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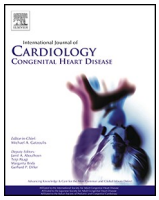

Sudden cardiac death in pulmonary arterial hypertension☆

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ABSTRACT

Pulmonary arterial Hypertension (PAH) is a progressive disease marked by significant morbidity and mortality due to pulmonary vasculopathy and right ventricular (RV) dysfunction. Despite advances in PAH medical therapies which have improved clinical outcomes and survival, patients continue to face severe complications, including a notable incidence of sudden cardiac death (SCD). The high arrhythmic burden, coupled with mechanical complications such as left main compression syndrome, pulmonary artery dissection, rupture, and severe hemoptysis, significantly contribute to the risk of SCD. Close monitoring and a meticulous diagnostic approach are essential for risk stratification and timely intervention, aiming to mitigate the risk of premature death in these patients. The aim of this review is to provide a comprehensive understanding of these risks and highlight strategies for improving patient outcomes through early identification, prevention and effective management.

1. Introduction

In the past half century, important advances in pulmonary arterial hypertension (PAH)-medical therapy, have improved clinical outcomes and survival in patients with PAH [1,2]. Still, progression of pulmonary vasculopathy and its impact on right ventricular (RV) function, continues to cause substantial morbidity and mortality in this population [1]. Besides right heart failure, approximately ~50 % of patients seem to die from other causes, with PAH as a contributing factor [3]. Interestingly, sudden cardiac death (SCD) is now encountered more often in PAH patients. Although little is known about the substrate for SCD in this population, both arrhythmic and non-arrhythmic causes seem to be involved.

The significant arrhythmic burden, as well as mechanical complications due to pulmonary artery dilation [left main compression syndrome (LMCS), pulmonary artry dissection (PAD), pulmonary artery rupture, and severe hemoptysis] are all complications of PAH leading to SCD [4–7]. In this review we discuss the etiology, preventive measures, and management of arrhythmic and non-arrhythmic causes of SCD among PAH patients.

2. Arrhythmic causes of sudden cardiac death

Several potential mechanisms seem to contribute to arrhythmia susceptibility in PAH patients [4,7]. Chronic right ventricular (RV) dilatation leads to functional tricuspid regurgitation with a subsequent increase in right atrial overload. The longstanding elevation of atrial pressure induces progressive atrial dilatation, atrial stretch, and fibrosis, altering the electrophysiologic properties of the atrial tissue (formation of heterogenous regions of low voltage and scar). Both structural alterations and electrical remodeling increase susceptibility to and propagation of supraventricular arrhythmias (SVAs), including atrial fibrillation (AF) and atrial flutter (AFL). Ventricular arrhythmias (VAs) can be precipitated by a dilated dysfunctional and hypertrophied right ventricle, increased sympathetic activity, or altered ventricular substrate in the form of scar, giving rise to pro-arrhythmic myocardium.

2.1. Supraventricular arrhythmias

Supraventricular arrhythmias are the most prevalent rhythm disturbances observed in patients with PAH and occur with greater incidence than in the general population [4,7]. The onset of SVA in this subgroup of patients often signals progressive RV failure and/or frequently precipitates clinical decompensation and death. Indeed, SVA

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Abbreviations:

AF	Atrial fibrillation
AFL	Atrial flutter
AT	Atrial tachycardia
AVNRT	Atrioventricular nodal reentry tachycardia
AVRT	Atrioventricular nodal reentry tachycardia
CCB	Calcium channel blocker
CI	Cardiac index
CO	Cardiac output
CTEPH	Chronic thrombo-embolic pulmonary hypertension
CTI	Cavotricuspid isthmus
DPAH	Drug- or toxin-associated pulmonary arterial hypertension
ERS	European respiratory society
ESC	European society of cardiology
IPAH	Idiopathic pulmonary arterial hypertension
LMCS	Left main compression syndrome
mPAP	Mean pulmonary arterial pressure
PAD	Pulmonary artery dissection
PAH	Pulmonary arterial hypertension
PAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
PAH-HIV	Pulmonary arterial hypertension associated with human immunodeficiency virus infection
PAWP	Pulmonary arterial wedge pressure
PAH-CTD	Pulmonary arterial hypertension associated with connective tissue disease
PH	Pulmonary hypertension
PoPH	Porto-pulmonary hypertension
PVR	Pulmonary vascular resistance
RV	Right ventricle/right ventricular
SCD	Sudden cardiac death
SVA	Supraventricular arrhythmia
VA	Ventricular arrhythmia

is poorly tolerated in PAH patients due to the loss of atrial kick and to the irregular rhythm (variable timing of diastole), that are both important factors contributing to the diastolic right ventricular filling.

