0.1% per year among people aged 55 – 60 years old. For people between 80 and 85, it is 2.7% per year. (Heeringa J. *et al.*, 2006)

3.2.3 Management of SVTs

Recent guidelines suggest several approaches that can be used in SVT management. The choice of a concrete therapy depends on many factors including the exact type of arrhythmia, risk stratification, patient preference, and others. The conservative approach (i.e., observation without any treatment) can be used if the symptoms are rare and the risk for the patient is low.

Pharmacological treatment usually includes beta blockers, calcium channel blockers, and antiarrhythmics. Nowadays, catheter ablation is a feasible and safe long-term treatment for most SVTs. Under specific circumstances, various surgical procedures can also be considered. Direct current cardioversion (DCCV) is commonly performed to stop the ongoing arrhythmia and restore the SR. (Kotadia I.D. *et al.*, 2020)

Several types of atrial arrythmias, including AF and AFL, are known to increase the risk of intracardiac thrombus formation. In those patients, long-term anticoagulation therapy is usually indicated after the individual assessment of bleeding and thrombotic risk. (Brugada J. *et al.*, 2020; Hindricks G. *et al.*, 2021)

3.2.4 A brief overview of selected types of supraventricular arrythmias

3.2.3.1 Atrial fibrillation (AF)

AF leads to uncoordinated electrical activation of the atria resulting in an ineffective contraction. Characteristic ECG features include irregular R-R intervals, the absence of distinct P-waves, and irregular atrial activations. (Hindricks G. *et al.*, 2021) AF is the most common arrhythmia in the world with an overall prevalence of 2 – 4% in adults. (Benjamin E.J. *et al.*, 2019) Important risk factors include higher age and comorbidities like arterial hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease, obesity, and obstructive sleep apnea. The pathophysiology of AF is complex with a specific interaction of triggers, perpetuators, and substrate. AF is a progressive disease, as its presence further promotes specific processes that are known to be important for AF occurrence. Therefore, the gradual transition from paroxysmal to permanent arrhythmia is common. AF represents an important burden to society, as it is known to significantly increase the risk of death, stroke, and heart failure, and leads to an impaired quality of life. (Hindricks G. *et al.*, 2021) Comprehensive AF management includes rate or rhythm control strategies. (Al-Khatib S.M. *et al.*, 2014) In an overall population, there is so far no solid evidence proving that any of those strategies would result in a different outcome and, according to the latest guidelines, the primary indication for rhythm control is symptom reduction and improvement of quality of life. Nowadays, catheter ablation is established as a safe and effective way to maintain SR. (Hindricks G. *et al.*, 2021)

3.2.3.2 Cavotricuspid isthmus-dependent macro-reentrant atrial tachycardia (Typical atrial flutter – AFL)

Macro-reentry circuit around the right atrial cavity using the cavotricuspid isthmus is a typical feature for the AFL. Counter-clockwise activation is more common. On the 12-lead ECG, this is presented as a regular atrial activation with the rate 250 – 330 bpm, negative saw-tooth waves in inferior leads, and positive waves in V1. In cases of clockwise activation, the arrythmia is then referred to as "typical reverse atrial flutter" and is characterized with broad and positive waves in inferior ECG leads. (Saoudi N. *et al.*, 2001) Antiarrhythmic drugs often fail in the acute setting and electric cardioversion may be necessary. For long-term management, catheter ablation is the most effective approach. (Brugada J. *et al.*, 2020)

3.2.3.3 Non-cavotricuspid isthmus dependent macro-reentrant atrial tachycardia (Atypical flutter)

These terms are used to describe the arrhythmias which are represented with flutter waves of other than the mentioned typical morphology. The reentrant circuit located in the right or left atria is not dependent on the cavotricuspid isthmus. (Brugada J. *et al.*, 2020)

3.2.3.4 Focal atrial tachycardia (AT)

Focal AT is characterized by an organized atrial activity with the rate >100 bpm. It originates from any site in either of both atria and spreads centrifugally. Typical sites are the crista terminalis, the tricuspid and mitral valve anulus, and within the thoracic veins joining the atria. The final ventricular rate depends on the conduction via the AV node and can vary quickly. For the diagnosis, the presence of a monomorphic P-wave with a stable cycle length on the standard 12-lead ECG is crucial. In an acute setting, focal AT can be terminated by synchronized cardioversion or pharmacologically using adenosine, verapamil/diltiazem, or beta blockers. For recurrent focal AT, catheter ablation is the treatment of choice. (Brugada J. *et al.*, 2020)

3.2.3.5 Atrioventricular nodal reentrant tachycardia (AVNRT)

Dual conduction of the AV node based on the presence of the fast and slow pathways is a necessary condition for AVNRT occurrence. Typical AVNRT (slow-fast AVNRT) appears as a regular narrow complex tachycardia with retrograde P-waves located closely to the QRS complex. In numerous cases the P-waves are masked by the QRS complex and therefore not

distinguishable. (Katritsis D.G. and Camm A.J., 2010) On the contrary, in atypical AVNRT the P-waves are clearly visible before the QRS, as the RP interval is longer than the PR interval. (Katritsis D.G. *et al.*, 2015) AVNRT can be terminated by vagal maneuvers, adenosine, verapamil/diltiazem, or beta blockers. Synchronized electrical cardioversion is rarely used in case of acute hemodynamical instability. Symptomatic and recurrent AVNRT should be treated with catheter ablation. (Brugada J. *et al.*, 2020)

3.2.3.6 Atrioventricular reentrant tachycardia (AVRT)

The existence of an accessory pathway that directly connects the atria and ventricles bypassing the physiological conduction system is necessary for the AVRT occurrence. (Ho S.Y., 2008) This arrhythmia is characterized by the macro-reentry circuit that consists of atrial and ventricular tissue, AV node, His bundle, and accessory pathway. Each part of the circuit has a different conduction velocity and refractory period. In such a setting, a critically timed premature atrial or ventricular beat can initiate the AVRT. During the arrhythmia, the conduction over the AV node can be antegrade or retrograde – resulting in orthodromic or antidromic AVRT. Orthodromic AVRT is much more common (>90% of AVRT cases). It is a rapid tachycardia resulting in a heart frequency of 150 – 220 bpm. Retrograde P-waves are usually clearly visible behind the QRS complex. (Brugada J. *et al.*, 2020) In contrast, antidromic AVRT is presented by a wide QRS complex and difficult to discern P-waves, because of the markedly pronounced ST-T segment changes. (Ceresnak S.R. *et al.*, 2012) Vagal maneuvers and intravenously administered adenosine represent first-line treatment for hemodynamically stable patients with orthodromic AVRT. In antidromic AVRT, antiarrhythmics like ibutilide, procainamide, flecainide, or propafenone should be considered. Synchronized electrical cardioversion should be used in hemodynamically unstable patients or in case of the drug therapy failure. Catheter ablation is the treatment of choice for patients with symptomatic and recurrent AVRT, according to the latest ESC guidelines. (Brugada J. *et al.*, 2020)

4. Heart rhythm disorders in pulmonary hypertension

Atrial arrhythmias are common in patients with PH, and their presence is often connected with clinical deterioration. In contrast, ventricular arrhythmias are rare in patients with PH. This was already described in 1979 by Kanemoto (Kanemoto N. and Sasamoto H., 1979) and confirmed by more recent trials, such as the observational study from Tongers et al. that did not report any malignant ventricular arrhythmia during the 6 year long follow-up in 231 PH patients. (Tongers J. *et al.*, 2007) In a different study, ventricular fibrillation was observed in only 8% of 132 PAH patients with witnessed cardiac arrest. (Hoeper M.M. *et al.*, 2002)

4.1 Epidemiology of SVTs in PH patients

Numerous trials have been performed to determine the burden of SVTs on PH patients. The first studies were based mainly on retrospective analysis. Later, larger prospective studies were performed. According to the current literature, the reported cumulative incidence of atrial arrhythmias among PH patients is 10-36%.

As already mentioned, Tongers at al. in 2007 conducted the first major observational study focused on arrhythmias in PH. It included 231 patients with PH of various etiologies (idiopathic PAH, PAH due to congenital heart disease or connective tissue disorder, PAH associated with HIV, portopulmonary hypertension, inoperable CTEPH). The annual incidence of SVTs was 2.8%, and the reported overall cumulative incidence after a 6-year long period was 11.7%. The number of patients who developed AF and AFL was the same, followed by fewer cases of AVNRT. (Tongers J. *et al.*, 2007) Other commonly cited retrospective studies focused only on PAH patients performed by Ruiz-Cano et al. and Wen et al. showed quite analogous SVTs prevalence of 10% and 14%, respectively. (Ruiz-Cano M.J. *et al.*, 2011; Wen L. *et al.*, 2014)

A higher incidence of atrial arrhythmias was reported by Olsson et al. in 2012. This 5-year prospective study assessed the incidence of SVTs among 239 patients with PAH (n = 157) and inoperable CTEPH (n = 82). During the follow-up, an episode of AF or AFL was recorded in 48 (20%) patients. AF was the most common (n = 24), 15 patients had an atypical flutter and typical AFL was described in 9 patients. The higher proportion of patients with an older age and more advanced disease in this study is commonly presented as a leading reason causing

higher arrhythmia occurrence compared to previously described analyses. (Olsson K.M. *et al.*, 2013)

Similar results were reported by the Italian group of authors in 2015. 77 patients with PAH without a history of SVT were enrolled in the study and during the follow-up (median 35 months), 22% (n = 17) experienced at least one episode of SVT. The most common type of arrhythmia was again the AF. (Cannillo M. *et al.*, 2015)

An even higher proportion of patients with SVT was reported by Rottlaender in 2011. In this 4 year-long, single-center, retrospective analysis arrhythmia's prevalence reached 31%. This excessively high number was probably caused by the inclusion of patients with post-capillary PH, a fact which is in contrast with the previously mentioned trials. From 225 patients, 23% (n = 52) were diagnosed with PH due to left heart disease. In those patients, the AF prevalence was particularly high (57.7% vs. 23.1% in other PH subtypes). (Rottlaender D. *et al.*, 2012)

According to the literature, patients with PAH related to congenital heart disease seem to be another group with high arrhythmia incidence. In Daliento's work focused on 188 patients with Eisenmenger syndrome, i.e., patients with congenital heart defect leading to a progressive elevation of mPAP and PAR finally resulting in a reversed shunting, the SVTs occurred in 35.5%. (Daliento L. *et al.*, 1998) We can speculate that specific anatomical changes and severe remodeling of the right heart due to the long lasting and extreme elevation of the pulmonary artery pressure are the leading proarrhythmogenic factors.

The relation between the concrete PH etiology and SVT incidence was studied by Fingrova et al., whose analysis, published in 2021, examined the dedicated registry of 755 consecutive patients diagnosed with PH in our center in Prague, Czech Republic, between 2003 and 2017. Patients with isolated pre-capillary PH had significantly lower SVT prevalence compared to patients with combined post- and pre-capillary PH (25% vs. 51%, $p < 0.0001$). The difference was mainly caused by the higher prevalence of permanent AF in the combined PH. However, the AF (regardless of the type) was the most prevalent arrhythmia in both groups. Among patients with isolated pre-capillary PH, the highest arrhythmia occurrence was found in patients with PAH associated with congenital heart disease (35%). On the contrary, patients with PH

due to lung disease and hypoxia showed the lowest SVT prevalence (16%). (Fingrova Z. *et al.*, 2021)

A typical attribute of some SVTs is their episodic character with spontaneous onset and termination. Given that patients could be asymptomatic in the presence of an arrhythmia, many SVTs probably remain undiscovered in routine clinical practice. Therefore, long-term continuous ECG monitoring is nowadays considered as the gold standard to determine the arrhythmia's burden. However, almost all available analyses relied on repeated short ECG recordings during clinical visits and hospitalizations, or intermittent ECG Holter monitoring. From that point of view a prospective study from Denmark that included 24 patients with PAH and 10 patients with CTEPH is exceptional. Each patient was equipped with an insertable cardiac monitor. During the continuous ECG monitoring with the median length of 594 days, SVT was recorded in 29% of patients (n = 10). According to the results, the vast majority of the episodes were short and self-limiting. It is also interesting to note that sustained ventricular arrhythmia was not recorded in any of the patients. (Andersen M.O. *et al.*, 2021)

4.2 Risk factors for SVT occurrence in PH

Based on the data available from the observational studies, several risk factors for the atrial arrhythmia occurrence have been identified. Olsson et al. identified that patients with advanced PH with higher right atrial pressure, mPAP and PVR values, and lower CO were in significantly higher risk of arrhythmia development. (Olsson K.M. *et al.*, 2013) Increased right ventricle diameter, left atrium area, higher right atrial pressure, and PVR, together with an elevated B-type natriuretic peptide level (BNP) and lower cardiac index, were associated with an increased risk for experiencing SVT in another analysis. (Wen L. *et al.*, 2014) Interestingly, along with the already mentioned higher right atrial pressure and NTproBNP, thyroid disease prevalence was also described as a risk factor in one study. (Mercurio V. *et al.*, 2018) Slightly different risk factors were identified based on the multivariable Cox regression model from the Smith et al. analysis. Older age, male sex, lower left ventricle ejection fraction, greater indexed left atrial volume, and greater right atrium area were independently associated with the presence of atrial arrhythmias in PAH patients. (Smith B. *et al.*, 2018) One study highlighted the association between SVT and the presence of pericardial effusion. (Malaczynska-Rajpold K. *et al.*, 2016)

Interestingly, in some registries, no clinical or instrumental characteristics at the baseline were able to predict the development of SVT. (Cannillo M. *et al.*, 2015)

4.3 Pathophysiological mechanisms causing SVTs in PH

Some pathophysiological mechanisms of arrhythmias are the same in patients with and without PH. Organized SVTs like AVNRT, AVRT, or typical AFL have well defined reentry circuits that can be proved even in PH patients. Also, classic AF triggers in pulmonary veins are common.

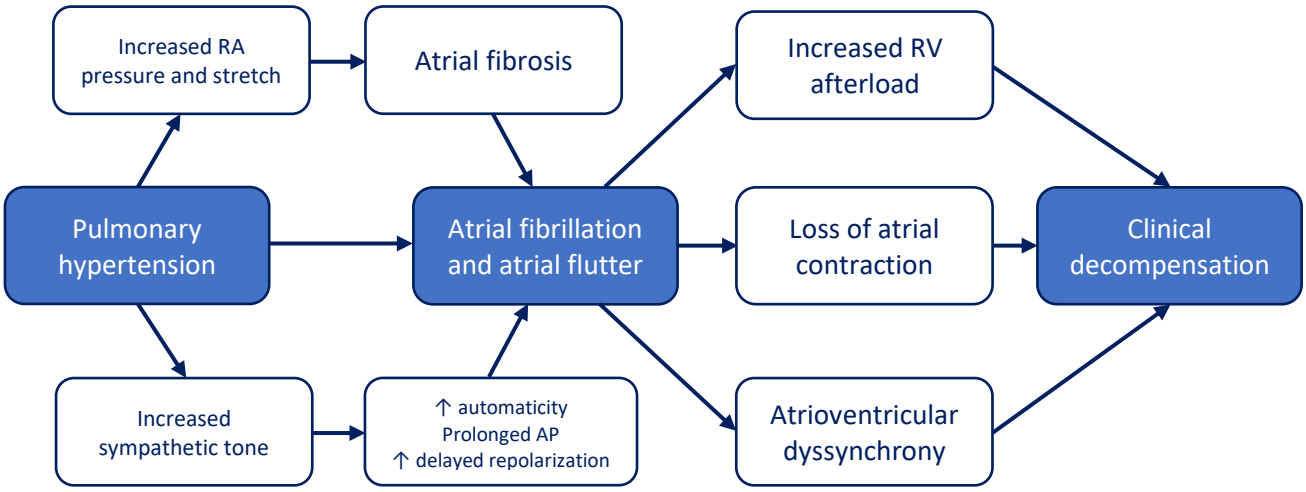
However, there are several factors that possibly cause increased incidence of arrythmias in PH patients. Long standing PH leads to an increased afterload of the right ventricle, as well as upstream enlargement of the right atrium. (Pietra G.G. *et al.*, 2004) This results in slow conduction, reduced tissue voltage, and even regions of electrical silence, so the role of right-sided arrhythmogenic substrate is obvious. (Medi C. *et al.*, 2012a) Based on the observational studies, the size of the right atrium and the right atrial pressure seem to be important risk factors for atrial arrhythmia development. (Olsson K.M. *et al.*, 2013; Wen L. *et al.*, 2014) There is also data proving that prolonged P-wave duration >110ms as a sign of impaired atrial conduction is associated with poor clinical outcomes in PH patients. (Bandorski D. *et al.*, 2016) However, it has been proven that the left sided substrate could play a role in arrhythmogenesis of complex atrial arrhythmias, even in isolated precapillary PH. (Fingrova Z. *et al.*, 2019) For atrial fibrillation, non-pulmonary vein triggers may play a more important role than in patients without PH (Santangeli P. *et al.*, 2016)

Generally, autonomic nervous system disbalance can trigger specific arrhythmias (Folino A.F. *et al.*, 2003; Schrier R.W. and Bansal S., 2008) and, according to the available data, sympathetic overactivity is an important AF risk factor. (Chen P.S. *et al.*, 2014; Katritsis D.G. *et al.*, 2013) It has already been proven that PH patients have significantly increased sympathetic activity. (Velez-Roa S. *et al.*, 2004) Targeted modulation of the autonomic system has already been tested as a possible treatment for arrhythmias. In the animal PAH model, ablation of the right anterior ganglionic plexi, resulting in decreased local sympathetic activity to the right atrium, reduced arrhythmias. (Zhao Q. *et al.*, 2015)

Even more complex are the probable proarrhythmogenic mechanisms in patients with PAH connected to the connective tissue disease. In those patients, chronic inflammation, myocardial fibrosis, immunological autoantibody mechanisms, and immunosuppressive treatment may all contribute to the development of arrhythmia. (Lazzerini P.E. *et al.*, 2014)

In patients with a post-capillary PH component, the mechanisms of arrhythmia seem to be more analogous to patients with substrate caused by the left heart involvement. (Rottlaender D. *et al.*, 2012) The left atrial remodeling caused by increased left atrial pressure is known to result in the high burden of AF. (Ausma J. *et al.*, 1997; Spach M.S. and Josephson M.E., 1994)

Figure 4: Pathogenesis of atrial arrhythmias in PH and their pathophysiological consequences.



