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Thesis outline

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Arrhythmias in Pulmonary Hypertension

Poruchy srdečního rytmu u plicní hypertenze

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

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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

1.1 Pulmonary hypertension

Pulmonary hypertension (PH) is a pathophysiological disorder characterized by abnormally high pressures in the pulmonary artery. The estimated overall prevalence of PH is about 1% of global population and it is still growing. Originally, PH was defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg. Recently, the PH definition was modified and in the latest European Society of Cardiology (ESC) guidelines, the PH is defined by an mPAP >20 mmHg measured at rest by right heart catheterization. Pulmonary artery wedge pressure (PAWP) and calculated pulmonary vascular resistance (PVR, PVR = (mPAP – PAWP)/CO[1]) are used to distinguish between pre-capillary and post-capillary. (Humbert M. *et al.*, 2022)

PH is commonly classified into 5 groups based on similar pathophysiological mechanisms, clinical and hemodynamic characteristics, and therapeutic possibilities (WHO classification). Group 1 comprises PAH characterized by pre-capillary PH with elevated PVR, which typically 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. 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)

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.). (Oldroyd S.H. *et al.*, 2023) Among echocardiographic findings typical for PH are: right ventricle enlargement and dysfunction, D-shape of the left ventricle, increased tricuspid and pulmonary regurgitation velocities, dilated right atrium, pericardial effusion. (Topyla-Putowska W. *et al.*, 2021) Right heart catheterization (RHC) using

[1] CO – Cardiac output

a dedicated Swan-Ganz catheter remains the gold standard for a PH confirmation.(Humbert M. *et al.*, 2022)

The main approach to the PAH treatment is pharmacological and includes several types of specific vasodilatory drugs (calcium channel blockers, phosphodiesterase 5 inhibitors, endothelin receptor antagonists, prostacyclin receptor agonist or prostacyclin analogues). (Humbert M. *et al.*, 2022) Both PH associated with left heart disease and PH associated with lung disease are usually managed by the treatment of the underlying pathology. (McDonagh T.A. *et al.*, 2021; Vahanian A. *et al.*, 2021) Beside lifelong anticoagulation, surgical treatment (pulmonary endarterectomy), percutaneous balloon pulmonary angioplasty and pharmacological therapy can be considered in PH associated with pulmonary artery obstructions (Bunclark K. *et al.*, 2020; Humbert M. *et al.*, 2022)

1.2. 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). 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. Electrocardiography (ECG) is a basic diagnostic tool for arrhythmia assessment.

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). 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)

Within my postgraduate study, I focused mainly on the topic of supraventricular tachycardias. On a 12-lead ECG, SVTs usually appear as a narrow-QRS tachycardia (QRS duration ≤120 milliseconds). However, under specific circumstances, SVTs can present as a wide QRS arrhythmia. Commonly reported symptoms of SVTs are palpitations, fatigue, light-headedness, dyspnea, dizziness, presyncope, or even syncope. Classic signs of heart failure can be found in case of development of a tachycardia induced cardiomyopathy (Zimetbaum P. and Josephson

M.E., 1998) Several types of atrial arrythmias, are known to increase the risk of intracardiac thrombus formation. (Hindricks G. *et al.*, 2021)
Generally, conservative approach (i.e., observation without any treatment), pharmacological treatment, catheter ablation and even surgical procedures can be considered in patients with SVT. Direct current cardioversion is a powerful tool used to stop the ongoing arrhythmia and restore the SR. (Kotadia I.D. *et al.*, 2020)

Atrial fibrillation (AF) is the most common arrhythmia in the world with an overall prevalence of 2 – 4% in adults. (Benjamin E.J. *et al.*, 2019) and is characterized by uncoordinated electrical activation of the atria and irregular heart rhythm. (Hindricks G. *et al.*, 2021) Typical atrial flutter (AFL) is another common arrhythmia. It is based on a macro-reentry circuit around the right atrial cavity using the cavotricuspid isthmus (Saoudi N. *et al.*, 2001) Other arrhythmias referred among SVTs are for example: non-cavotricuspid isthmus dependent macro-reentrant atrial tachycardias (atypical flutters), focal atrial tachycardias (AT), atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT). (Brugada J. *et al.*, 2020)