Most of the early data regarding the burden and clinical implications of SVAs in PAH patients were derived from retrospective single center studies (Table 1) [8–14]. Later on, prospective studies have confirmed the relatively high incidence of SVAs in PAH patients and have attempted to identify the clinical features of patients at risk of developing such arrhythmias [15–19]. Overall, these observational studies have several limitations, due to the heterogeneity of the pulmonary hypertenstion (PH) groups and the intermittent surveillance of patients for detection of SVAs. Recognizing the limitations of observational studies, these data suggest that: 1) there are no discrete baseline characteristics predicting SVA susceptibility, 2) SVA often precipitates clinical decompensation and/or death, 3) some SVAs may be subclinical, the incidence thus is underestimated, and 4) the maintenance of sinus rhythm, when feasible, should be considered a treatment goal in patients with PAH.

Management

Rhythm versus rate control. There are no randomized studies comparing rate and rhythm control strategies in PAH patients; mostly because these patients have been excluded from clinical trials on AF therapy [20,21]. Few observational studies, given the poor tolerance of these arrhythmias and their association with adverse outcomes in PAH, report an initial attempt with rhythm control strategy including pharmacological cardioversion with antiarrhythmic drugs, electrical cardioversion, and/or catheter ablation (Table 2) [8–10,12–17,19]. Based on this paucity of data, recent European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines for PH management recommend a rhythm control strategy as the preferred approach in PAH patients with SVAs [1].

Antiarrhythmic drugs. Recommendations for antiarrhythmic drug therapy in this population are limited due to potential harmful/unknown drug–drug interactions with PAH drugs as well as adverse effects [4]. In small observational studies, a variety of pharmacologic strategies have been used including digitalis, amiodarone, dronedarone, and class IC antiarrhythmic agents (flecainide, propafenone). Overall, class III agents such as amiodarone and sotalol have been used in patients with PAH, with amiodarone perhaps being preferable due its neutral effect on myocardial contractility; still the long-term use of amiodarone may not be an option especially in young patients with PAH. The use of class IC agents theoretically should not be used in patients with structural heart disease; still it is not clear whether this can be extended to PAH patients with or without right ventricular dysfunction.

Catheter Ablation. Catheter ablation is a first-line approach to the management of cavotricuspid isthmus (CTI)-dependent AFL in patients with PAH [21]. Due to the right atrial dilation and tricuspid annular dilation in these patients, CTI ablation is often more technically challenging than in patients with structurally normal right heart chambers [22]. Still, the relative success of this intervention may be attributed to the right-sided location of typical flutter (or re-entrant pathways), allowing thus to avoid *trans*-septal puncture thereby reducing procedural risks. In a retrospective analysis of 38 patients with PAH and CTI ablation, bidirectional block was achieved in all patients; however, the PAH group had longer procedure time, required a larger number of ablation lesions and had a longer total ablation time compared with the group of patients without PAH [23].

The safety and efficacy of ablation techniques for AF specifically in the PAH population is uncertain [24]. While the pulmonary veins are still the most promising ablation targets for AF in these patients, it is possible that other triggers may play a more important role due to ultrastructural and electrical remodeling of the RA.

Anticoagulation. A number of unresolved questions regarding the use of anticoagulation in patients with PAH (with or without atrial arrhythmias) remain. It is unknown whether the presence of PAH and right heart enlargement and/or dysfunction allows for reliable risk estimation with the use of the traditional CHA2DS2VASc score [21]. In terms of the choice of anticoagulation agent, there are no obvious contraindications to the use of direct oral anticoagulants in patients with PAH. Still, clinicians pursuing stroke prophylaxis with these agents also need to be mindful of potential drug–drug interactions relevant to PAH therapies.

2.2. Ventricular arrhythmias

Ventricular arrhythmias in PAH are predominantly described in patients with congenital heart disease (tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries, univentricular heart disease) and are mostly associated with the specific anatomic substrate [25,26]. In these patients, arrhythmias represent an increasingly frequent cause of morbidity and mortality, and algorithms for risk stratification have been established based on symptoms, anatomic substrate, as well as non-invasive and invasive measures of arrhythmic burden [27]. An implantable cardioverter defibrillator is indicated for secondary prevention, provided that a reversible cause for the cardiac arrest has been excluded.