Adapted from Wanamaker et al. (Wanamaker B. et al., 2018).
Abbreviations: AP – action potential; RA – right atrium; RV – right ventricle

4.4 Clinical significance of SVTs in PH

In PH patients, the presence of arrhythmia is associated with disease severity and clinical deterioration. In an observational study from Tongers et al., 84% of patients with SVTs manifested with a worsened NYHA class or even heart failure decompensation. (Tongers J. *et al.*, 2007) This was confirmed by the Olsson's study, where almost all patients (97.5%) clinically deteriorated in the presence of SVT. (Olsson K.M. *et al.*, 2013) Other studies showed significant reduction in the 6-minute walk test (Ruiz-Cano M.J. *et al.*, 2011), worsening echo

parameters of the right heart function, and elevated BNP levels in the presence of arrhythmia. (Cannillo M. *et al.*, 2015) In those studies, restoration of the SR was associated with clinical improvement.

There are several possible reasons for such malign effects of SVT presence in patients with PH. It has been shown that in PH, atrial contraction resulting in active emptying of the atria plays an important role in maintaining the cardiac output. (Willens H.J. *et al.*, 2008) The diastolic filling is further impaired due to the fast heart rate. Ongoing tachycardia leads to decreased contractility and increased afterload, altogether resulting in altered right ventricular function. (Metkus T.S. *et al.*, 2016) Eventually, significantly increased right ventricle wall stress can even lead to insufficient coronary perfusion and ischemia of the right ventricle, further deteriorating its function. (Bogaard H.J. *et al.*, 2009)

Numerous studies have also provided data on the relation between SVT occurrence and mortality in PH patients. In Cannilo's and Wen's trials, SVTs were generally associated with a significantly increased risk of death. (Cannillo M. *et al.*, 2015; Wen L. *et al.*, 2014) In Tongers' cohort, the cumulative mortality reached a striking 81.8% among patients in whom a stable SR could not be established and remained in AF. In contrast, low cumulative mortality (6.3%) was observed in patients in whom the SR was restored. (Tongers J. *et al.*, 2007) A significantly shorter survival for PAH and CTEPH patients with arrhythmia was also described by Smith et al. in 2018. In an unadjusted Cox regression model, a diagnosis of AF or AFL was associated with a 3.81-fold increase in the hazard of death (95% CI 2.64 – 5.52, $p < 0.001$). (Smith B. *et al.*, 2018)

The results of Olsson's analysis confirm the poor prognosis of PH patients in the presence of atrial arrhythmia and provides some interesting details. The hazard ratio of death in patients who developed AF or AFL compared to those who remained in SR was 1.75 (95% CI 1.1 – 3.0; $p = 0.0042$). The higher mortality in the group of patients with SVT was mainly driven by patients with permanent AF in whom the SR could not been restored. Those patients had significantly worse 1-, 2-, 3-, and 5-year survival rates compared to patients with transient episodes of arrhythmias. The survival rates for patients with transient episodes of arrhythmia did not differ significantly from patients without a history of any arrhythmia. Those findings

again highlight the importance of the SR restoration in this population. (Olsson K.M. *et al.*, 2013)

However, conflicting data can be found, as some studies did not confirm those findings. Analysis of the patients with various PH etiology published by Fingrova et al. suggested that advanced age, male sex, larger right atrium diameter, higher right atrial pressure, and worsened functional parameters were stronger predictors of mortality than the presence of arrhythmia. (Fingrova Z. *et al.*, 2021)

It is obvious that clinically inapparent episodes of arrhythmia also occur in PAH patients. The data about frequency, however, remain inconclusive. According to Tongers et al., only 5 SVT episodes out of 31 (16%) did not lead to clinical worsening. (Tongers J. *et al.*, 2007) In the already cited Spanish trial, inapparent arrhythmia episodes counted for 18%. (Ruiz-Cano M.J. *et al.*, 2011) In the more recent retrospective, observational study from the cardiological center in Poznan, SVT was detected in 17 (35%) of 48 patients with pre-capillary PH. In 10 patients (59%), arrhythmia onset resulted in clinical deterioration. 7 episodes (including even a new onset AF) were clinically silent and detected incidentally during the routine follow-up. (Malaczynska-Rajpold K. *et al.*, 2016) Not surprisingly, mostly short and spontaneously terminating arrhythmias, which did not result in clinical deterioration, were detected in the study using continuous ECG monitoring. (Andersen M.O. *et al.*, 2021)

4.5 SVT treatment in PH patients

As already stated, because of the specific pathophysiological conditions, the presence of arrhythmias in patients with PH impairs not only the quality of life, but also worsens the prognosis. Therefore, restoration of the SR is an important treatment goal in PH patients. (Humbert M. *et al.*, 2022) This contrasts with patients with arrhythmias without PH, where the rhythm control strategy did not prove to bring mortality benefit compared to the rate control. (Caldeira D. *et al.*, 2012; Sethi N.J. *et al.*, 2017)

4.5.1. Pharmacotherapy

Despite the lack of data comparing the efficacy of different antiarrhythmic drugs in PH patients, they are being used standardly and are also recommended in guidelines as a part of the rhythm control management. (Humbert M. *et al.*, 2022)

It is widely known that Class 1c antiarrhythmics like flecainide, procainamide, or propafenone are contraindicated in patients with a history of myocardial infarction or left ventricular dysfunction. (Echt D.S. *et al.*, 1991) On the contrary, they are widely used in PH patients and according to the available observational studies seem to be well tolerated. However, no controlled data exists. (Reddy S.A. *et al.*, 2021)

Beta blockers (class 2 antiarrhythmics) remain controversial in PH patients because of their negative effect on chronotropy and inotropy. PH patients have a fixed stroke volume and rely on heart rate acceleration to maintain sufficient cardiac output. Also, a slower heart rate resulting in a longer diastolic filling time further increases right ventricle stretching and right ventricle end diastolic pressure. This, together with directly decreased contractility, can worsen the patient's hemodynamic state. On the other hand, beta blockers can efficiently suppress the detrimental sympathetic overactivity. (Reddy S.A. *et al.*, 2021) Several preclinical studies on pulmonary hypertension animal models have shown the benefits of beta blockers (decreased pulmonary pressures and right ventricular mass, increased right ventricular function, …). (Bogaard H.J. *et al.*, 2010; de Man F.S. *et al.*, 2012; Fowler E.D. *et al.*, 2018) In clinical practice, beta blockers seem to be dangerous mainly during the acute decompensation (Peacock A. and Ross K., 2010) and there is data proving that for stable PH patients they are safe to use but do not bring any significant benefit. (Bandyopadhyay D. *et al.*, 2015; Farha S. *et al.*, 2017; Thenappan T. *et al.*, 2014) According to the latest ESC guidelines, beta blockers are generally not recommended in PAH patients unless required by comorbidities, among which arrhythmias are mentioned. (Humbert M. *et al.*, 2022) This is thought to be valid for sotalol as well. (Reddy S.A. *et al.*, 2021)

Despite the lack of controlled data, amiodarone (class 3, potassium channel blocker) should be considered as a first line antiarrhythmic drug in PH because of its minimal negative inotropic effect. (Humbert M. *et al.*, 2022) This is, however, offset by the relatively high risk of adverse

effects when used chronically. The most feared pulmonary fibrosis is likely caused by both the direct free radical cytotoxic effect and T cell-mediated hypersensitivity, and may lead to further PH exacerbation or even death. (Goldschlager N. *et al.*, 2007) The concomitant use may be problematic with bosentan (endotelin receptor antagonist used to treat PAH). Amiodarone is a known cytochrome P450 inhibitor and therefore can significantly increase the plasma levels of bosentan. (Dwyer N. and Kilpatrick D., 2011) The use of dronedarone is limited by its contraindication in patients with severe heart failure and its lower efficiency. (Piccini J.P. *et al.*, 2009) Novel class 3 drugs like ibutilide and dofetilide can also be considered, but the evidence of their use in PH patients is scarce. Because of the possible QT prolongation, the ECG must be monitored regularly in all patients taking any of the class 3 antiarrhythmics. (Reddy S.A. *et al.*, 2021)

Calcium channel blockers (class 4) are used as a part of PAH treatment in patients with maintained vasoreactivity. In such a patient with concomitant arrhythmia, the use of non-dihydropyridine calcium channel blocker can be advantageous. Because of the negative ino- and chronotropy, cautious dose titration is required just as with beta blockers. (Reddy S.A. *et al.*, 2021)

Digoxin can be safely used on PH patients when rhythm control is not achievable and there is data suggesting its positive effect in patients with right ventricle failure. (Rich S. *et al.*, 1998; Tongers J. *et al.*, 2007) Adenosine is commonly and safely used in an acute setting to terminate arrhythmias dependent on the AV node as in the rest of the population. (Reddy S.A. *et al.*, 2021)

Anticoagulation is recommended to be managed in PH patients with atrial arrhythmias as in the rest of the population given the absence of specific evidence. (Humbert M. *et al.*, 2022)

4.5.2 Direct current cardioversion (DCCV)

DCCV is an important part of the rhythm control management that is highly recommended in PH patients, as already mentioned. It is widely used to acutely terminate the atrial arrhythmias and restore the SR. However, the available data suggests higher rates of arrhythmia recurrence. In PH patients, slower conduction velocities through the right atrium compared to patients without pulmonary hypertension were described. (Medi C. *et al.*, 2012b) At the same time,

abnormal atrial conduction was proven as an independent predictor of an arrhythmia recurrence. (Biffi M. *et al.*, 2002) Also, the specific risks of general anesthesia in PH patients must be considered when planning a DCCV. Therefore, it should be performed in a PH center by experienced personnel. (Reddy S.A. *et al.*, 2021)

4.5.3 Catheter ablation

Several studies have confirmed that catheter ablation for atrial arrythmias is feasible and safe in PH patients. (Bandorski D. *et al.*, 2014; Ruiz-Cano M.J. *et al.*, 2011; Showkathali R. *et al.*, 2011) However, because of the right heart remodeling due to the PH, ablation procedures are typically technically more challenging and the use of 3D electroanatomical mapping and steerable sheets should always be considered. Nowadays, radiofrequency ablation is the treatment of choice for AVRT, AVNRT, atrial flutter, and atrial tachycardias in PH patients, as in the rest of the population. (Reddy S.A. *et al.*, 2021) The role of catheter ablation for atrial fibrillation is, however, not that well-established. (Humbert M. *et al.*, 2022) The risk of AF recurrence after the ablation is higher in PH patients. This is probably connected to more frequently found arrhythmia triggers outside of the pulmonary veins – the site being standardly treated during the AF ablation procedure. (Zhang Y.Q. *et al.*, 2018) Also, the risk of complication associated with the procedure is suggested to be higher in PH patients than the standardly reported 4-8%. Current knowledge is again based mainly on the observational data and prospective randomized trials are needed. (Reddy S.A. *et al.*, 2021) In cases where all the attempts to restore the SR have failed, pacemaker implantation and the AV node ablation ("pace and ablate") seem to be a safe and effective rate control approach even in PH patients. (Bandorski D. *et al.*, 2014)

5. Objectives and hypotheses

The main objective of this thesis is to further investigate the epidemiology and specific pathophysiological mechanisms that lead to the increased incidence of atrial arrhythmias in patients with PH and that are responsible for their detrimental effects. Four independent analyses were designed to fulfill the objectives and to test the stated hypotheses.

Objective 1: To analyze the impact of a surgical treatment (pulmonary endarterectomy) in patients with CTEPH on the pathophysiological mechanisms related to the occurrence of atrial arrhythmias.

Hypothesis 1: In patients with CTEPH indicated to surgical treatment (pulmonary endarterectomy), the incidence of SVTs after the successful pulmonary endarterectomy will decrease thanks to the improved hemodynamic conditions and possible positive reverse remodeling of the right heart.

Objective 2: To analyze the prevalence and pathophysiological mechanisms of atrial arrhythmias in patients with pre-capillary PH in relation to the different values of PAWP.

Hypothesis 2: In patients with isolated pre-capillary PH, the incidence of AF/AT will increase with growing PAWP reflecting the post-capillary component.

Objective 3: To analyze the acute hemodynamic and pathophysiological consequences of the termination of atrial arrhythmia and SR restoration in patients with pre-capillary PH.

Hypothesis 3: In patients with pre-capillary PH, the acute termination of an atrial arrhythmia and the SR restoration will lead to the hemodynamic improvement and increased cardiac output.

Objective 4: To analyze the severity and localization of an arrhythmogenic substrate and the effect of its catheter ablation in patients with pre-capillary PH.

Hypothesis 4: In patients with pre-capillary PH, extensive right atrial arrhythmogenic substrate is common and; therefore, extended catheter ablation targeting this substrate will lead to better clinical results and lower rate of an arrhythmia recurrence compared to the standardly performed catheter ablation.

6. Results

The results of this thesis consist of four independent analyses, which are all related to the pathophysiological mechanisms of arrhythmias in pulmonary hypertension. Each of the analyses was published in a peer-reviewed journal with an impact factor.

The first article **"Atrial fibrillation and Atrial Tachycardia in Patients with Chronic Thromboembolic Pulmonary Hypertension Treated with Pulmonary Endarterectomy"** was based on the retrospective analysis of a dedicated registry of patients with CTEPH indicated to a pulmonary endarterectomy. The characteristics of patients without any arrhythmia occurrence were compared to those patients with documented SVT. The incidence and spectrum of arrhythmias before and after the surgery were analyzed to evaluate the effect of surgical treatment of CTEPH.

The second article **"The Role of Pulmonary Artery Wedge Pressure on the Incidence of Atrial Fibrillation and Atrial Tachycardias in Patients with Isolated Pre-capillary Pulmonary Hypertension"** was again based on the retrospective analysis. The data available from the previous research indicated the possible connection between the incidence of arrhythmias and the actual PAWP values in patients with pre-capillary PH (i.e. PAWP<15 mmHg). Therefore, we evaluated patients' characteristics, epidemiology, and types of arrhythmias in detail according to the PAWP values.

The third article **"The Impact of Atrial Fibrillation and Atrial Tachycardias on the Hemodynamic Status of Patients with Pulmonary Hypertension"** presents the results of a prospective observational study comparing patients with pre-capillary PH to patients with left-sided heart failure and controls. Repeated RHC was performed at the beginning and at the end of catheter ablation. The recorded changes in the hemodynamic parameters were evaluated and compared between the study subgroups.