1.3 Heart rhythm disorders in pulmonary hypertension

Atrial arrhythmias are common in PH patients with the reported cumulative incidence 10-36%. (Andersen M.O. *et al.*, 2021; Cannillo M. *et al.*, 2015; Daliento L. *et al.*, 1998; Olsson K.M. *et al.*, 2013; Rottlaender D. *et al.*, 2012; Ruiz-Cano M.J. *et al.*, 2011; Tongers J. *et al.*, 2007; Wen L. *et al.*, 2014). In contrast, ventricular arrhythmias are surprisingly rare in patients with PH. (Hoeper M.M. *et al.*, 2002; Kanemoto N. and Sasamoto H., 1979; Tongers J. *et al.*, 2007)

Commonly cited risk factors for an SVT development are higher right atrial pressure, right and left atrium dilatation, higher PVR, lower CO, and elevated B-type natriuretic peptide level (Mercurio V. *et al.*, 2018; Olsson K.M. *et al.*, 2013; Smith B. *et al.*, 2018; Wen L. *et al.*, 2014)

The role of right-sided arrhythmogenic substrate in increased incidence of arrythmias in PH patients is obvious. (Medi C. *et al.*, 2012; Pietra G.G. *et al.*, 2004) 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) Other proposed mechanisms include

for example increased sympathetic activity. (Velez-Roa S. *et al.*, 2004; Zhao Q. *et al.*, 2015), chronic inflammation and myocardial fibrosis (Lazzerini P.E. *et al.*, 2014)
Generally, patients with combined post- and pre-capillary PH tend to have higher SVT prevalence (Fingrova Z. *et al.*, 2021) and the mechanisms of arrhythmia in those patients seem to be more analogous to patients with substrate caused by the left heart involvement. (Ausma J. *et al.*, 1997; Rottlaender D. *et al.*, 2012; Spach M.S. and Josephson M.E., 1994)

The presence of an SVT in PH patient has a huge clinical impact as it is associated with disease severity and clinical deterioration. Contrary, the termination of arrhythmia leads to clinical improvement. (Cannillo M. *et al.*, 2015; Olsson K.M. *et al.*, 2013; Ruiz-Cano M.J. *et al.*, 2011; Tongers J. *et al.*, 2007) Numerous studies have even provided data on the relation between SVT occurrence and mortality in PH patients.(Cannillo M. *et al.*, 2015; Olsson K.M. *et al.*, 2013; Smith B. *et al.*, 2018; Tongers J. *et al.*, 2007; Wen L. *et al.*, 2014) Therefore, restoration of the SR is an important treatment goal. (Humbert M. *et al.*, 2022)

Despite the lack of data in PH patients, antiarrhythmic drugs are recommended as a part of the rhythm control management. Amiodarone is advantageous because of its minimal negative inotropic effect. (Humbert M. *et al.*, 2022) Class 1c antiarrhythmics seem to be also well tolerated according to the observational studies. On the other hand, the use of betablockers remain controversial (Bandyopadhyay D. *et al.*, 2015; Farha S. *et al.*, 2017; Peacock A. and Ross K., 2010; Reddy S.A. *et al.*, 2021; Thenappan T. *et al.*, 2014) Direct current cardioversion is an important part of the rhythm control approach. However, the specific risks of general anesthesia in PH patients must be considered (Reddy S.A. *et al.*, 2021). Catheter ablation for atrial arrythmias is generally feasible and safe in PH patients. (Bandorski D. *et al.*, 2014; Ruiz-Cano M.J. *et al.*, 2011; Showkathali R. *et al.*, 2011) Because of the heart remodeling, ablation procedures are typically technically more challenging with higher rates of both arrhythmia recurrence and complications. (Humbert M. *et al.*, 2022; Reddy S.A. *et al.*, 2021; Zhang Y.Q. *et al.*, 2018).

2. 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.

3. 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.