Ventricular arrhythmias are not frequently observed in other forms of PAH, despite plausible pathophysiologic changes in the right ventricular tissue. A series of papers by Bandorski et al. has investigated the

Table 1
Studies of supraventricular arrhythmia (SVA) in PAH. Incidence and clinical relevance.

Study	Study Design	N	Follow-up	Subgroup (%)	Age (years)	Female (%)	6 min walk test distance (m)	Right heart catheterization hemodynamics mPAP (mmHg) PAWP (mmHg) CI (l/min/m^2)/ CO [l/min]	Incidence of SVA (%)	Type of SVA (%)	Mortality in SVA group (%)
Tonger J et al., 2007 [8]	Single-center, retrospective	231	6 years	Group 1: -IPAH: 69.6% -PAH-CTD: 8.7 % -PAH-HIV: 1.3 % -PoPH: 5.2 % -PAH-CHD: 3.5 % Group 4: 11.7 %	48 ± 14 years	65 %	314 ± 128 m	mPAP: 54 ± 12 mmHg PAWP: 8 ± 3 mmHg CI: 2.1 ± 0.6 l/min/m^2	11.7 %	AF: 42 % AFL: 48 % AVNRT: 10 %	6.3 %, if sinus rhythm restored, 82 % in sustained AF
Ruiz-Cano M et al., 2011 [9]	Single-center, retrospective	282	–	Group 1: -IPAH: 26.1 % -DPAH: 26.1 % -PAH-CTD: 30.4 % -PAH-CHD: 17.4 %	47.3 ± 14.3 years	61 %	423.7 ± 74.6 m	–	10 %	AF: 43 % AFL: 43 % AVNRT: 14 %	26.1 %
Olsson K et al., 2013 [15]	Single-center, prospective	239	5 years	Group 1: -IPAH: 38.5 % -PAH-CTD: 10.9 % -PAH-HIV: 0.8 % -PoPH: 6.3 % -PAH-CHD: 9.2 % Group 4: 34.3 %	55 (49–66) years	61 %	335 (292–429) m	mPAP:47 (37–53) mmHg CI: 2.5 (2.0–2.8) l/min/m^2	25.1 %	AF: 50 % AFL: 50 %	Survival rate (5 year): 47 %
Wen L et al. 2014 [16]	Multicenter, prospective	280	31 ± 17 months	Group 1: -IPAH: 100 %	39 ± 15 years	68 %	383 ± 95 m	mPAP: 62 ± 15 mmHg PAWP :9 ± 5 mmHg CI: 2.5 ± 1.4 l/min/m^2	1st year: 4 % 3rd year: 12.4 % 6th year: 15.8 %	AF: 40 % AFL: 33 % AT: 28 %	SVA: 40 % No SVA : 17 %
Cannillo M et al., 2015 [10]	Single-center, retrospective	77	35 months	Group 1: -IPAH: 21 % -DPAH: 1 % -PAH-CTD: 23 % -PAH-HIV: 3 % -PoPH: 12 % -PAH-CHD: 6 % Group 3: 16 % Group 4: 18 %	63 (48; 70.7) years	53 %	340 (188.7; 428.7) m	mPAP: 44 (35; 54) mmHg CI: 2.6 (2.2; 3.4)	22 %	Persistent AF: 47 % Permanent AF: 17 % AT: 12 % AVNRT: 6 % AFL: 12 %	SVA : 53 % No SVA:13 %
Malaczynska-Rajpold K et al., 2015 [11]	Single-center, retrospective	48	28.8 ± 17.7 months	Group 1: -IPAH: 63 % -PAH-CTD: 21 % -PAH-CHD: 17 %	49 (19–77) years	69 %	No arrhythmia: 341.3 ± 97.8 m Arrhythmia: 314 ± 114 m	No arrhythmia: mPAP: 53.3 ± 9.1 mmHg Arrhythmia: mPAP: 53.9 ± 11.4 mmHg	35 %	AF: 38 % AFL: 31 % AT: 31 %	Overall mortality: 29 % SVA: 35 % No SVA: 26 %
Mercurio V et al., 2017 [17]	Single-center, prospective	317	67 ± 51 months	Group 1: -IPAH: 36.5 % -PAH-CTD: 63.4 %	56.7 ± 14.4 years	83.9 %	327.6 ± 128.6 m	mPAP: 45.5 ± 14 mmHg PAWP : 10.6 ± 4.0 mmHg CO: 4.4 ± 1.6	13.2 % at 5 years follow-up	Overall, in patients with atrial arrhythmias (n = 44): AF: 34 episodes AFL: 18 episodes AT: 5 episodes	Overall mortality: 53.6 % SVA: 69 % No SVA: 51 %
Smith B et al., 2018 [12]	Single-center, retrospective	297	6 months -1 year	Group 1: 89.5 % Group 4: 10.4 %	57.6 ± 14.7 years	67.3 %	–	mPAP: 45.8 ± 12.0 mmHg PAWP	27 %	AF: 58.2 % AFL: 31.6 %	32.5 % (30