The fourth article **"Catheter ablation of atrial fibrillation and atrial tachycardia in patients with pulmonary hypertension: a randomized study"** summarizes the results of a prospective randomized trial comparing extensive ablation to the standard approach. The arrhythmogenic substrate and its characteristics were assessed using electroanatomical mapping. Patients were

followed-up after the procedure to evaluate the efficacy and safety of both the standard and extended approach.

6.1 Original Article 1: Atrial fibrillation and Atrial Tachycardia in Patients with Chronic Thromboembolic Pulmonary Hypertension Treated with Pulmonary Endarterectomy

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

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KEYWORDS
Chronic thromboembolic pulmonary hypertension;
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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.[1,2] The incidence of CTEPH has gradually increased in recent years.[3] Without treatment the prognosis of CTEPHs is unfavourable.[4] Although performing a balloon pulmonary angioplasty or using medical therapy may be suitable,[3] a surgical pulmonary endarterectomy (PEA) is the treatment of choice for operable CTEPH.[1] The majority of patients experience substantial relief from symptoms

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and near-normalization of haemodynamics after surgery.[1,2,5]

Supraventricular tachycardias have been frequently (range of cumulative incidence 10–25%) observed in patients with pulmonary hypertension (PH),[6–11] including inoperable CTEPH.[7,10] 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.[7,8,10,11] 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.[6,7,9–11]

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.[12] In short, all patients underwent a routine baseline in-hospital work-up according to contemporary standards[1] 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[13,14] was used with some modifications.[15] 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 χ^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.

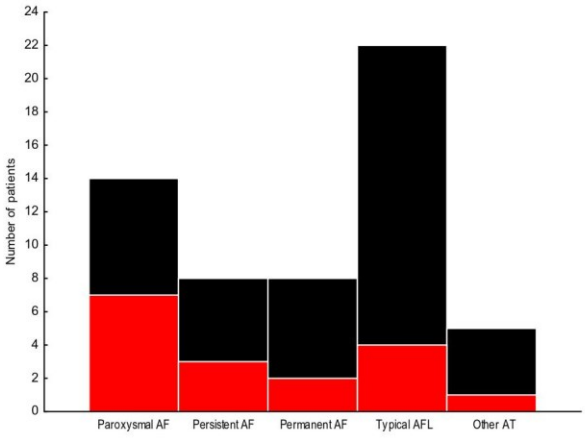

Figure 1 The spectrum of detected arrhythmia. The red columns visualize patients with arrhythmia manifested before the pulmonary endarterectomy; black columns refer to patients with arrhythmia diagnosed during a long-term follow-up after the surgery. AF, atrial fibrillation; AFL, atrial flutter; AT,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

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 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 (34-12) 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.[8-10,16] The most prevalent arrhythmias reported were AF and AFL.[6,7,9-11] 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.[17] A long-standing PH is associated with slowing conduction, reduced tissue voltage and regions of electrical silence in both the RA and the RV,[18] and modulations of the autonomic system may trigger and perpetuate arrhythmia.[19,20] In addition, the performed cardiac surgery

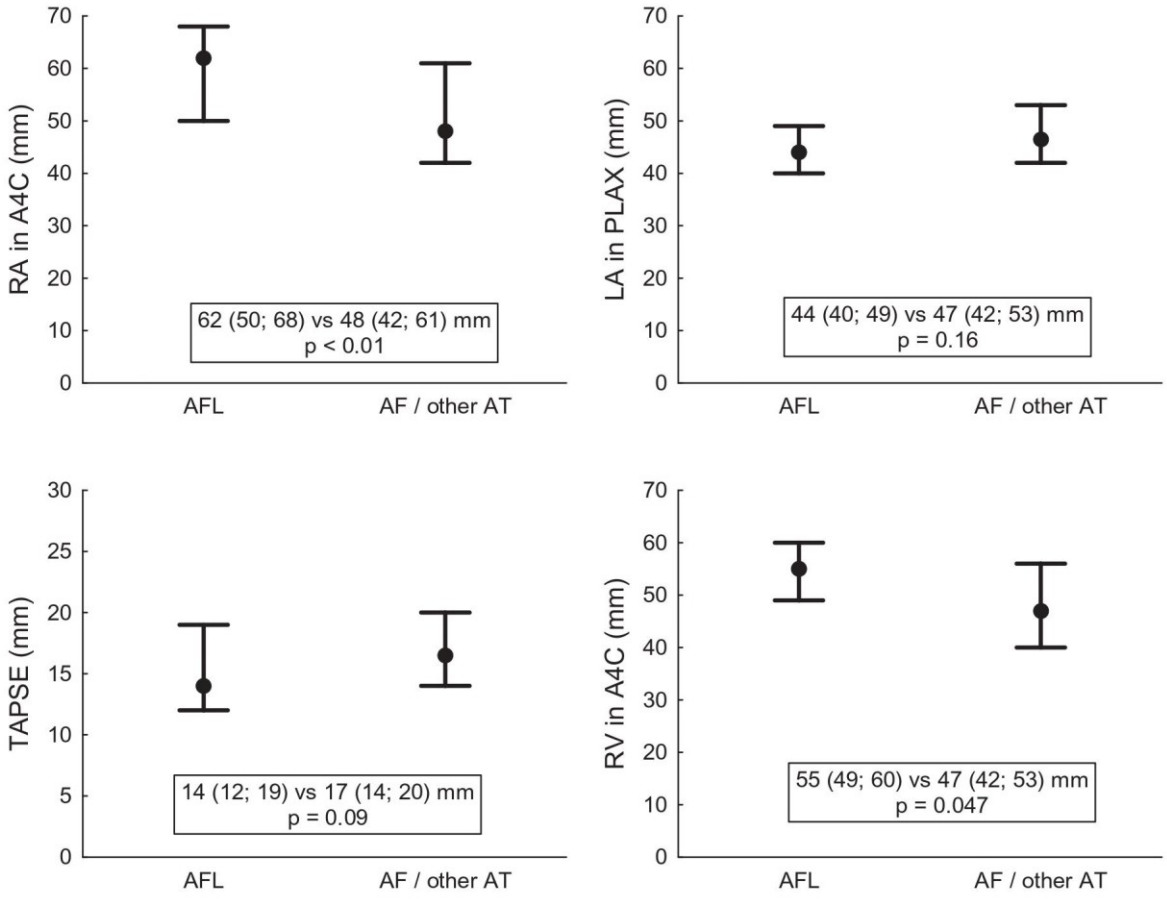

Figure 2 Comparison of patients with Type I atrial flutter and atrial fibrillation or other atrial tachycardia. AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; LA in PLAX, left atrial size in parasternal long-axis view; RA in A4C, right atrium size in apical four-chamber view; RV 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.[12] 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[21,22] 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.[23,24]

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.[25,26] Despite post-operative AF being associated with an increased length of hospital stay and higher rates of complications including mortality,[25,26] the clinical profile of patients with perioperative AT/AF after PEA in our study is similar to patients

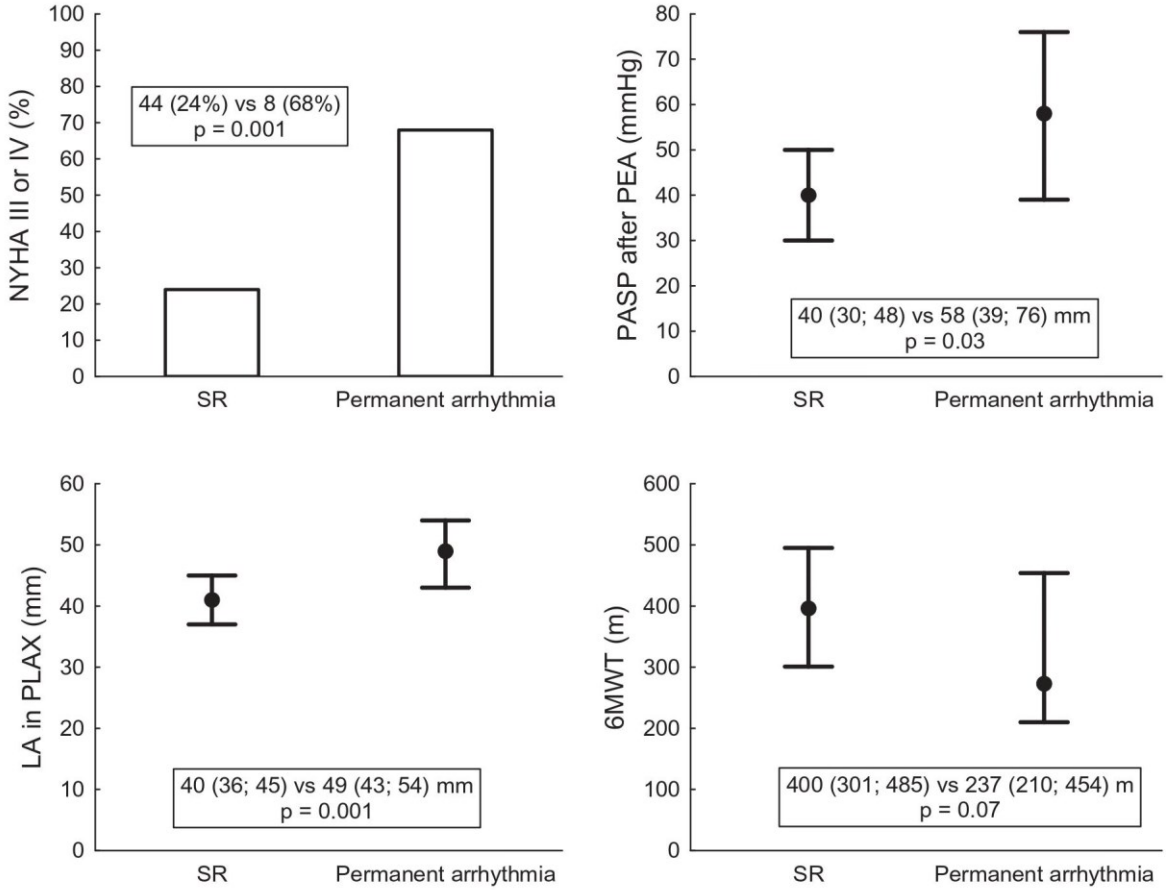

Figure 3 Comparison between patients with permanent arrhythmia and those with sinus rhythm at the end of the follow-up. NYHA, New York Heart Association; LA in PLAX, left atrium in parasternal long-axis view; PASP, pulmonary artery systolic pressure; PEA, pulmonary endarterectomy; SR, sinus rhythm; 6MWT, 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.[6,7,9-11,17] Olsson *et al.*[7] 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.[11] 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.[1,27]

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.

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6.2 Original Article 2: The Role of Pulmonary Artery Wedge Pressure on the Incidence of Atrial Fibrillation and Atrial Tachycardias in Patients with Isolated Pre-capillary Pulmonary Hypertension

The Role of Pulmonary Artery Wedge Pressure on the Incidence of Atrial Fibrillation and Atrial Tachycardias in Patients With Isolated Pre-capillary Pulmonary Hypertension

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Summary

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. 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). 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 mmHg), p<0.05 in all comparisons. 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

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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)

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(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).

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

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.

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 Fig. 3.

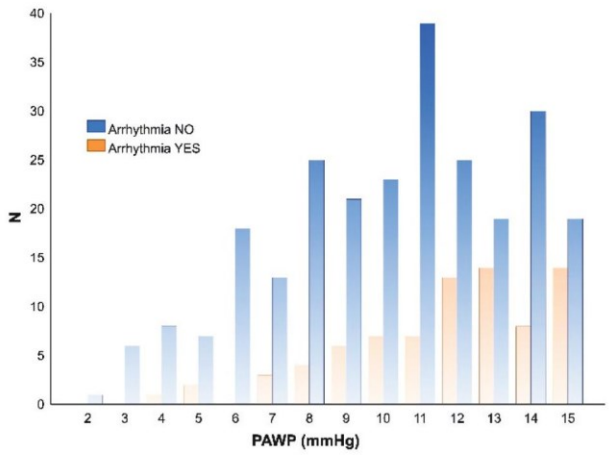

Fig. 1. Proportions of pulmonary artery wedge pressures in patients with and without atrial fibrillation or atrial tachycardia. PAWP – pulmonary artery wedge pressure.

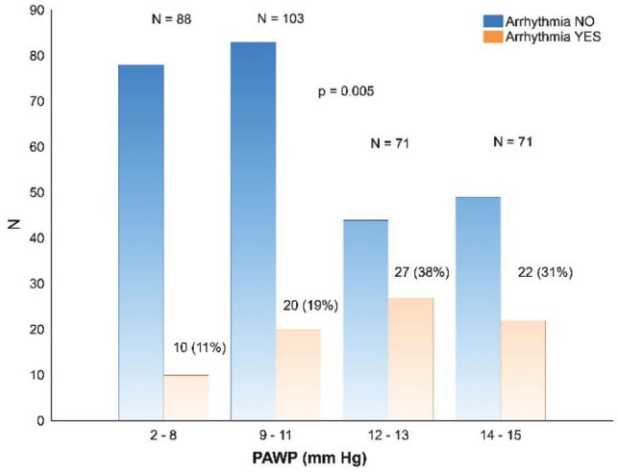

Fig. 2. Proportion of patients with and without atrial fibrillation or atrial tachycardia according to the values of pulmonary artery wedge pressure. PAWP – pulmonary artery wedge pressure.

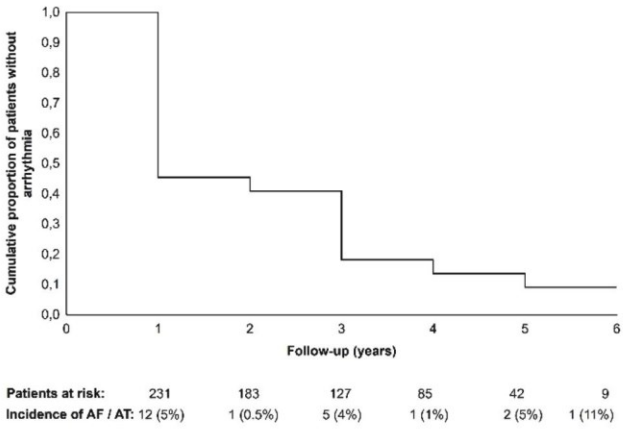

Fig. 3. Annual incidence of arrhythmia during follow-up. AF / AT – atrial fibrillation / atrial tachycardia.

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.

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	136 (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

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 %)	-

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

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.

Conflict of Interest

There is no conflict of interest.

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6.3 Original Article 3: The Impact of Atrial Fibrillation and Atrial Tachycardias on the Hemodynamic Status of Patients with Pulmonary Hypertension

The Impact of Atrial Fibrillation and Atrial Tachycardias on the Hemodynamic Status of Patients with Pulmonary Hypertension

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Summary

The impact of atrial fibrillation and atrial tachycardias (AF/AT), and their optimal treatment strategy in PH patients is still being discussed. The goal of this study was to evaluate the effect of AF/AT termination on the hemodynamic parameters in PH patients. We compared patients with pre-capillary pulmonary hypertension (PH group), left ventricular heart failure (LV-HF group), and a Control group. A repeated right heart catheterization was performed during the catheter ablation (CA) procedure. The first measurement was done in arrhythmia, the second after the sinus rhythm (SR) was restored. High frequency atrial stimulation was used to simulate AT in patients without arrhythmia presence at the time of the CA. The variation of pressure parameters in PH patients did not differ significantly from the Controls. There was a significant increase in the right ventricle pressure after the SR restoration in the LV-HF group compared to the Controls and PH group (+4 vs. -2 vs. -3 mmHg, $p<0.05$). The cardiac index (CI) variation was not significant when compared between the study groups. An increase of the CI after the SR restoration was found in those patients with AF (+0.31 l/min/m² [IQR 0.18; 0.58]) in contrast to those patients with organized AT/high frequency atrial stimulation (-0.09 l/min/m², [IQR - 0.45; 0.19]). This difference was statistically significant ($p<0.05$). The acute hemodynamic response to arrhythmia termination was not significantly different in the PH patients when compared to the Controls. In contrast to AT/high frequency stimulation, the restoration of SR in AF patients leads to an increased CI, irrespective of the presence or absence of PH.