3.1 Atrial fibrillation and Atrial Tachycardia in Patients with Chronic Thromboembolic Pulmonary Hypertension Treated with Pulmonary Endarterectomy

The first article 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 registry consisted of data from overall 197 patients (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 significantly 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 pulmonary endarterectomy [38 (30–47) vs. 45 (38–71) mmHg].

Out of all the patients with AF/AT (n = 57), in 17 subjects (30%) occurred the arrhythmia prior to the pulmonary endarterectomy. In remaining 40 patients (70%) arrhythmia appeared during the long-term follow-up after the operation. The differences in the spectrum of diagnosed arrhythmias before and after pulmonary endarterectomy did not reach statistical significance (P=0.07). In addition to the 57 patients with AF/AT, 20 (10%) patients developed AF/AT in the early post-operation period (<30 days after surgery).

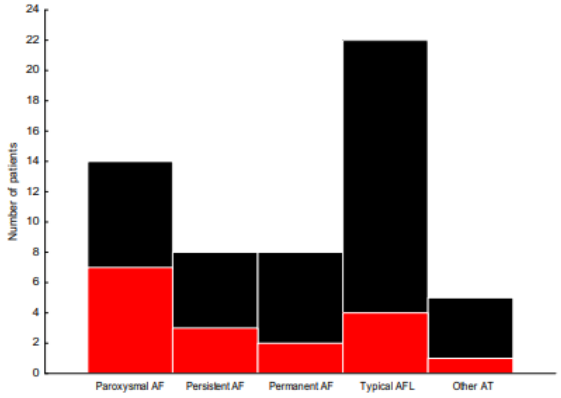

Figure 1 The spectrum of detected arrhythmia. The red columns visualize patients with arrhythmia manifested before the pulmonary endarterectomy; black columns refer to patients with arrhythmia diagnosed during a long-term follow-up after the surgery. AF, atrial fibrillation; AFL, atrial flutter; AT,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

During the follow-up with a median 4.2 (1.6–6.3) years, 45 (23%) patients died. According to our results, arrhythmias were associated with reduced functional capacity but not with mortality.

3.2 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 second article 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.

In the overall study population of 333 patients with pre-capillary idiopathic / familiar PAH or inoperable CTEPH (mean age 61±15 years, 44 % males), 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.

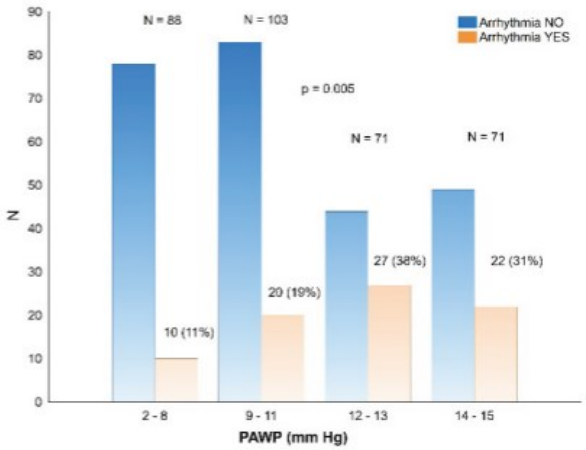

Fig. 2. Proportion of patients with and without atrial fibrillation or atrial tachycardia according to the values of pulmonary artery wedge pressure. PAWP – pulmonary artery wedge pressure.

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

The third article presents the results of a prospective observational study comparing patients with pre-capillary PH (PH group) to patients with left-sided heart failure (LV-HF group) and controls (Control group). Repeated RHC was performed at the beginning and at the end of catheter ablation. The first measurement was done in arrhythmia, the second after the SR was restored. High frequency atrial stimulation was used to simulate AT in patients without arrhythmia presence at the time of the catheter ablation. The recorded changes in the hemodynamic parameters were evaluated and compared between the study subgroups.

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 ($p<0.05$).