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	N	Follow-up	Subgroup (%)	Age (years)	Female (%)	6 min walk test distance (m)	Right heart catheterization hemodynamics mPAP (mmHg) PAWP (mmHg) CI (l/min/m^2)/ CO [l/min]	Incidence of SVA (%)	Type of SVA (%)	Mortality in SVA group (%)
								: 10.0 ± 3.15 mmHg CO: 4.63 ± 1.43 [l/min]			days after SVA)
Drakopoulou et al., 2018 [13]	Single-center, retrospective	310	6.1 years	Group 1: -Eisenmenger syndrome: 58.4 % -Pre-tricuspid defect: 3.9 % -Post-tricuspid defect: 46.9 % -Complex anatomy: 49.2 % -After defect correction: 15.2 % -Other: 26.5 %	34.9 ± 12.3 years	63.2 %	–	–	20.6 %	SVA: 11 % AF: 4.5 %	21.9 % overall
Waligóra M et al., 2018 [18]	Single-center, prospective	97	3 years	Group 1: -IPAH: 54.6 % -PAH- CTD: 15.4 % -PAH-CHD: 30.0 %	47.6 ± 16.9 years	67 %	356.1 ± 112 m	mPAP: 57.1 ± 21.6 mmHg PAWP: 9.1 ± 4.6 mmHg CI: 2.1 ± 1.2 (l/min/m^2)	46.4 %	AF: 17.8 % Paroxysmal AF: 22.2 % AFL: 4.3 % Other: 24.7 %	–
Fingrova Z et al., 2021 [14]	Single-center, retrospective	755, (641 isolated precapillary PH)	3.8 ± 2.8 years	Group 1: -IPAH: 34 % -PAH-CTD: 10 % -PAH-CHD: 8 % Group 3: 22 % Group 4: 20 % Group 5: 6 %	60 ± 15 years	59 %	321 ± 122 m	Overall: mPAP: 48 ± 16 mmHg PAWP: 12 ± 5 mmHg For isolated pre-capillary: mPAP: 47 ± 16 mmHg PAWP: 10 ± 3 mmHg	Group 1: -IPAH: 25 % -PAH-CTD:29 % -PAH-CHD:35 % Group 3: 16 % Group 4: 30 % Group 5: 27 %	In isolated pre-capillary PH: AF: 17 % AFL: 4.4 %	55 %
Sammut A et al., 2023 [19]	Single-center, prospective	84 (ASPIRE registry)	26 months	Group 1: -IPAH: 31 % -PAH-CTD: 21.4 % -PAH-CHD: 8.3 % -PoPH: 1.1 % Group 4: 38.1	66 (57–73)	46 %	–	mPAP: 48 (41–58) mmHg PAWP: 11 (8–14) mmHg CI: 2.4 (1.9–2.7) (l/min/m^2)	–	AFL: 71 % AF: 29 %	64 % (22 months after SVA)

AF: atrial fibrillation, AFL: atrial flutter, CO cardiac output CI cardiac index, DPAH: Drug- or toxin-associated pulmonary arterial hypertension IPAH: Idiopathic pulmonary arterial hypertension, mPAP: Mean pulmonary arterial pressure, PAH: Pulmonary arterial hypertension, PAH-CHD: Pulmonary arterial hypertension associated with congenital heart disease, PAH-HIV: pulmonary arterial hypertension associated with human immunodeficiency virus infectionPortopulmonary hypertension, PAWP: Pulmonary arterial wedge pressure, PAH-CTD: Pulmonary arterial hypertension associated with connective tissue disease, PH: Pulmonary hypertension, PoPH: Porto-pulmonary hypertension, PVR: Pulmonary vascular resistance, RV: Right ventricle/right ventricular, SVA: supraventricular arrhythmia.

Table 2
Management strategies and success rates of therapy for SVA in PAH.