Key words

Pulmonary hypertension • Hemodynamics • Arrhythmia • Atrial fibrillation • Pulmonary artery catheterization

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Introduction

Pulmonary hypertension (PH) is a hemodynamic state defined by a mean pulmonary artery pressure (mPAP) of 25mmHg or more measured at rest, according to the latest ESC guidelines [1]. The worldwide prevalence of PH is estimated to be around 1 % [2]. Irrespective of the concrete cause of PH, it is generally associated with greater morbidity and mortality. Based on its etiology, clinical manifestation, and pathophysiological mechanisms, PH can be divided into 5 groups (pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to lung disease/hypoxia, chronic thromboembolic PH (CTEPH), and PH with unclear/multifactorial mechanisms) [3]. An echo-cardiography is a well-established screening tool for PH [4]. However, a right heart catheterization is required to confirm the diagnose of pulmonary hypertension and to distinguish between precapillary and postcapillary (i.e. connected to the left heart disease) PH [3]. To get reliable results, right heart catheterization should be performed under defined conditions, including sinus rhythm (SR) [5].

Supraventricular arrhythmias (SVTs), including atrial fibrillation (AF) and type 1 atrial flutter (AFL), are common in patients with PH. The prevalence of SVTs in all types of PH varies between 10-36 % [6-12]. A recent

analysis of the registry of patients from our centre showed a very high prevalence of SVTs, mainly permanent AF, in patients with post-capillary PH [8].

According to ESC guidelines, maintenance of a stable SR in all PH patients should be considered as an important treatment goal [3], as the presence of an arrhythmia is often connected with further clinical deterioration and SR restoration can relieve patient's symptoms [7, 9, 10, 13]. Nevertheless, the optimal treatment strategy for SVTs in PH patients has not yet been established due to the lack of robust prospective data [3]. As well as the pharmacological antiarrhythmic treatment, radiofrequency catheter ablation (CA) is currently a safe and effective method for rhythm control in patients with atrial fibrillation and other atrial tachycardias (AF/AT), and is successfully performed in even PH patients [14].

According to our knowledge, the effect of an arrhythmia presence and SR restoration on concrete hemodynamic parameters has not yet been studied in detail. It remains unclear as to whether the rhythm control strategy is hemodynamically beneficial for PH patients, and if it is connected with the cardiac output improvement. For PH patients with persistent arrhythmia, there is a lack of data on performing the hemodynamic assessment and interpreting its results when the examination is done in AF/AT. Therefore, we designed a study with the aim of identifying the differences in intracardiac pressures and cardiac output during CA in PH patients.

Methods

In this prospective observational trial, we compared the acute haemodynamic response to rhythm change in consecutive patients with known precapillary pulmonary hypertension (PH group), patients with the left heart failure (LV-HF group), and a Control group of patients. The trial 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. 15/20). All patients gave written informed consent agreeing to data collection and analysis for scientific purposes.

Subjects

The main inclusion criterion for all subjects was a diagnosis of paroxysmal, persistent or long-standing persistent atrial fibrillation (AF), or atrial tachycardia (AT) including AFL indicated to the treatment by CA based on the current guidelines. We set up the exclusion criteria as follows: an age of less than 18 or over 85 years, the presence of another arrhythmia that makes valid hemodynamical measurement impossible (frequent atrial or ventricular extrabeats, other clinically relevant arrhythmia than AF / AT indicated to CA, stimulated rhythm), significant valvular disease, NYHA IV, cardiogenic shock or severe peripheral oedema, or the non-cooperation of the patient.

For the purpose of our study, precapillary pulmonary hypertension was defined as mPAP $\geq$ 25 mmHg, pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg, and pulmonary vascular resistance (PVR) $\geq$ 3 W.U. measured by right heart catheterization. For the diagnosis of the left heart failure, the presence of both signs (clinical and echo findings, NTpro-BNP elevation) and symptoms (dyspnoea, fatigue, etc.) was required. We did not set any cut-off in left ventricular ejection fraction values, i.e. patients with heart failure with reduced as well as preserved ejection fraction were included. The control group consisted of patients without known pulmonary hypertension, heart failure, or another structural heart disease.

Study procedures

All study procedures were performed during standard hospitalization for CA. At the time of admission, all patients had underwent a complex assessment including personal data and medical history collection, evaluation of symptoms, physical examination by a doctor, and laboratory tests (routine biochemistry, blood count, NT-proBNP). A 12-lead ECG was obtained in every patient.

Hemodynamic measurement:

The main study procedure was a repeated right heart catheterization using the Swan-Ganz catheter (Corodyn TD TouchFree 7F. 110cm, B. Braun, Melsungen AG, Germany) done at the beginning and at the end of the CA. The catheter ablation was performed in a fasting state under mild analgosedation with fentanyl and midazolam. Briefly, in patients with AF, the CA was guided by electroanatomic mapping using a CARTO^{TM} system (Biosense-Webster, Diamond Bar, CA, USA) and intracardiac echocardiography (AcuNav^{TM} catheter, Siemens, Germany) according to

local standards. The double transseptal puncture was used to enter the left atrium (LA). A single 20-polar circular catheter (Lasso™, Biosense-Webster, Diamond Bar, CA, USA) was placed at the ostia of the pulmonary veins (PV) to record PV potentials. An open irrigation 3.5-mm-tip ablation catheter (NaviStar Thermocool, Biosense-Webster) was used both for electroanatomic mapping of the LA and radiofrequency (RF) ablation. The standard procedure consisted of an isolation of the pulmonary veins. A single circumferential set of RF lesions was created point-by-point to isolate ipsilateral pulmonary veins. The extension of ablation of extrapulmonary substrate was left to the operator's discretion. In patients with ATs, the concrete consecution of CA differed according to the exact type and mechanism of arrhythmia. Cavo-tricuspid ablation was done in all patients with typical AFL.

Direct current electrical cardioversion under sedation with propofol using a synchronized biphasic shock with energy 120-200J (according to the discretion of physician) was standardly performed at the end of the CA procedure if the SR was not previously restored. The administration of the antiarrhythmic drugs during the CA was not standardized and depended on the operator's decision.

The first hemodynamic assessment was done in arrhythmia and the second assessment was done after the SR was restored. In patients without the presence of actual arrhythmia during the catheter ablation (mainly patients with paroxysmal arrhythmia), the anterograde Wenckebach point (e. g. the lowest atrial pacing rate at which atrioventricular block is observed) was determined. High frequency atrial stimulation (stimulation rate = Wenckebach point + 10 bpm) was used to simulate the AT with irregular ventricular response.

In each of the measurements we acquired a complete dataset of pressure curves taken from the right atrium (RA), right ventricle (RV), pulmonary artery, and the PAWP curve. The pressure curves were optimally recorded at the end of exhalation during calm breathing. The systolic and diastolic values as well as the mean pressures were deducted. Cardiac output was measured by the thermodilution technique. Standardly, three measurements of the cardiac output were made and the mean value was used for further calculations. In case the variation between the measurements was bigger than 10 %, another measurement was performed and the most distinct value was omitted to reduce possible mistakes. The calculated cardiac index, i.e. cardiac output indexed on the patient's body surface area, was used for statistical analysis instead. Later, the pressure and cardiac index values obtained in the arrhythmia were subtracted from the SR values in order to evaluate the size and significance of the SR restoration on each of the hemodynamical parameters.

Transthoracic echocardiogram:

A transthoracic echocardiogram was performed on the day after the CA. All echocardiograms were performed on Vivid 9 or Vivid E95 ultrasound machines (GE Healthcare, Chicago, IL, USA). Interventricular septal thickness, LV end-diastolic diameter, LV posterior wall thickness, and the left atrial diameter were assessed by 2D measurements in the parasternal long axis view. Left ventricular volumes, the ejection fraction, and the left atrial volume were measured in the apical four chamber view using biplane Simpson's method. Trans-mitral flow and tissue velocities on the mitral and tricuspidal annulus were recorded using a pulsed-wave Doppler. The function of the right ventricle was evaluated using a tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (FAC), and right ventricular free wall strain. The right atrial area was measured in the apical four chamber view, and dimensions of the inferior vena cava were measured using the subxiphoid view. All measurements were performed in accordance with current recommendations [15].

Statistical analysis

The data acquired was statistically analysed using the software Statistica, ver. 12 (StatSoft, Inc., Tulsa, USA). The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. The continuous variables were expressed as medians with interquartile range (IQR). The categorical variables were expressed as a quantity and percentages. Non-parametrical statistical methods were used to evaluate the differences between the groups (U test, F test, Kruskal-Wallis test, Spearman's correlation coefficient). A P-value of < 0.05 was considered as statistically significant.

Results

Subjects' characteristics

The baseline clinical and demographical characteristics of the study groups are summarised in

Table 1. Overall, 27 patients (13 males; age range 41 – 85 years) completed the study. Both the PH group and the LV-HF group finally consisted of 10 subjects, and there were 7 patients in the Control group. Four more patients had to be excluded from the study. One patient did not meet the hemodynamic inclusion criteria, despite the previously known diagnosis of precapillary PH. In one patient the SR restoration during the CA was not successful. In two patients, various technical problems occurred during the hemodynamic assessment leading to the failure of relevant measurements.

Table 1. Baseline study groups characteristics.

	Controls	**PH**	**LV-HF**
No. of subjects	7	10	10
Man / women	5/2	5/5	3/7
Age (years)	55 (47; 60)	72 (67; 76)	66 (60; 69)
Atrial fibrillation (total)	5 (71 %)	6 (60 %)	9 (90 %)
- *Paroxysmal*	4 (57 %)	3 (30 %)	5 (50 %)
- *Non-paroxysmal*	1 (14 %)	3 (30 %)	4 (40 %)
Atrial tachycardia	3 (43 %)	7 (70 %)	3 (30 %)
Arterial hypertension	5 (71 %)	10 (100 %)	8 (80 %)
Diabetes mellitus	0 (0 %)	4 (40 %)	0 (0 %)
Coronary artery disease	1 (14 %)	2 (20 %)	2 (20 %)
CHA_2DS_2 - VASc	1 (1; 2)	4 (3; 5)	4 (3; 4)
NT-proBNP (pg/ml)	185 (152; 247)	883 (747; 1625) *	706 (540; 1859) *
Beta-blocker	5 (71 %)	6 (60 %)	9 (90 %)
Amiodarone / propafenone	3 (43 %)	1 (10 %)	6 (60 %)
CA in sinus rhythm	4 (57 %)	6 (60 %)	5 (50 %)
DC cardioversion during CA	3 (43 %)	8 (80 %)	4 (40 %)
Hemodynamic parameters (sinus rhythm)			
Systolic blood pres. (mmHg)	110 (96; 133)	130 (127; 147)	134 (105; 141)
Diastolic blood pres. (mmHg)	68 (60; 82)	67 (60; 76)	72 (61; 78)
Right atrium mean pres. (mmHg)	12 (7; 18)	20 (17; 23)	21 (15; 24)
Right ventricle mean pres. (mmHg)	20 (17; 24)	31 (26; 32) *	27 (25; 32) *
Pulmonary artery mean pres. (mmHg)	23 (18; 28)	39 (37; 46) *	33 (30; 38) *
Pulm. capillary wedge pres. (mmHg)	17 (12; 21)	21 (20; 23)	25 (20; 29)
Transpulmonary gradient (mmHg)	5 (3; 8)	20 (15; 24) *	8 (3; 12)
Cardiac index ($l/min/m^2$)	2,7 (2,2; 2,9)	2,3 (1,9; 2,5)	2,2 (2,1; 2,7)
Echocardiographic parameters			
Left ventricle EF (%)	61 (57; 62)	70 (64; 72)	56 (47; 62)
Left ventricle EDD (mm)	48 (46; 52)	53 (48; 55)	52 (47; 55)
Left atrium diameter (PLAX)	42 (38; 45)	46 (43; 48)	45 (44; 55)
LAVi (ml/m^2)	47 (45; 53)	43 (32; 54)	47 (42; 70)
TAPSE (mm)	25 (20; 27)	23 (21; 25)	23 (22; 26)
Right ventricle free wall strain (%)	28 (26; 28)	15 (13; 18) *	28 (24; 33)
Right ventricle FAC (%)	53 (51; 56)	32 (28; 36) *	42 (41; 46)
Right ventricle diameter	38 (35; 40)	43 (39; 47)	38 (35; 44)
Right atrium area (cm^2)	20 (18; 23)	24 (22; 26)	21 (19; 26)

Data are expressed as N (%) or median (IQR). *p<0.05. CA – catheter ablation, DC – direct current, EF – ejection fraction, EDD – end-diastolic diameter, FAC – fractional area change, LAVi - indexed left atrial volume by body surface area, pres. – pressure, TAPSE – Tricuspid annular plane systolic excursion

Table 2. Differences between arrhythmia and SR in measured pressure and cardiac index in study groups.

	Controls	PH	LV-HF
RA mean pressure (mmHg)	+2 (-1; +2)	0 (-3; +3)	+2 (0; +4)
RA max pressure (mmHg)	0 (-3; +6)	+4 (-4; +5)	+2 (-1; +6)
RA min pressure (mmHg)	-2 (-6; +2)	+1 (-4; +4)	-1 (-2; +2)
RV mean pressure (mmHg)	-2 (-3; -2)	-3 (-4; -1)	+4 (+1; +6) *
RV max pressure (mmHg)	0 (-6; +2)	+5 (+1; +9)	+4 (+3; +7) *
RV min pressure (mmHg)	+3 (-1; +3)	0 (-2; +2)	+4 (+1; +6)
PA mean pressure (mmHg)	0 (-1; +1)	0 (-2; +3)	+2 (-4; +7)
PA max pressure (mmHg)	-1 (-4; +3)	+2 (-1; +6)	+6 (0; +11)
PA min pressure (mmHg)	0 (-4; +1)	0 (-2; +3)	0 (-7; +5)
PAW mean pressure (mmHg)	-2 (-6; 0)	-1 (-2; 0)	-1 (-2; +2)
PAW max pressure (mmHg)	-2 (-11; -1)	-2 (-5; +2)	+1 (-1; +5) *
PAW min pressure (mmHg)	+2 (0; +4)	+1 (0; +2)	+3 (-2; +4)
Cardiac index (l/min/m^2)	0.14 (-0.48; +0.33)	-0.02 (-0.11; +0.19)	-0.07 (-0.41; +0.29)

Data are expressed as median (IQR). Difference means parameter in SR minus parameter in arrhythmia (i. e. positive value means increase after the sinus rhythm restoration). *p < 0.05. PA – pulmonary artery, PAW – pulmonary arterial wedge, RA – right atrium, RV – right ventricle

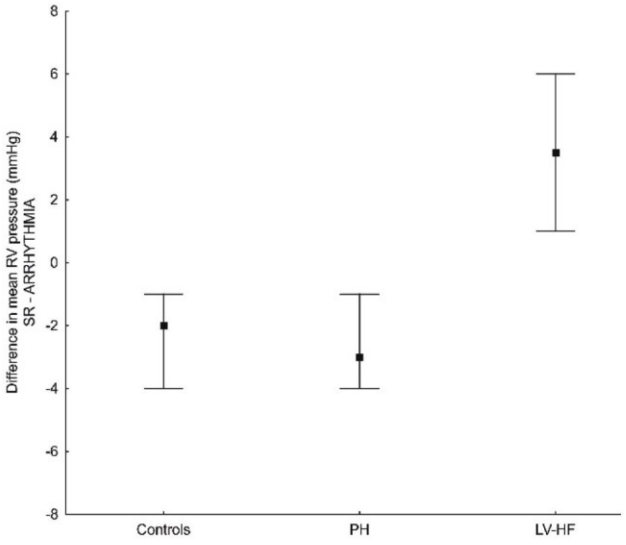

Fig. 1. Difference in mean right ventricular pressure in arrhythmia and in sinus rhythm. Box and whiskers show median and IQR. LV-HF – left heart failure; PH – pulmonary hypertension; RV – right ventricle; SR – sinus rhythm.

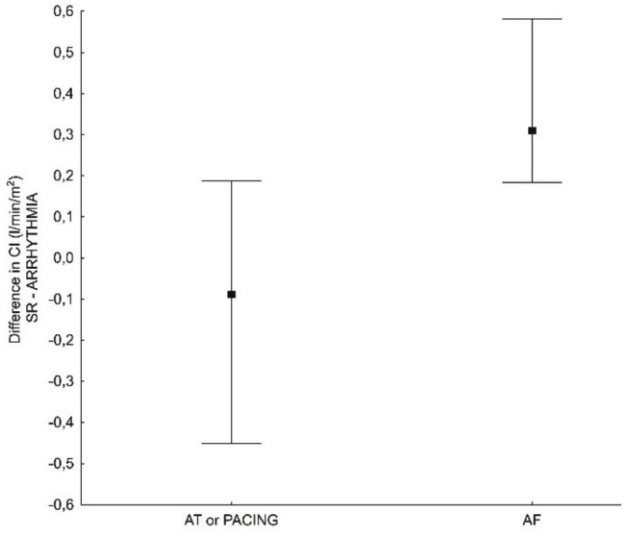

Fig. 2. Difference in cardiac index between arrhythmia and sinus rhythm. Box and whiskers show median and IQR. AF – atrial fibrillation; AT – atrial tachycardia; CI – cardiac index; SR – sinus rhythm.