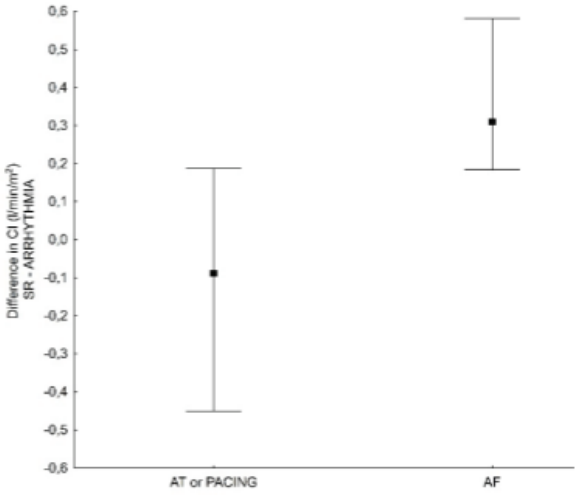

Fig. 2. Difference in cardiac index between arrhythmia and sinus rhythm. Box and whiskers show median and IQR. AF – atrial fibrillation; AT – atrial tachycardia; CI – cardiac index; SR – sinus rhythm.

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

The fourth article summarizes the results of a prospective randomized trial based on the hypothesis 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 PH and SVTs.

Patients with combined post- and pre-capillary or isolated pre-capillary PH and SVT indicated to catheter ablation were enrolled in three centers 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 arrhythmogenic substrate and its characteristics were assessed using electroanatomical mapping. 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. Despite enormous right atrial enlargement, regions with low-voltage and abnormal atrial electrograms were found rarely.

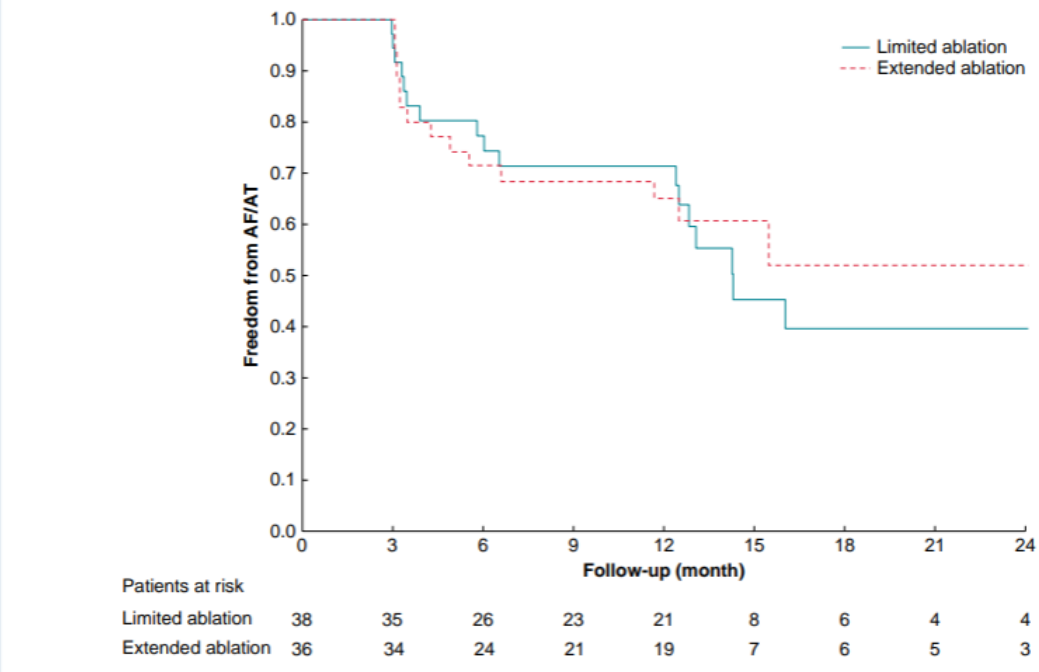

Figure 2 Event-free survival for arrhythmia recurrence (primary endpoint). Kaplan–Meier curves: solid blue for the Limited ablation group; dashed red for the Extended ablation group.

4. 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**". 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.*, 2012) 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.

5. 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 CI 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.

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7. List of author's publications

7.1 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**

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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**

7.2 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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