Study	Strategy	DCCV (%)	Ablation (%)	Overdrive pacing (%)	Pharmacologic	Sinus rhythm obtained	Recurrence of SVA (%)
Tonger J et al., 2007 [8]	Rhythm control	AFL: 40 % AF: 15.4 %	AFL: 33 % AVNRT: 100 %	AFL: 20 %	AFI: 6.6 %, digoxin	AFL: 100% AVNRT:100%, AF: 15.3%	12.5 % after ablation
Olsson K et al., 2013 [15]	Rhythm control	AFL: 37.5 % AF: 75 %	AFL: 12.5 %,	AFL: 4.2 %	AFL: 45.8 % AF: 12.5 %, amiodarone, dronedarone, digoxin, flecainide	AFL: 100 % AF: 88 %	18.8 % after ablation AFL: 21% AF: 21%
Wen L et al., 2014 [16]	Rhythm control	5.0 %	2.5 %	–	92.5 %, amiodarone, digoxin	AT : 100 %, AF: 25 %, AFL: 46.1 %	15 %
Cannillo M et al., 2015 [10]	76% rhythm control	61.5 %	23.1 %	–	76.9 %, sotalol, amiodarone, 1C antiarrhythmic	64.7 %	52.9 %
Małaczynska-Rajpold K et al., 2015 [15]	Rhythm control (AF: 82.4%, AFL: 100%)	AFL: 76.4 % AF: 5.8 % AT: 5.8 %	AFL: 11.7 %	AFL: 5.8 %	AF: 5.8 %, amiodarone, propafenone, sotalol AT: 5.8 %, amiodarone	92.8 %	29 %
Mercurio V et al., 2017 [17]	Rhythm control	30.9 %	30.9 %	–	amiodarone, digoxin, metoprolol/ carvedilol, verapamil/diltiazem, flecainide	–	64.3 %
Smith B et al., 2018 [12]	39.2% rhythm control	45.1 %	54.8 %	–	86 % , atrioventricular nodal blocking and/or anti-arrhythmic agent)	–	–
Drakopoulou et al., 2018 [13]	69.4% rhythm control	32.4 %	32.4 %	2.9 %	14.7 %	100%	31.7%
Fingrova Z et al., 2021 [14]	65% rhythm control	–	AT:100 % AFL: 71 % AF: 5 %.	–	AFl: 13 % amiodarone, 16 % b-blockers AF: 22 % amiodarone, 7% propafenone, 5 % sotalol, 38% b-blockers, 9% verapamil 9 %, 6% digoxin.	AFL: 86 %	21 %
Sammut A et al., 2023 [19]	74% rhythm control	52 %	–	–	Rate control: 56 % digoxin, 6 % CCB, 22 % digoxin, bisoprolol Rhythm control : 41 % amiodarone, 50 % digoxin and amiodarone, 9 % CCB, amiodarone	33 % (rate control), 59 % (medical rhythm control), 95 % (DCCV)	–

AF: atrial fibrillation, AFL: atrial flutter, AT: atrial tachycardia, AVNRT: Atrioventricular nodal reentrant tachycardia, AVRT: Atrioventricular re-entry tachycardia, CCB: calcium-channel blocker, DCCV: electrical cardioversion, SVA: supraventricular arrhythmia.

incidence and impact of VAs on the outcome of patients with PAH [28–30]. An initial retrospective, dual-center study, analyzed data from 55 patients presenting with PH (Group 1: 14 patients) and an indication for electrophysiological study [30]. Fifteen patients (Group 1: 3 patients) showed non-sustained ventricular tachycardia (NSVT) during Holter-ECG monitoring and a programmed ventricular stimulation protocol was performed; no ventricular tachycardia or fibrillation was induced. This study showed that the presence of NSVT was not associated with inducible VAs in programmed electrical stimulation. It has to be noted however, that the value of programmed electrical stimulation in the risk stratification of PAH patients has not been validated by prospective studies. Moreover, extrapolation of data from such a study is challenging due to the small number of patients. In a larger study, Bandorski et al. sought to determine the incidence of VAs in asymptomatic non-group 2 PH patients [29]. Ninety-two patients were enrolled, all of whom were on PAH-specific medication. During 72-h Holter monitoring, relevant arrhythmias were newly detected in 17 patients (18.5 %) and among other arrhythmias, NSVT was the most prevalent (12 patients, 70.5 %). In this study, the authors highlighted that ventricular tachycardias occur more often than previously reported and recommend the use of Holter monitoring for the earlier detection of arrhythmias. In a follow-up study, Bandorski et al. sought to determine the prognostic significance of NSVT in patients with PAH or inoperable CTEPH [28]. Overall, 78 patients were included in the study, of whom 12 had newly detected NSVT by Holter ECG monitoring. In this study, NSVT was not correlated with increased mortality in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH). Still, the study was limited by the lack of routine and sustained rhythm monitoring; thus, the possibility that VAs contribute to a higher proportion of SCD cannot be excluded.