In the PH group, there were 6 patients with idiopathic PAH, one patient with PAH associated with connective tissue disease, 2 patients with inoperable CTEPH, and one patient had residual PH after the pulmonary endarterectomy. The LV-HF group contained 1 patient with heart failure with reduced ejection fraction, 3 patients with heart failure with mildly reduced ejection fraction, and 6 patients with preserved ejection fraction. As we can see in Table 1, patients in the Control group were significantly younger and their NT-proBNP levels were lower.

The echo parameters used for the evaluation of the right ventricle systolic function were significantly decreased in the PH group (RV fractional area change (p=0.004), RV free wall strain (p=0.01)). There was no significant difference in other echocardiographic characteristics across the groups.

Hemodynamic measurement

Overall, in 15 patients the CA was started in the SR. 6 patients presented with the AF, and AT was the first recorded rhythm during the CA procedure in 6 patients.

The pulmonary artery and right ventricle pressures were significantly higher in the PH and LV-HF groups compared to the control group. The PH patients differed from the rest of the study population with a significantly higher transpulmonary gradient. Other resulting hemodynamical parameters were comparable, as listed in Table 1.

The magnitudes of the changes in particular hemodynamic parameters after restoration of SR are described in Table 2. Overall, the studied parameters did not vary significantly between our study groups, except the different dynamics of the RV mean pressure. In the controls and PH patients, the RV mean pressure slightly decreased in SR after arrhythmia termination. In the LV-HF group, an increase of the mean and maximal RV pressure was detected in SR. This difference reached statistical significance ($p<0.05$) (Table 2, Fig. 1).

In patients with organized AT (or high frequency atrial stimulation), the CI remained the same in the arrhythmia (pacing) and in SR (CI difference -0.09 (-0.45; +0.19) l/min/m^2). This data contrasted with the significant rise of CI after the SR restoration in AF patients (CI difference +0.31 (+0.18; +0.58) l/min/m^2). The disparity between CI change in AF and AT (pacing) patients was significant ($p < 0.05$), and this reaction was uniform in each of our three groups (Fig. 2).

Discussion

The presence of an AF/AT affects the hemodynamical state through numerous mechanisms. SVTs generally lead to a faster heart rate, irregular ventricular contractions, and diminished contractile function of the atria resulting especially in an impaired ventricular filling [16].

Right heart catheterization is required to confirm the diagnosis of pulmonary hypertension [3] and it should be performed under defined conditions to obtain reliable results [5]. In our clinical practice, we attempt to restore the SR before the planned right heart catheterization. However, this is not always feasible and mainly in patients with longstanding persistent or permanent AF/AT we are forced to perform the assessment during arrhythmia, which can lead to distorted results. For example, it has already been proven that the relationship between the PAWP and the left ventricular end-diastolic pressure (LVEDP) depends on the heart rhythm. In AF patients, the PAWP is higher than LVEDP. This can produce significant mistakes when distinguishing between pre-capillary and post-capillary PH [17]. Although an acute effect of cardioversion or CA is not known, hemodynamics is frequently evaluated immediately after the restoration of SR in routine clinical practice.

To be thorough, we decided to compare the data obtained for the population of interest, i.e. patients with a pre-capillary PH, not only with a Control group, but also with an added LV-HF group representing patients with a post-capillary PH, typically evaluated in cath labs. As expected, the Control group consists of younger patients with low NT-proBNP values, which documents the absence of any other heart disease except AF/AT. In each of our three groups, the median PAWP was higher than 15mmHg, which is arbitrarily set as a cut-off value for distinguishing between pre-capillary and post-capillary PH. We assume that this can be caused by the applied study protocol, when the right heart catheterization in the SR was performed at the very end of the CA procedure, which is always connected with significant intravenous fluid intake. Extensive RF lesion creation and atrial stunning after periprocedurally performed DC version, could also lead to increased PAWP. On the other hand, there is some evidence that the tendency to higher PAWP values could be typical for pre-capillary PH patients who suffer from recurrent arrhythmias. In previous works from our centre we have documented the important role of the LA substrate in arrhythmogenesis in PH patients and an increased incidence of SVTs in pre-capillary PH patients with near to elevated PAWP [18, 19].

Both the PH and LV-HF groups fulfil the PH criteria with mPAP of 25mmHg and more. However, the high PAWP with low transpulmonary gradient value (TPG) in the LV-HF group emphasises the impact of the post-capillary component. In the Control group, the mPAP values were higher than expected, although not reaching the criteria for PH presence. With a TPG being low, this is mainly caused by an observed higher PAWP, as already discussed above.

According to our measurement, there were generally only slight differences between the hemodynamical parameters measured in the SR and arrhythmia. It is questionable how much this is caused by the short-term design of our study. It has already been

proven that the real mechanical function of the atrium lags behind the actual electrical activity, and atrial stunning after the DC cardioversion is a generally known phenomena. There is data proving that the full recovery of mechanical atrial function can take up to even one month in patients with prolonged AF [20]. In other words, we assume that the hemodynamic characteristics could become more distinct if those two hemodynamical assessments were performed with a greater time interval. However, further studies are needed to prove this theory.

The hemodynamic reaction of the PH patients to the SR rhythm restoration did not differ significantly from the Control group. In the LV-HF group, the RV pressure after the SR restoration increased significantly compared to the Control and PH group. We believe that the presence of AF/AT in patients with a chronic heart failure leads to decreased pressures in the pulmonary circulation, being parallel to a decrease of the systemic arterial pressure, which is attributed mainly to the lack of atrial contraction and impaired diastolic filling of the ventricle because of the tachycardia and irregular heart rate [21, 22]. It is probable that patients in the Control group, who do not suffer from any other cardiac disease than arrhythmia, can handle the presence of arrhythmia better and maintain the values of both systemic and pulmonary pressures. The reason for the absence of a significant variation of the chronically elevated RV pressure in the PH patients is probably different. In those patients, pulmonary pressures are mainly determined by a pathological remodelling of pulmonary vessels and the presence or absence of arrhythmia is not significant enough to affect it.

The CI did not change significantly in any of our groups after the SR restoration. However, we observed a significant increase of the CI when we analysed the data of patients with AF regardless of the concrete study group. This is well in line with the currently available literature data proving the significant reduction in CI in patients with chronic AF and a heart failure [23, 24]. On the other hand, we did not observe the improvement of CI after the arrhythmia termination in patients with other AT except AF. We assume that the organized ATs do not have such a negative impact on CI, because of the absence of several features which are usually put into context with impaired diastolic filling of the ventricle and therefore decreased CI in AF. ATs differs from AF by the more organized mechanical activity of atria leading to much more regular ventricular response. This means avoidance of excessive tachycardia with very short cycles, and probably the preservation of some atrial contribution even in running AT, at least in some patients [16, 25]. The dependence of cardiac output on heart rate can be described as an inverted U-shape. By other words, cardiac output increases to a maximum with increasing HR and then declines with further HR increase [26]. Therefore, certain “reasonable” tachycardia can play an important role in preserving cardiac output when the function of the ventricle is reduced. This is a possible explanation of the decrease in the cardiac output after the SR restoration that was observed in some patients with AT. Those findings corroborate the importance of rhythm control strategy in patients with atrial fibrillation.

An echo was performed standardly on the day after CA in order to avoid the distortion possibly caused by intravenous fluid intake during the CA and to maximize the portion of patients examined in the SR. TAPSE as a standardly used parameter for assessment of the right ventricle systolic function did not differ between our groups. However, other parameters characterising the systolic function of the RV – the FAC and the free wall strain - were significantly decreased in the PH group. Those findings corroborate the use of the RV FAC and the RV free wall strain, instead of TAPSE for monitoring PH patients [27, 28].

The main limitations of our study are its single-centre and short-term design. The hemodynamic response to the arrhythmia termination would have become more pronounced if the second assessment had been performed in a greater time interval. Nevertheless, this would mean the necessity of performing a second invasive procedure only for the purpose of this study, which we found ethically unacceptable. Also, the continuous invasive arterial pressure monitoring during the procedure could have provided important data but was not performed in order to not further increase the risk for the patient connected with the participation in this study.

Conclusion

The presence of AF/AT affects the hemodynamic state of the patient. The hemodynamic response to the arrhythmia termination was not significantly different in the PH patients compared to the Control group. There was a significant increase in the RV pressure after the SR restoration in the LV-HF group. The SR restoration improved the CI in AF patients emphasizing the rhythm control strategy. In patients with organized AT, the CI did not change significantly.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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6.4 Original Article 4: Catheter ablation of atrial fibrillation and atrial tachycardia in patients with pulmonary hypertension: a randomized study

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CLINICAL RESEARCH

Catheter ablation of atrial fibrillation and atrial tachycardia in patients with pulmonary hypertension: a randomized study

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Aims Atrial fibrillation (AF), typical atrial flutter (AFL), and other atrial tachycardias (ATs) are common in patients with pulmonary hypertension. Frequently, several supraventricular arrhythmias are successively observed in individual patients. We investigated the hypothesis of whether more extensive radiofrequency catheter ablation of the bi-atrial arrhythmogenic substrate instead of clinical arrhythmia ablation alone results in superior clinical outcomes in patients with pulmonary arterial hypertension (PH) and supraventricular arrhythmias.

Methods and results Patients with combined post- and pre-capillary or isolated pre-capillary PH and supraventricular arrhythmia indicated to catheter ablation were enrolled in three centres and randomized 1:1 into two parallel treatment arms. Patients underwent either clinical arrhythmia ablation only (Limited ablation group) or clinical arrhythmia plus substrate-based ablation (Extended ablation group). The primary endpoint was arrhythmia recurrence >30 s without antiarrhythmic drugs after the 3-month blanking period. A total of 77 patients (mean age 67 ± 10 years; 41 males) were enrolled. The presumable clinical arrhythmia was AF in 38 and AT in 36 patients, including typical AFL in 23 patients. During the median follow-up period of 13 (interquartile range: 12; 19) months, the primary endpoint occurred in 15 patients (42%) vs. 17 patients (45%) in the Extended vs. Limited ablation group (hazard ratio: 0.97, 95% confidence interval: 0.49–2.0). There was no excess of procedural complications and clinical follow-up events including an all-cause death in the Extended ablation group.

Conclusion Extensive ablation, compared with a limited approach, was not beneficial in terms of arrhythmia recurrence in patients with AF/AT and PH.

Clinical Trials Registration ClinicalTrials.gov; NCT04053361.

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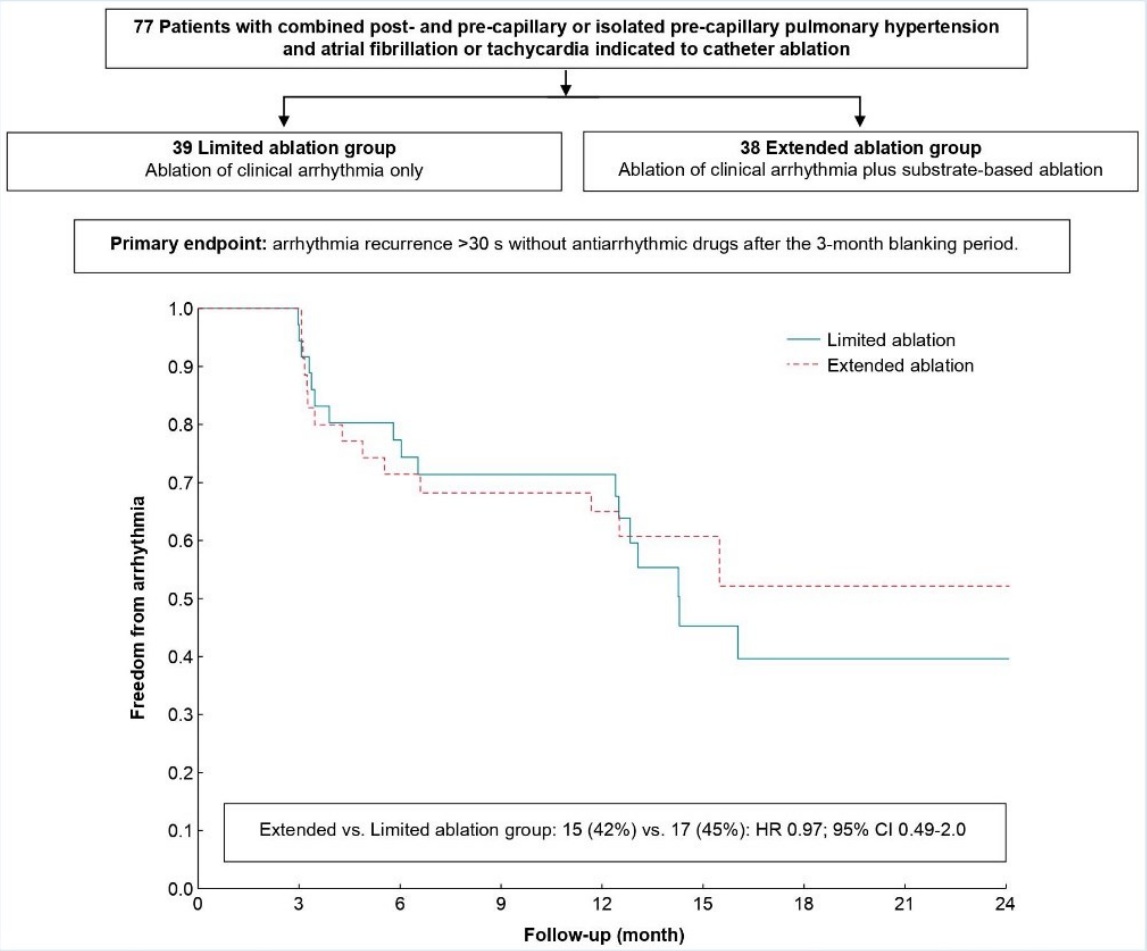
Graphical Abstract



Keywords Atrial fibrillation • Atrial tachycardia • Catheter ablation • Pulmonary hypertension

What's New?

- Extensive catheter ablation does not reduce arrhythmia recurrence in patients with pulmonary hypertension and atrial fibrillation/tachycardia.
- Despite enormous right atrial enlargement, regions with low-voltage and/or abnormal atrial electrograms are rare in patients with pulmonary hypertension.

Introduction

Various treatment strategies have been established in patients with pulmonary arterial hypertension (PH) that improve haemodynamics, exercise capacity, and quality of life.[1,2] Despite those advancements, PH is still a progressive disease with a generally inauspicious prognosis.

Supraventricular tachycardias (SVTs) have been frequently observed with a cumulative incidence of 10–29% in patients with both idiopathic[3] and secondary PH,[4–7] including chronic thromboembolic pulmonary hypertension, either inoperable[4,6] or treated with pulmonary endarterectomy.[8] The SVTs are associated with clinical deterioration and adversely impact the prognosis.[3,4,6,9] Conversely, maintenance of sinus rhythm (SR) appeared to improve the clinical outcome.[3,6,10] However, antiarrhythmic drugs may not be a feasible option because of their negative inotropic properties and interaction with specific therapy for PH.[11,12]

Radiofrequency catheter ablation (RFCA) of typical atrial flutter (AFL), atrioventricular nodal re-entrant tachycardia (AVNRT), and other focal or macroreentrant atrial tachycardias (AT) was reported to be effective (acute success rate of 86–100%) and safe in patients with PH according to retrospective studies with a limited number of patients.[5,10,13–16] However, the long-term results were much less favourable with freedom from arrhythmia in only 50–78% of patients.[13,14,16] Importantly, new-onset arrhythmias (different than their index SVT) were observed in 30–48% of recurrent cases.[13,14]

Although typical AFL can frequently be found as the first manifestation of SVT in patients with PH, atrial fibrillation (AF) is even more prevalent.[3–6] In this respect, data on the optimum rhythm control strategy of AF/AT, including RFCA, is lacking. Given the knowledge of the sequential manifestation of different SVTs in individual patients, it was plausible to hypothesize that first-line bi-atrial RFCA of all potentially arrhythmogenic substrates (i.e. not only ablation for index arrhythmia) could reduce the risk of arrhythmia recurrence and improve the clinical

outcomes compared to procedure targeting the clinical arrhythmia only. We investigated this hypothesis in a randomized fashion.