Management. Therapeutic options are unclear concerning antiarrhythmic drugs and device therapy for SCD prevention in patients with PAH, given the absence of any clinical trials demonstrating clear benefit in this cohort [31]. Moreover, the application of guidelines for the management of arrhythmia in left heart failure raises some skepticism in patients with RV failure and do not seem to apply, due to differences in the underlying disease processes [32].

3. Non-arrhythmic causes of sudden cardiac death

The most relevant mechanisms for SCD in PAH seem to be related to severe dilatation of the pulmonary artery and its subsequent mechanical complications [5]. Pulmonary artery dilation is a common finding in patients with PAH as a consequence of long-term elevated pressures and may reflect disease duration and severity. The complications of pulmonary artery dilation include LMCS, PAD, pulmonary artery rupture, and massive hemoptysis (Fig. 1).

3.1. Left main compression syndrome

LMCS was first described by Corday et al. in 1957 as compression of the left main coronary artery between the aorta and the enlarged main pulmonary artery with subsequent coronary insufficiency [33]. The true incidence of the syndrome is unknown and ranges from 5 % to 44 % in

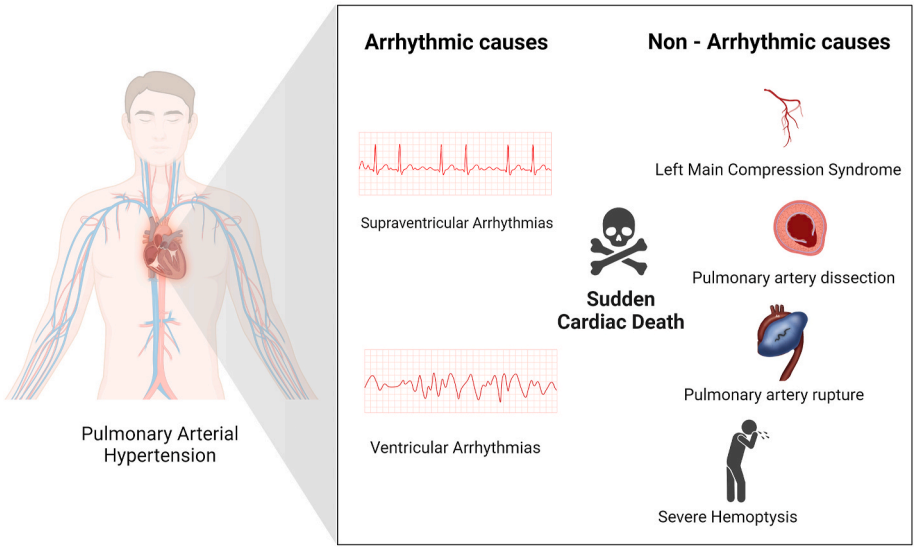

Fig. 1. Arrhythmic and non-arrhythmic causes of sudden cardiac death. Created with Biorender.com.

patients with PAH [34]. It is an uncommon cause of angina, left ventricular dysfunction, VAs and/or SCD [35,36].

Diagnosis. In patients with PAH and substantial dilation of the main pulmonary artery or patients with symptoms, further evaluation should be performed to exclude LMCS. Non-invasive screening with cardiac computed tomography or magnetic resonance angiography are useful tools for diagnosis; invasive coronary angiography, however, with the use of intravascular ultrasound and fractional flow reserve estimation seem to evaluate the compression severity in asymptomatic patients. Myocardial perfusion techniques do not seem to be of any additive value in establishing the diagnosis [37].

Management. Left main compression syndrome manifests as a slight narrowing of the left main coronary ostium with progressive recovery in the distal diameter, whereas the remaining coronary circulation remains normal. In symptomatic patients, it is crucial to restore unobstructed coronary flow. Surgical correction of the dilated pulmonary artery has been reported and is associated with a reduction in left main coronary artery stenosis [38]. It should be discouraged though in patients with severe PAH and right ventricular failure. Thus, percutaneous coronary intervention with stent implantation, is the procedure of choice as its seems to be a safe and effective option, avoiding the postoperative risk of right ventricular failure in patients with significantly increased pulmonary vascular resistance. For asymptomatic patients with LMCS or non-severe compromise of its anatomy, evaluation with intravascular ultrasound or fractional flow reserve estimation may help to avoid unnecessary interventions which may result in a high complication rate [39]. In 2001, Rich et al. reported a successful left main coronary artery stenting in 2 patients with idiopathic pulmonary arterial hypertension and LMCS [40]. Since then, several other authors, have also reported successful angiographic and short-term clinical outcomes. Of note, all reported cases involved compression of the ostium or proximal left main coronary artery, sparing the left main bifurcation, so single stent placement was always sufficient with a high procedural success rate and a low restenosis risk at follow-up. However, since only successful results tend to be published in such circumstances there is publication bias.

3.2. Pulmonary artery dissection and rupture

The first description of a case with PAD in the literature was by Helmbrecht in 1842 and followed by other publications of case reports [41]. In patients with PAH, PAD is considered the result of chronically elevated intravascular pressure and is related to medial degeneration, with fragmentation of elastic fibers and weakening of the arterial wall. Chronic increase of intravascular pressure causes elevated shear stress which may eventually lead to the development of an intimal tear and rupture. The site of dissection typically involves the pulmonary artery trunk (without involvement of its branches) or the site of the localized aneurysm. Unlike aortic dissection, PAD progresses rapidly and its false lumen typically tends to rupture rather than develop a re-entry site. Almost all the available literature considers PAD as an extremely rare condition with a very high mortality rate.

Diagnosis. The diagnosis of PAD and rupture is usually made post-mortem, as the majority of these patients experience sudden death. In patients with PAH and a high index of suspicion, that is patients presenting with acute dyspnea on exertion, retrosternal chest pain of acute onset, central cyanosis, or sudden hemodynamic decompensation, further evaluation should be performed. The transthoracic echocardiogram, remains a first line diagnostic tool, but cardiac computed tomography and magnetic resonance angiography, are the gold standards for confirming the diagnosis (Fig. 2) [42,43].

Management. The low likelihood of this complication in PAH patients has not allowed for a consensus on treatment strategy. Although surgical management is considered the optimal treatment strategy and mandatory, the overall prognosis and survival remains poor [5]. Other procedures include lung isolation (to protect the contralateral lung and decrease bleeding in the affected lung), endovascular techniques, stent graft implantation, therapeutic embolism of the segmental artery and embolization of the vessel. Besides the above treatment options, urgent listing the patient for lung transplantation should be considered when possible.

3.3. Hemoptysis

Spontaneous bleeding events are common in PAH and are usually minor and self-limiting [44,45]. Massive hemoptysis however, one of the most perilous complications in the clinical course of PAH, is correlated with substantial morbidity and mortality and impaired quality of life. The underlying pathophysiology of hemoptysis in PAH remains intricate and involves various, complex mechanisms, such as hypoxic vasoconstriction and hemostatic abnormalities with intravascular thrombosis leading to reduction of the total surface of the pulmonary circulation and eventually bronchial artery proliferation and enlargement. As a consequence, the source of hemoptysis is predominantly the bronchial circulation (rather than the pulmonary circulation) and in a minority of cases it may originate from the aorta and/or the systemic arterial supply to the lungs [46].