Methods

The study was a multicentre, parallel-group, open-label, randomized trial. It was performed according to good clinical practice and in compliance with the Helsinki declaration. The multicentric and local Ethics committees at all centres approved the study protocol. Individual written consent was obtained from each patient. The trial protocol is available in Supplementary material online, *Appendix S1*.

Patients

Participants were men or women, 18 years of age or older, who had pre-capillary or combined post- and pre-capillary PH of any aetiology, and documented symptomatic AF (paroxysmal, persistent, or long-standing persistent) or AT (typical AFL included) who were indicated for RFCA according to clinical practice guidelines.[17] Patients were excluded if they had any condition that might jeopardize patient safety or limit their participation in the study. The key exclusion criteria were complex congenital heart defects (corrected or uncorrected), isolated post-capillary PH, previous RFCA for AF, AT or AFL, NYHA Class IV, and life expectancy <1 year.

Study procedures and follow-up

Covariate adaptive 1:1 randomization was used to allocate enrolled patients into two parallel treatment arms to undergo clinical arrhythmia ablation only (Limited ablation group) or clinical arrhythmia plus substrate-based ablation (Extended ablation group). Covariates were applied as follows: age, gender, type of PH, and clinical arrhythmia.

Electrophysiological study

Patients were treated under conscious sedation or general anaesthesia at the discretion of the operator. The procedure was done on uninterrupted oral anticoagulation with the international normalized ratio between two and three in patients on vitamin K antagonists. In patients on direct oral anticoagulants, only the morning dose on the day of the procedure was omitted. All procedures were done under visual control of intracardiac echocardiography. Heparin was administered before transseptal puncture, and the doses were adjusted to achieve an activation clotting time of >300 s during the procedure.

In patients with SR at baseline, arrhythmia was induced by programmed, incremental, or burst atrial pacing. If present or induced arrhythmia differed from an arrhythmia that was documented non-invasively before the enrollment, the decision on what is 'clinical' arrhythmia was made by the operator. Point-by-point electroanatomical maps of both right (RA) and left (LA) atrium, each with a minimum of 100 mapping points, were acquired in consistent rhythm (SR/AF/AT) for meaningful assessment of low-voltage zones (CARTO 3, Biosense-Webster). Two-level quantification (bipolar voltages either <0.1 or <0.5 mV in SR; and either <0.04 or <0.2 mV in AF/AT) of low-voltage zones was applied separately for RA and LA.

Catheter ablation

Initial treatment was identical in both study arms. If clinical arrhythmia was fairly documented AF or typical AFL, pulmonary vein isolation (PVI) or cavotricuspid isthmus (CTI) ablation was performed. If AF persisted after PVI, electrical cardioversion was performed. When clinical arrhythmia was AT, it was induced (if not persistent), identified using activation and/or entrainment mapping, and ablated.

In patients in the Limited ablation group, no ablation was performed if AT was not inducible or if incidental (or induced) ATs were considered non-clinical. After clinical arrhythmia ablation, no induction protocols were attempted unless the non-inducibility was the principal endpoint of arrhythmia ablation, like in the case of AVNRT or microreentrant AT.

In patients in the Extended ablation group, substrate-based ablation continued after the initial ablation steps described above. This consisted of empirical lesion set within RA: superior vena cava (SVC) isolation, posteroseptal intercaval line, and CTI ablation (if not already done) and homogenization of low-voltage zones (if any) in LA/RA defined by bipolar voltage <0.5 mV in SR or <0.2 mV in AF/AT. These cut-off voltages were adapted (set lower) in severely diseased atria to identify reasonably smaller zones (<20% of the atrial surface) that were feasible to ablate. Arrhythmia induction protocol was performed consisting of 10-s burst atrial pacing with a cycle length of 300 ms decremented by 10 ms up to 1:1 atrial capture or cycle length of 200 ms. Induced ATs were mapped and ablated if feasible. In the case of inducible AF with a duration of >5 min, PVI was performed if not previously done as per protocol.

Follow-up and study objectives

During regular follow-up visits at 3-month intervals, symptoms and relevant clinical events were collected, and standard ECG was recorded. All class Ic or III antiarrhythmic drugs were discontinued at Month 3. Persistent arrhythmia (if observed at Month 3) was electrically cardioverted. Seven-day ECG monitoring was done 6 and 12 months after RFCA, and additional ECG monitoring was scheduled in patients with symptoms suggestive of non-documented arrhythmia. In case of arrhythmia recurrence, antiarrhythmic drugs were initiated and a repeated RFCA was considered.

The primary endpoint of the study was documented arrhythmia recurrence >30 s without antiarrhythmic drugs after the 3-month blanking period after the index ablation. Secondary endpoints were set up as follows: documented on-drugs arrhythmia recurrence, symptoms of arrhythmia, number of emergency visits, number of hospitalizations, mortality, procedure-related major complication rate, antiarrhythmic drugs, re-ablation, pacemaker implantation, and atrioventricular junction ablation. Major procedural complications were defined as events that occurred within 30 days of the ablation, were clearly or could probably be related to the procedure, and resulted in long-term disability, requiring intervention or prolonging hospitalization.

Statistical analysis

An independent statistician replicated and verified the analyses. All study objectives were analysed by standard statistical methods (*t*-test or Mann–Whitney U test for continuous variables or a Chi-square or two-tailed Fisher exact test for categorical variables). Time-to-event data were investigated by Kaplan–Meier analysis with log-rank statistics and by multivariate Cox regression models. A *P*-value <0.05 was considered significant. All analyses were performed using the STATISTICA vers.12 software (StatSoft, Inc., Tulsa, USA).

Results

From May 2018 to August 2021, a total of 77 patients (42 males) with a median age of 70 [interquartile range (IQR): 61; 75] years were enrolled at three sites in the Czech Republic. Thirty-nine patients were treated in the Limited ablation group, and 38 patients were treated in the Extended ablation group. At the time of randomization, the presumable clinical arrhythmia was AF in 38 and AT in 36 patients, including typical AFL in 23 patients (*Table 1*). One patient in the Limited ablation group (with left atrial appendage thrombosis) and two patients in the Extended ablation group (one with severe mitral regurgitation, and one who declined to participate) were later excluded (consort diagram, *Figure 1*). The baseline characteristics of the 74 patients who were scheduled for RFCA are shown in *Table 1*.

At the beginning of the index RFCA, arrhythmia different from that during the screening was seen in 5 of 38 and 8 of 36 patients from the Limited and Extended ablation groups, respectively. During the procedure, multiple distinct SVTs were observed in 5 and 4 patients from the Limited and Extended ablation groups, respectively.

In the Limited ablation arm, the RFCA procedure was completed per protocol in 36 (95%) out of the 38 patients. In one patient with enormous RA dilatation, transseptal puncture failed and CTI ablation only was performed. In another patient, extreme venous tortuosity prevented catheter insertion from the groin access. The RFCA was extended beyond assumed clinical arrhythmia in eight (21%) patients. This was done mainly because of conversion of the initial arrhythmia to a different one (three cases), spontaneous onset or induction of

Table 1 Baseline characteristics

	All patients $n = 74$	Limited ablation group $n = 38$	Extended ablation group $n = 36$	P
Age (years)	71 (61; 75)	70 (61; 75)	71 (60; 74)	NS
Males	41 (55%)	24 (63%)	17 (47%)	NS
Aetiology of PH				
– Idiopathic	41 (55%)	23 (61%)	18 (50%)	NS
– Chronic thromboembolic	22 (30%)	10 (26%)	12 (33%)	NS
– Lung disease/hypoxia	11 (15%)	5 (13%)	6 (17%)	NS
Index arrhythmia				
– Atrial fibrillation	38 (51%)	19 (50%)	19 (53%)	NS
– Paroxysmal	11 (15%)	6 (16%)	5 (14%)	NS
– Persistent	22 (30%)	10 (26%)	12 (33%)	NS
– Long-standing persistent	5 (7%)	3 (8%)	2 (6%)	NS
– Atrial tachycardia	36 (49%)	19 (50%)	17 (47%)	NS
– Typical atrial flutter	23 (31%)	12 (32%)	11 (31%)	NS
Symptoms of arrhythmia				
– Palpitation	28 (38%)	13 (34%)	15 (42%)	NS
– Dyspnea	47 (64%)	24 (63%)	23 (64%)	NS
– Peripheral oedema	26 (35%)	12 (32%)	14 (39%)	NS
Comorbidities				
– Arterial hypertension	59 (80%)	31 (82%)	28 (78%)	NS
– Diabetes mellitus	26 (35%)	12 (32%)	14 (39%)	NS
– Coronary artery disease	14 (19%)	5 (13%)	9 (25%)	NS
– Stroke/transient ischaemic attack	6 (8%)	4 (11%)	2 (6%)	NS
CHA_2DS_2-VASc score	3 (2; 4)	3 (2; 4)	3 (2; 4)	NS
HAS-BLED score	1 (0; 1)	1 (0; 1)	1 (0.5; 1)	NS
Treatment				
– Amiodarone	14 (19%)	8 (21%)	6 (17%)	NS
– Propafenone	3 (4%)	2 (5%)	1 (3%)	NS
– Sotalol	2 (3%)	1 (3%)	1 (3%)	NS
– Beta-blockers	27 (36%)	13 (34%)	14 (38%)	NS
– Warfarin	37 (50%)	18 (47%)	19 (53%)	NS
– Direct oral anticoagulants	31 (42%)	18 (47%)	13 (36%)	NS
– Specific therapy for PH	26 (35%)	14 (37%)	12 (33%)	NS
Functional status				
– NYHA I	0	0	0	NS
– NYHA II	17 (23%)	9 (24%)	8 (22%)	NS
– NYHA III	57 (77%)	29 (76%)	28 (78%)	NS
– NYHA IV	0	0	0	NS
– 6-minute walking test (m)	369 (280; 422)	363 (280; 413)	376 (300; 436)	NS
EQ-VAS	58 (40; 72)	56 (34; 74)	60 (42; 70)	NS
Laboratory				
– NT-proBNP (pg/mL)	1267 (732; 2317)	903 (724; 1979)	1587 (922; 3182)	NS
– Haemoglobin (g/L)	138 (128; 148)	145 (135; 148)	131 (117; 147)	NS
– Creatinine (μmol/L)	94 (80; 113)	95 (81; 112)	94 (73; 114)	NS
Echocardiography				
– LV end-diastolic diameter in PLAX (mm)	49 (44; 54)	49 (45; 54)	49 (44; 54)	NS
– LV ejection fraction (%)	60 (55; 63)	60 (55; 62)	60 (56; 64)	NS

Continued

Table 1 ***Continued***

	All patients $n = 74$	Limited ablation group $n = 38$	Extended ablation group $n = 36$	P
– LA indexed volume (mL/m^2)	41 (31; 50)	39 (28; 51)	43 (32; 50)	NS
– RA diameter in A4C (mm)	53 (46; 59)	51 (46; 59)	54 (47; 59)	NS
– RV diameter in A4C (mm)	48 (41; 53)	49 (41; 52)	48 (42; 56)	NS
– Tricuspid annular plane systolic excursion (mm)	18 (14; 20)	17 (14; 20)	19 (14; 20)	NS
– Pulmonary artery systolic pressure (mmHg)	69 (50; 84)	72 (55; 87)	64 (48; 82)	NS
– LA appendage emptying velocity (m/s)	0.45 (0.34; 0.70)	0.49 (0.38; 0.70)	0.40 (0.30; 0.70)	NS
Haemodynamics				
– RA mean pressure (mmHg)	11 (6; 16)	13 (8; 18)	9 (5; 12)	0.02
– Pulmonary artery mean pressure (mmHg)	46 (38; 55)	47 (38; 54)	45 (36; 55)	NS
– Pulmonary capillary wedge pressure (mmHg)	11 (9; 15)	12 (10; 19)	11 (9; 13)	NS
– Cardiac index (L/min/m^2)	2.4 (2.0; 2.9)	2.35 (2.0; 2.8)	2.4 (2.0; 2.9)	NS

Data represent the number of cases (percentage) or median (interquartile range).
A4C, apical four-chamber view; EQ-VAS, European Quality of Life Group instrument self-report questionnaire visual analogue scale; NS, not significant; LA, left atrium; LV, left ventricle; PH, pulmonary hypertension; PLAX, parasternal long axis view; RA, right atrium; RV, right ventricle.

>1 arrhythmia during the procedure (two cases), and history of two clinically relevant arrhythmias in three cases, more details are in Supplementary material online, *Table S1*.

In the Extended ablation group, the RFCA procedure was completed per protocol in 33 (92%) out of 36 patients. Despite being assigned to extensive ablation, no RFCA was done in one patient without inducibility of any clinically relevant arrhythmia and lack of clear arrhythmogenic substrate. In two more patients, CTI block was not unequivocally demonstratable.

The RA lesions were significantly less frequently done in the Limited than in the Extended ablation group [22 (58%) vs. 33 (92%); $P < 0.001$]. The difference was mainly driven by the completion of per-protocol lesion set on top of CTI ablation (SVC isolation, posteroseptal intercaval line, and homogenization of low-voltage zones). On the other hand, the extent of LA lesions was comparable between the study groups. Electrical cardioversion for AF during the procedure was performed more often in the Limited than in the Extended ablation group [10 (26%) vs. 4 (11%) patients; $P = 0.04$]. Compared to patients in the Limited ablation group, procedural time and radiofrequency time were significantly prolonged in the Extended ablation group. The procedural details including performed lesions in both groups are provided in *Table 2* and Supplementary material online, *Table S1*.

The median duration of the follow-up period was 13 (IQR: 12; 18) months in the Limited ablation group and 14 (IQR: 12; 21) months in the Extended ablation group. The primary endpoint occurred comparably in 15 patients (42%) vs. 17 patients (45%) in the Extended vs. Limited ablation group [hazard ratio (HR): 0.97, 95% confidence interval (CI): 0.49–2.0], *Table 3*, *Figure 2*.

The secondary endpoints analysis is shown in *Table 3*. There were no other significant differences between the study groups except for the antiarrhythmic medication after the blanking period that was more frequently used in the Limited ablation group. There were 10 (28%) vs. 9 (24%) deaths in the Extended vs. Limited ablation group (HR: 0.92, 95% CI: 0.36–2.32). Corresponding Kaplan–Meier curves are presented in *Figure 3*.

Manifestation of new arrhythmia (different from all arrhythmias previously noticed) was seen in 9/31 patients with arrhythmia recurrence during the follow-up: 6 and 3 patients in Extended and Limited ablation groups, respectively. Typical AFL did not reoccur during the follow-up. Out of four patients with documented arrhythmia after CTI ablation, two had AF and two patients manifested atypical AFL (see Supplementary material online, *Table S2*).

Clear procedure-related complications were recognized in three patients: a prolonged severe vagal reaction during sheath removal at the end of the procedure with the necessity of short cardiopulmonary resuscitation, periprocedural progression of conservatively treated pericardial effusion, and surgically treated arteriovenous fistula. Three more adverse events could probably be related to RFCA. Of them, two patients manifested low cardiac output after RFCA, which led to prolonged hospitalization in one patient and slow progression to terminal heart failure and death in the second patient. One patient died suddenly (pulseless electrical activity) 1 day after the ablation of AVNRT without evidence of any periprocedural complication as assessed by autopsy. Hypoxia and end-stage heart failure were most likely responsible for this event. The other three patients manifested severe sinus bradycardia and sinus arrest episodes after the termination of persistent arrhythmia; however, ablation in these patients was not done in proximity to the sinus node. Major procedural complications and serious adverse events in the study are in more detail shown in Supplementary material online, *Table S3*.

Discussion

In this first multicentre randomized trial in a patient population with AF/AT and PH, extensive RFCA, compared with a limited approach, did not significantly reduce the recurrence of arrhythmia, symptoms, cardiovascular hospitalizations, and mortality.

Several retrospective studies with a limited number of patients have reported that RFCA of typical AFL or other less complex SVT was feasible, acutely effective, and safe in patients with PH.[5,6,10,13–16] Long-term clinical outcome after RFCA, however, was found to be less optimistic and more divergent. Bradfield *et al.*[13] reported that only 5 of 10 patients with acutely successful CTI ablation were completely arrhythmia-free at 3 months and three patients had recurrent arrhythmias different from their initial typical AFL. In 23 patients ablated for typical AFL and other organized SVTs, arrhythmia occurred in 12 patients during a 5-year follow-up, of whom the new onset of arrhythmia was seen in 10 cases.[14] On the contrary, a more favourable outcome was found in the recent retrospective study in 32 patients with successful ablation of typical AFL, who had a recurrence rate of ~20% during a follow-up of 3–108 months. However, the proportion of recurrence of index arrhythmia and onset of new arrhythmias was not provided.[16]

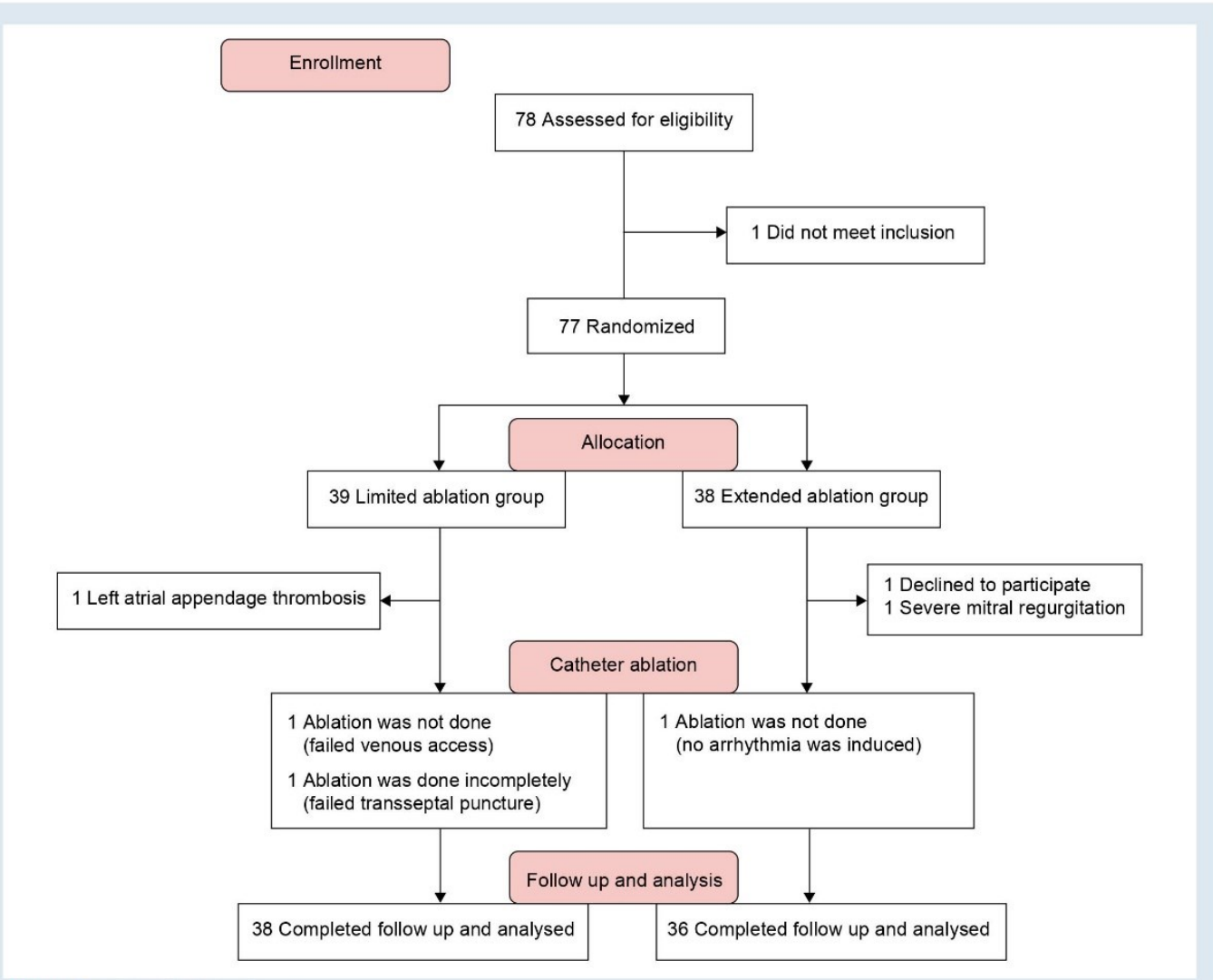


Figure 1 CONSORT flow diagram.

In our study, we prospectively evaluated the clinical outcome of two ablation strategies in PH patients with various types of supraventricular arrhythmia. The extensive ablation was intended to reduce a long-term arrhythmia recurrence rate by ablation of all inducible arrhythmias, including those that did not manifest clinically prior to the procedure, and by preventative modification of arrhythmogenic substrate for potentially new and currently non-inducible arrhythmias. Unlike previous studies, we also enrolled patients with AF.

The relatively high arrhythmia recurrence rate after the RFCA for AF/AT in patients with PH in both study arms was comparable to that in non-paroxysmal AF in non-PH patients with a low prevalence of structural heart disease.[18–20] A recent meta-analysis reported a pooled median success rate of 66.7% (95% CI 60.8–72.2%) after the single RFCA for non-paroxysmal AF.[18] Beyond PVI, a range of trigger and left atrial substrate modification ablation strategies have been proposed to improve success in non-paroxysmal AF. However, the randomized controlled trial STAR AF II indicated that adjunctive RF ablation strategies did not improve outcomes over PVI alone but were associated with higher fluoroscopy and procedure times.[19] Our study investigated different population of patients with highly suspected right over left atrial arrhythmogenic substrate because of right-sided pressure and volume overload, so tailored targeting of right atrial arrhythmogenic substrate seemed justified. Our study also included patients with paroxysmal AF (30% of all AF cases) and patients with AT including typical AFL.

No recurrence of typical AFL was observed in our cohort. This finding is far more favourable than previously reported long-term data.[13,14] We speculate that RFCA with 3D-electroanatomical mapping and direct visual control using intracardiac echocardiography could be responsible for such an outcome. Significant elimination of triggers (PVI in 62% of patients) may also play a role. The data overall indicate that CTI ablation in PH could be effective in patients with documented or highly suspected typical AFL. However, the reoccurrence of different arrhythmias in AFL patients in both study arms was noticed during follow-up, which is in concordance with previous results.[13,14]

Apart from the well-known reasons for the failure of additional substrate ablation in the general AF population, several other explanations for what is behind the lack of benefit from an extensive ablation in this trial can be offered. Although enlargement of RA, conduction slowing, reduced tissue voltage, and regions of electrical silence in RA were described in patients with PH,[21,22] we were not able, however, to detect a significant prevalence and extent of regions with low-voltage and/or abnormal atrial electrograms in our population despite expectedly dilated RA. We cannot exclude that our bipolar cut-off voltage for low-voltage zones was not sensitive and specific enough to identify RA arrhythmogenic substrate. We can

Table 2 Procedural characteristics

	All patients $n = 74$	Limited ablation group $n = 38$	Extended ablation group $n = 36$	P
Clinical arrhythmia present at baseline	28 (38%)	17 (45%)	11 (31%)	NS
SR present at baseline, clinical arrhythmia inducible	19 (26%)	11 (29%)	8 (22%)	NS
SR present at baseline, clinical arrhythmia non-inducible or not induced	14 (19%)	5 (13%)	9 (25%)	NS
Other than clinical arrhythmia present/induced at baseline	9 (12%)/4 (5%)	3 (8%)/2 (5%)	6 (17%)/2 (6%)	NS
>1 arrhythmia in the history	10 (14%)	6 (16%)	4 (11%)	NS
>1 arrhythmia during the procedure	9 (12%)	5 (13%)	4 (11%)	NS
RA mapping time (min)	18 (13; 24)	20 (13; 27)	16 (13; 22)	NS
LA mapping time (min)	18 (13; 23)	18 (13; 24)	17 (12; 22)	NS
Total procedure time (min)	173 (135; 210)	155 (130; 180)	205 (150; 225)	0.004
General anaesthesia	9 (12%)	4 (11%)	5 (14%)	NS
Fluoroscopy time (min)	2.4 (1.4; 5.1)	2.2 (1.4; 5)	3.3 (1.7; 7.3)	NS
Radiofrequency time (min)	39 (24; 56)	26 (14; 42)	49 (32; 65)	<0.0001
CARTO RA volume (mL)	196 (159; 250)	206 (155; 260)	191 (162; 249)	NS
CARTO LA volume (mL)	122 (99; 143)	122 (104; 142)	116 (62; 153)	NS
CARTO RA surface (cm^2)	198 (172; 228)	201 (173; 230)	182 (171; 213)	NS
CARTO LA surface (cm^2)	135 (120; 154)	137 (125; 156)	134 (119; 153)	NS
RA LVAs (% of the surface)	5 (1;12)	4 (1; 11)	5 (2; 13)	NS
LA LVAs (% of the surface)	2 (0; 10)	4 (1; 11)	2 (0; 22)	NS
Acute success of ablation	69 (93%)	36 (95%)	33 (92%)	NS
Ablation not done	3 (4%)	2 (5%)	1 (3%)	NS
Procedural ECV	16 (22%)	11 (29%)	5 (13%)	NS
Procedural ECV in AF patients	14/38 (37%)	10/19 (53%)	4/19 (21%)	0.04
LA ablation	48 (65%)	21 (55%)	27 (75%)	NS
– PVI alone	24 (32%)	10 (26%)	14 (39%)	NS
– PVI + additional lesions	22 (30%)	9 (24%)	13 (36%)	NS
– LA ablation without PVI	2 (3%)	2 (5%)	0 (0%)	NS
– LA foci	5 (7%)	3 (8%)	2 (3%)	NS
– CFAE	8 (11%)	3 (8%)	5 (14%)	NS
– LVAs	14 (19%)	4 (11%)	10 (28%)	NS
– CS	7 (9%)	4 (11%)	3 (8%)	NS
– Linear lesions	16 (%)	6 (16%)	10 (28%)	NS
RA ablation	55 (74%)	22 (58%)	33 (92%)	0.0009
– CTI alone	17 (23%)	14 (37%)	3 (8%)	0.004
– CTI + additional lesions	31 (42%)	2 (5%)	29 (81%)	<0.0001
– RA ablation without CTI	7 (9%)	6 (16%)	1 (3%)	NS
– SVC isolation	27 (36%)	1 (3%)	26 (72%)	<0.0001
– CFAE/LVA	14 (19%)	1 (3%)	13 (36%)	0.0002
– Intercaval line	26 (35%)	1 (3%)	25 (69%)	<0.0001
– RA/CS focal activity	4 (5%)	2 (5%)	2 (6%)	NS
– AVN slow pathway	3 (4%)	3 (8%)	0 (0%)	NS

Data represent the number of cases (percentage) or median (interquartile range).
AF, atrial fibrillation; AVN, atrioventricular node; CFAE, complex fragmented atrial electrograms; CS, coronary sinus; CTI, cavotricuspid isthmus; ECV, electrical cardioversion; LA, left atrium; LVA, low voltage area; NS, not significant; PVI, pulmonary vein isolation; RA, right atrium; SR, sinus rhythm; SVC—superior vena cava.

also speculate that elevated right-sided filling pressure with associated RA hypertrophy could mask the voltage-attenuation effects of spontaneous atrial scarring and dilatation. When abnormal myocardium could not be found, mainly empirical lesions (i.e. CTI block, SVC isolation, or intercaval line) constituted an extension of ablation, and such lesions alone might not be the most efficacious ablation targets in PH patients. We cannot also exclude the possibility that our strategy of extended ablation did not target sufficiently the uncommon type of ATs involving both atria and inter-atrial

Table 3 Study endpoints

	Limited ablation group $n = 38$	Extended ablation group $n = 36$	*P*
Primary endpoint			
– Documented arrhythmia recurrence >30 s without antiarrhythmic drugs after the 3-month blanking period	17 (45%)	15 (42%)	NS
Secondary endpoints			
– Documented on-drug arrhythmia recurrence	10 (26%)	7 (19%)	NS
– Symptoms of arrhythmia	13 (34%)	10 (28%)	NS
– Patients with emergency visits/number of emergency visits per patient	11 (29%)/2 (1; 3)	9 (25%)/2 (1; 2)	NS/NS
– Patients with hospitalization/number of hospitalizations per patient	14 (37%)/1 (1; 2)	13 (36%)/2 (1; 2)	NS/NS
– Patients with cardiovascular emergency visits or hospitalization/number of events per patient	13 (24%)/1 (1; 3)	11 (31%)/1 (1; 2)	NS/NS
– Mortality	9 (24%)	10 (28%)	NS
– Antiarrhythmic drugs (post-blanking period)	16 (42%)	7 (19%)	0.046
– Antiarrhythmic drugs (at the end of follow-up)	11 (29%)	7 (19%)	NS
– Reablation rate	5 (13%)	3 (8%)	NS
– Pacemaker implantation	3 (8%)	1 (3%)	NS
– AV junction ablation	0	1 (3%)	NS
Other objectives (12-month visit—baseline difference)			
– 6-minute walking test (m)	−10 (−27; 55)	9 (−28; 163)	NS
– EQ-VAS	−4 (−12; 14)	0 (−18; 22)	NS
– NT-proBNP (pg/mL)	239 (−312; 1120)	98 (−512; 695)	NS
Major procedural complications	5 (13%)	4 (11%)	NS

Data represent the number of cases (percentage) or median (interquartile range).
Details on major procedural complications are provided in Supplementary material online, *Table S3*.
EQ-VAS, European Quality of Life Group instrument self-report questionnaire visual analogue scale; NS, not significant.

connections.[23] Abnormal modulation of the intrinsic cardiac autonomic system has been identified as an arrhythmogenic mechanism in patients with PH.[24,25] The arrhythmia sources because of this mechanism are difficult to identify and modify by conventional ablation strategies. The high recurrence rate of arrhythmia in combination with PH, as a severely limiting underlying condition, was likely responsible for the absence of improvement in quality of life, functional capacity, and natriuretic peptides.

The results may be also biased by post-randomization deviations from protocol-specified care that could attenuate the difference in clinical outcome between study arms. For example, ablation on top of limited selective RFCA was done in eight (21%) patients in the Limited ablation group with more than one documented type of arrhythmias or when other arrhythmias were seen during the index procedure. This was done at the investigator's discretion if believed to be beneficial for the subject's welfare. Similarly, the investigators tended to perform more complex LA ablation in non-paroxysmal AF irrespective of the study treatment allocation, which finally resulted in a small difference in the LA lesion set between study arms. On the contrary, in the Extended ablation group, the lesion set was not completed in several patients. In one case with AT, ablation was not done when no arrhythmia was induced. Moreover, in two patients with AFL and two patients with AF, the full lesion set in RA was not completed mainly because of a prolonged and poorly tolerated procedure in combination with extreme enlargement of the right atrium preventing successful ablation.

It has been shown that the use of general anaesthesia could increase the single procedure success rate of RFCA of complex atrial arrhythmia, and shorten fluoroscopy and procedural time without increasing procedural complications.[26] However, the concern about severe complications related to general anaesthesia in PH patients exists. The PH is a serious condition, and the induction of general anaesthesia can incur additional sudden haemodynamic stress.[27] It is also known that patients with severe PH have increased rates of delayed extubating, heart failure, and mortality after non-cardiac surgery.[28] On the other hand, conscious sedation may result in inadvertent hypoventilation episodes with their consequences. Operators preferred to use conscious sedation, which is a common way of performing RFCA even for complex arrhythmias in our country.

Importantly, a considerable number of adverse events were recorded during the follow-up. There was no excess of clinical events including all-cause death in the Extended ablation group, and only a few events were directly procedure-related while all others could be considered the natural course of the underlying disease. Therefore, RFCA appeared safe even in the population of frailty PH patients when performed by experienced operators.

The left atrial stiff syndrome is a plausible long-term side effect of extensive complex RFCA in LA resulting in pulmonary venous hypertension[29,30] that can aggravate PH. The potentially higher risk of left atrial stiff syndrome with its consequences in PH patients is one of the arguments against routine extensive ablation in the left atrium in that population. This risk was not, however, investigated in our study.