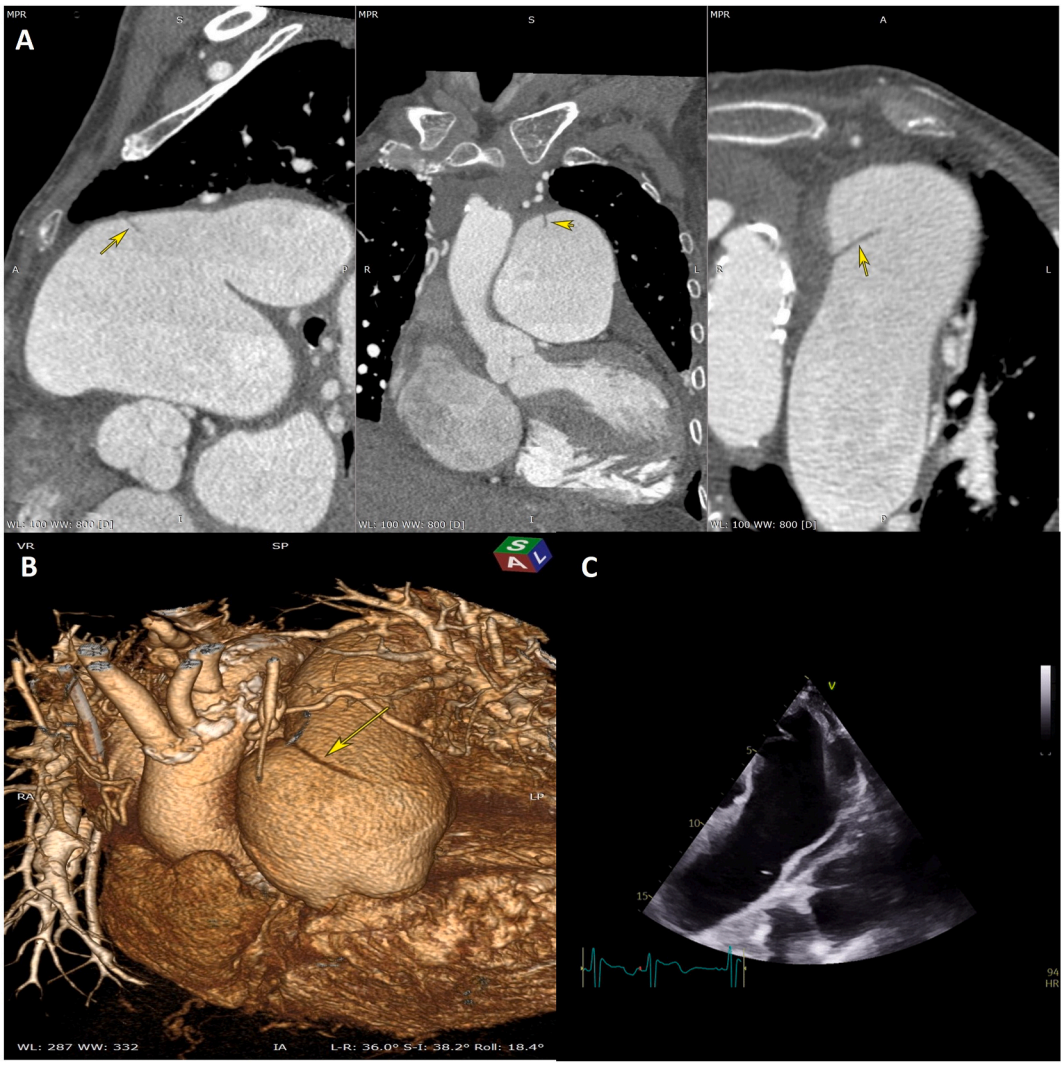

Fig. 2. 67 year-old woman with severe CTEPH and advanced right heart failure was admitted with sharp, tearing chest pain of abrupt onset. Non-invasive imaging with cardiac computed tomography (A, B) and transthoracic echocardiography (C) demonstrated a dissection of a dilated pulmonary artery. chronic thromboembolic pulmonary hyperetension.

Diagnosis. Diagnostic options for massive hemoptysis include radiography (chest x-ray), bronchoscopy, and computed tomography, in an effort to elucidate the location of the bleeding and guide potential treatment options. Routine chest x-ray is readily available and may reveal dilated, calcified, or aneurysmal central pulmonary arteries; however, due to low discriminative ability, it is diagnostic for hemoptysis in only half of cases. Bronchoscopy is more accurate and constitutes a valuable tool for evaluating and treating hemoptysis; however, its role in the setting of massive active hemoptysis is controversial due to the excessive blood in the bronchi and the risk of airway compromise due to sedation and hypoxia. Lastly, contrast-enhanced computed tomography scan with an arterial phase is extremely valuable in localization of bleeding, with higher accuracy than bronchoscopy since it can detect both bronchial and non-bronchial vessels.

Management. An immediate initial therapeutic approach is recommended including airway protection, prevention of hypoxia and hemodynamic stabilization [5]. Thereafter, quantification of hemoptysis and cessation of bleeding is also paramount. Neutralization of oral anticoagulants with vitamin K, reversal of heparin with protamine, administration of antifibrinolytic agents (tranexamic acid), bronchoscopy and selective embolization are the usual steps. The selection of arteries to be embolized is based on the findings of computed tomography, bronchoscopy, and angiography, always in relation to the clinical situation [47]. Based on recent ESC Guidelines, lung transplant should be considered in patients with recurrent and severe hemoptysis despite optimized treatment [48]. Last but not least, since many PAH patients may be treated with anticoagulants, these agents should be discontinued in case of a hemoptysis event.

4. Summary- conclusions

Pulmonary arterial hypertension is a chronic disease characterized by progression of pulmonary vasculopathy leading to RV dysfunction and substantial morbidity and mortality. Besides RV failure, premature death seems to be associated with the occurrence of arrhythmias, as well as mechanical complications related to the dilation of pulmonary artery. Early identification of the PAH population at risk for SCD would warrant closer monitoring for symptoms and aggressive diagnostic approach for potentially therapeutic intervention.

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CRediT authorship contribution statement

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Declaration of competing interest

There are no conflicts of interest.

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