Limitations

The study has several limitations. First, the patient population was heterogeneous in terms of the type and aetiology of PH. Second, high-

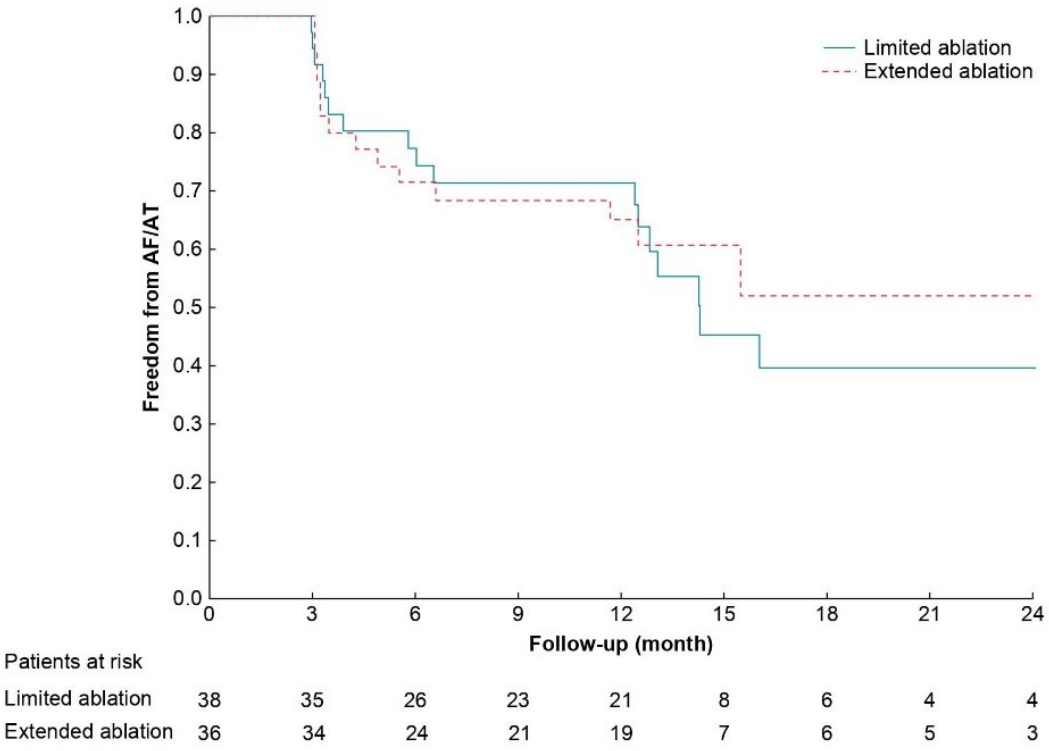


Figure 2 Event-free survival for arrhythmia recurrence (primary endpoint). Kaplan–Meier curves: solid blue for the Limited ablation group; dashed red for the Extended ablation group.

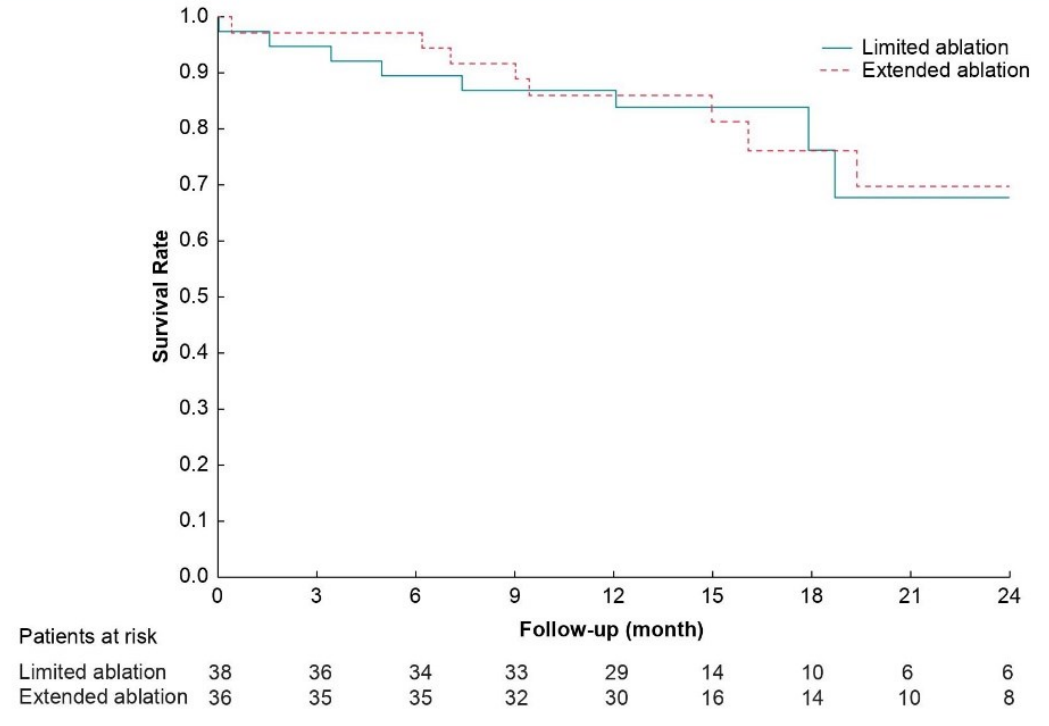


Figure 3 Event-free survival for all-cause mortality. Kaplan–Meier curves: solid blue for the Limited ablation group; dashed red for the Extended ablation group.

density mapping was not used to identify an arrhythmogenic substrate. Third, operators tended to deviate from the protocol (by performing more than simply PVI) in patients with persistent AF who were randomized to a limited ablation strategy. Fourth, pulsed electrical field ablation technology was not available during the study enrollment period. Fifth, the arrhythmia burden that would be a better procedural endpoint than the first arrhythmia recurrence was not assessed.

Conclusions

Extensive RFCA, compared with a limited approach, was not beneficial in terms of arrhythmia recurrence in patients with AF/AT and PH. The absence of clear advance in the context of the prolonged procedural time in the PH population warrants the conclusion that performing additional, and perhaps unnecessary, ablation lesions should be generally avoided.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: None declared.

Data availability

All relevant data are in the manuscript. Relevant dataset is available on request.

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7. Discussion

The topic presented in the first article "**Atrial fibrillation and Atrial Tachycardia in Patients with Chronic Thromboembolic Pulmonary Hypertension Treated with Pulmonary Endarterectomy**" is unique, as it is to our knowledge the first analysis aimed on the prevalence of arrhythmias in the population of CTEPH patients treated with pulmonary endarterectomy. Overall, our hypothesis based on the beneficial effect of pulmonary endarterectomy on the hemodynamic status which could theoretically result in decreased arrythmia incidence was not proven. The whole surgical procedure seems to bear a rather pro-arrhythmogenic effect.

According to the results, from the total of 197 patients arrythmia was found in 57 (29%). Before the pulmonary endarterectomy, SVT was known only in 17 (30%) of them. In 40 patients (40%), the arrythmia occurred during the post-operation follow up. Therefore, our data suggests that the operation itself may actually increase the risk of arrythmia. This can be explained by the increased risk of post-incisional AF/AT resulting from the RA incision performed during the pulmonary endarterectomy. (Lindner J. *et al.*, 2006) The theory can be further corroborated by the relatively high number of newly diagnosed AFL after the endarterectomy, i.e. arrhythmia emerging from the RA. However, it is important to note that the differences in the spectrum of diagnosed arrhythmia before and after the pulmonary endarterectomy did not reach statistical significance. In addition, 20 patients (10%) developed AF/AT during the early post-operative period (<30 days after surgery), with AF being excessively prevalent. This is not surprising as AF is common in the general population after routinely performed cardiac surgeries like CABG (coronary artery bypass graft) or valve surgery. (Arsenault K.A. *et al.*, 2013; Mathew J.P. *et al.*, 2004)

Previous analyses have shown that the LA substrate could play an important role in arrhythmogenesis, even in precapillary PH patients. (Fingrova Z. *et al.*, 2019) The presented detailed analysis of the CTEPH population further supported this finding as CTEPH patients with AF/AT history had increased LA size and less pronounced RA enlargement. Also, patients with AF/AT showed higher residual PASP values after the pulmonary endarterectomy and we hypothesized that this can be caused by, among other things, the co-existence of a subtle post-capillary component.

Consequently, the assessment of a post-capillary component characterized by the PAWP value and its possible effect on the arrhythmia occurrence in pre-capillary PH patients (defined as mPAP ≥25 mmHg, PAWP <15 mmHg) was a main goal of our next retrospective analysis published under the 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**". From the total of 333 patients, AF/AT was diagnosed in 79 (24%). The median PAWP in the overall study population was 11 mmHg. The proportion of patients with arrhythmia was significantly higher in the subgroup of patients with PAWP above the median (i.e. PAWP >11mmHg). This was well in line with the hypothesis that the incidence of AF/AT will increase with growing PAWP. Interestingly, typical risk factors like higher age, arterial hypertension, diabetes, and LA dilatation were more common in the high PAWP subgroup. Therefore, we dare to conclude that the abnormally high arrhythmia prevalence in those patients is probably a result of the combination of both proarrhythmogenic mechanisms typically found in PH patients (right-sided substrate, RA dilatation, …) (Medi C. *et al.*, 2012a) and mechanisms documented in patients with left heart disease (LA remodeling, increased LV end-diastolic pressure). (Ausma J. *et al.*, 1997; Rottlaender D. *et al.*, 2012)

The available data, including our retrospective analysis, indicate the logical connection between the AF/AT occurrence and the patient's hemodynamic status. Besides, as already stated, the presence of arrhythmia in PH patients relates to further clinical deterioration and SR restoration can improve the symptoms. However, the pathophysiology and direct effect of arrhythmia or SR on the hemodynamics had not previously been studied in detail. Therefore, we designed the prospective observational study "**The Impact of Atrial Fibrillation and Atrial Tachycardias on the Hemodynamic Status of Patients with Pulmonary Hypertension**". We expected that the SR rhythm restoration will lead to acute hemodynamic improvement.

To prove our hypothesis, the RHC was performed at the beginning and at the end of standardly performed catheter ablation. The data of patients with pre-capillary PH were compared to the patients with left-heart failure and to the patients with arrhythmia without any other cardiological disease. Surprisingly, we observed generally only slight differences in the hemodynamic parameters measured in the presence of SR compared to arrhythmia, and we failed to prove the expected hemodynamic improvement in SR in all three subgroups. The

possible explanation can be the short-term design of our study, as it has been proven that it can take up to even one month to fully restore the mechanical function of the LA after the DCCV. (Manning W.J. *et al.*, 1994) However, this theory needs to be proven by another analysis with a different design.

Nevertheless, the results of the presented project were not completely negative. In patients with AF only (irrespective of the concrete study subgroup), the CI increased significantly after SR restoration. Contrarily, the CI did not change in patients with organized ATs. We assume that more organized mechanical atrial activity, more regular ventricular response, and certain reasonable tachycardia are crucial pathophysiological mechanisms to maintain the CI during the ongoing AT. (Raymond R.J. *et al.*, 1998; Viswanathan K. *et al.*, 2001) The conclusion therefore corroborates the rhythm control strategy, especially in patients with AF.

The results of the previously discussed projects brought us to designing a randomized prospective trial "**Catheter ablation of atrial fibrillation and atrial tachycardia in patients with pulmonary hypertension: a randomized study**". The available data showed us that extensive bi-atrial substrate could be commonly involved in AF/AT formation in PH patients. (Fingrova Z. *et al.*, 2019) Furthermore, the detrimental effects of an arrhythmia presence and possible benefits of rhythm control strategy have been proven. (Tongers J. *et al.*, 2007; Wen L. *et al.*, 2014) Based on the literature, catheter ablation is recognized as a feasible tool in a rhythm control strategy, even in PH patients. (Kamada H. *et al.*, 2021; Ruiz-Cano M.J. *et al.*, 2011; Showkathali R. *et al.*, 2011; Zhou B. *et al.*, 2021) The most efficient procedure strategy, however, remains unknown. We hypothesized that, particularly in PH patients, detailed substrate mapping and subsequent extensive radiofrequency ablation targeting all possible arrhythmogenic regions will lead to improved SR preservation.

However, the results did not confirm our hypothesis as the arrhythmia recurrence rate during the 13 month long follow-up did not differ significantly after the "limited" ablation compared to the "extensive" approach. In contrast to the available data and despite the significant RA enlargement in our study population, we could not detect vast regions with low-voltage or abnormal atrial electrograms. We can hypothesize that it was this inability to accurately localize the pathophysiological substrate that hampered reaching the desired results. Therefore, it may

be reasonable to modify, or even try to develop completely new, ways of arrhythmogenic substrate identification in the PH population. Other possible explanations and limitations of the study are thoroughly discussed in the original article.

8. Conclusion

Pulmonary hypertension affects about 1% of population. Regardless of the exact pathophysiological mechanisms leading to its development, it significantly worsens a patient's clinical state and prognosis. Although SVTs occur commonly in those patients, the topic of arrhythmias in PH patients has not yet been studied sufficiently. This thesis presents the results of four analyses focused on the epidemiology and pathophysiological mechanisms of heart rhythm disorders in PH.

Through the retrospective analysis of the registry of patients with CTEPH, we found out that the **incidence of arrhythmias after the successful pulmonary endarterectomy did not decrease**. Despite the improved hemodynamic state, more atrial arrhythmias occurred during the follow up after the surgery.

We proved that the **incidence of AF/AT in patients with pre-capillary PH increases with growing PAWP**. In PH patients with near to elevated PAWP, the concurrent LA involvement is probably the reason for the observed higher incidence of SVTs.

Despite the available data indicating the detrimental effects of SVTs in the presence of PH, **we did not confirm that the SR restoration improves acutely the hemodynamic state in this population.** However, we observed significant increase in the CO specifically after the AF termination irrespective of PH.

In a prospective randomized setting, **we failed to prove that the extensive catheter ablation targeting the entire possibly arrhythmogenic substrate will lead to the lower rate of an arrhythmia recurrence** compared to the standardly performed ablation.

In future, further research is needed to gain deeper knowledge about the mechanisms of heart rhythm disorders in PH to finally establish the best possible ways of their management.

9. References

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10. List of author's publications

10.1 Publications directly related to the thesis

Havranek S, Fingrova Z, Ambroz D, Jansa P, Kuchar J, **Dusik M**, Lindner J, Kunstyr J, Aschermann M, Linhart A. Atrial fibrillation and atrial tachycardia in patients with chronic thromboembolic pulmonary hypertension treated with pulmonary endarterectomy. Eur Heart J Suppl. 2020 Jul;22(Suppl F):F30-F37. doi: 10.1093/eurheartj/suaa096. Epub 2020 Jul 15. **IF_{2020} = 1,80**

Dusik M, Fingrova Z, Ambroz D, Jansa P, Linhart A, Havranek S. The Role of Pulmonary Artery Wedge Pressure on the Incidence of Atrial Fibrillation and Atrial Tachycardias in Patients With Isolated Pre-capillary Pulmonary Hypertension. Physiol Res. 2021 Dec 30;70(6):841-849. doi: 10.33549/physiolres.934706. **IF_{2021} = 2,10**

Dusik M, Fingrova Z, Marek J, Dytrych V, Jansa P, Havranek S. The impact of atrial fibrillation and atrial tachycardias on the hemodynamic status of patients with pulmonary hypertension. Physiol Res. 2022 Dec 16;71(6):791-799. **IF_{2022} = 2,10**

Havranek S, Fingrova Z, Skala T, Reichenbach A, **Dusik M**, Jansa P, Ambroz D, Dytrych V, Klimes D, Hutyra M, Kautzner J, Linhart A, Wichterle D. Catheter ablation of atrial fibrillation and atrial tachycardia in patients with pulmonary hypertension: a randomized study. Europace. 2023 May 13;25(5):euad131. doi: 10.1093/europace/euad131. **IF_{2023} = 6,10**

10.2 Other publications

Dusik M, Daud A, Smid O, Havranek S, Vitkova I, Revelo MP, Stehlik J, Linhart A, Belohlavek J. Giant cell myocarditis in an older patient - reassessing the threshold for endomyocardial biopsy. ESC Heart Fail. 2020 Oct;7(5):3165-3168. doi: 10.1002/ehf2.12756. Epub 2020 Jul 9. **IF_{2020} = 4,41**

Havranek S, Fingrova Z, Rob D, Smalcova J, Kavalkova P, Franek O, Smid O, Huptych M, **Dusik M**, Linhart A, Belohlavek J. Initial rhythm and survival in refractory out-of-hospital cardiac arrest. Post-hoc analysis of the Prague OHCA randomized trial. Resuscitation. 2022 Dec;181:289-296. doi: 10.1016/j.resuscitation.2022.10.006. **IF_{2022} = 6,50**

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