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Cardiac Arrhythmias in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: Mechanistic Insights, Pathophysiology, and Outcomes

Abdulrahman Abouzaid[1] | Khansa Ali[2] | Suniya Jatoi[2] | Mansoor Ahmed[2] | Gulfam Ahmad[2] | Ahsan Nazim[2] |
Amin Mehmoodi[3] 🆔 | Jahanzeb Malik[4]

[1]Department of Medicine, East Lancashire Teaching Hospital, Lancashire, UK | [2]Department of Medicine, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan | [3]Department of Medicine, Ibn e Seena Hospital, Kabul, Afghanistan | [4]Department of Cardiology, Cardiovascular Analytics Group, Islamabad, Pakistan

Correspondence: Amin Mehmoodi (amin.doctor21@gmail.com)

ABSTRACT

Arrhythmias are increasingly recognized as severe complications of precapillary pulmonary hypertension, encompassing pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). Despite their significant contribution to symptoms, morbidity, in-hospital mortality, and potentially sudden death in PAH/CTEPH, there remains a lack of comprehensive data on epidemiology, pathophysiology, and outcomes to inform the management of these patients. This review provides an overview of the latest evidence on this subject, spanning from the molecular mechanisms underlying arrhythmias in the hypertrophied or failing right heart to the clinical aspects of epidemiology, diagnosis, and treatment.

1 | Introduction

Pulmonary hypertension (PH) involves an elevation of mean pulmonary artery pressure (mPAP) to 25 mmHg or higher at rest, confirmed through right heart catheterization (RHC) (Galie et al. 2015). The condition is categorized into five groups by the latest guidelines from the European Society of Cardiology (ESC) and European Respiratory Society (ERS): Group 1 (pulmonary artery hypertension [PAH], including various causes), Group 2 (PH due to left heart disease), Group 3 (PH due to lung diseases or hypoxia), Group 4 (chronic thromboembolic PH [CTEPH]), and Group 5 (PH with unclear or multifactorial mechanisms) (Gall et al. 2017). Survival rates over 5 years for PH range from 38% to 59%, depending on the underlying cause, with Group 3 PH currently carrying the worst prognosis (D'Alonzo et al. 1991; Wijeratne et al. 2018). A recent epidemiological study found a sevenfold increase in standardized mortality rate among PH patients (Demerouti et al. 2013; Hoeper et al. 2002).

In PAH, right heart failure is often the primary cause of death, directly linked to elevated PAP. However, around half of PAH patients in some studies succumb to other causes, where PH plays a contributing role. Arrhythmias, including sinus tachycardia, atrial fibrillation (AF), atrial flutter (AFl), sinus bradycardia, ventricular tachycardia (VT), and ventricular fibrillation (VF), are recognized as severe, late-stage complications of PAH and CTEPH (Tonelli et al. 2013; Rajdev, Garan, and Biviano 2012; Anand et al. 2016; Bandyopadhyay et al. 2015). Despite their known impact on symptom burden, morbidity, in-hospital mortality, and possibly sudden death, there is limited data on the epidemiology, pathophysiology, and outcomes of PAH patients with arrhythmias (Tongers et al. 2007; Kanemoto and Sasamoto 1979; James 1962).

This review delves into the maladaptive and arrhythmogenic responses of the right heart in patients with Group 1 and Group 4 PH. We examine the current trends in clinical management, highlight evidence-based approaches, and explore options for managing arrhythmias in PH. Additionally, we pinpoint areas where knowledge is lacking and suggest future research directions.

While arrhythmias are known to occur across all PH subgroups, our focus in this review is primarily on Group 1 PH (PAH) and CTEPH. This choice is driven by two main factors. Firstly, the majority of basic science investigations related to this subject have been carried out in animal models of PAH, and clinical studies have predominantly involved patients with PAH (Group 1) and/or CTEPH (Group 4). Secondly, other subgroups, particularly Groups 2 and 3, have distinct causes and pathophysiologies, likely leading to differences in arrhythmia mechanisms, types, incidence, and outcomes. To maintain clarity and coherence in the text, we collectively refer to patients with Group 1 (PAH) and Group 4 (CTEPH) as PAH/CTEPH, unless specified otherwise.

2 | Right Ventricular Arrhythmogenesis in Pulmonary Hypertension

Several potential mechanisms have been identified that contribute to increased susceptibility to arrhythmias in patients with elevated pulmonary artery pressures (PAPs) and pressure- and volume-overloaded right atrium and ventricle. One of the earliest studies observed vascular degeneration and infarction in the sinus and atrioventricular (AV) nodes, along with instances of sudden death in patients diagnosed with primary PH (now termed idiopathic pulmonary arterial hypertension [IPAH])

(James 1962). Over subsequent decades, a more detailed exploration of these mechanisms has unfolded, revealing intricate alterations in the structure, electrophysiology, metabolism, and signaling pathways within the right heart. Figure 1 illustrates the pathogenesis of arrhythmogenesis in PH.

2.1 | Autonomic Nervous System

The autonomic nervous system plays a critical role in the development and progression of pulmonary arterial hypertension (PAH) and right heart failure, and it has been implicated in the pathogenesis of arrhythmias and sudden cardiac death (SCD) (Vaillancourt et al. 2017). Sympathetic overactivity in PAH is evidenced by reduced heart rate variability, impaired baroreflex function, and decreased exercise capacity, and it is associated with worsened clinical outcomes. This heightened sympathetic activity has also been linked to premature ventricular contractions and ventricular arrhythmias in PAH patients (Franciosi et al. 2017; Ciarka et al. 2010; Velez-Roa et al. 2004; Wensel et al. 2009).

Iodine-123-metaiodobenzylguanidine (123I-mIBG) myocardial imaging, a technique used to assess cardiac sympathetic nervous activity via single-photon emission computed tomography (SPECT), supports these observations (Folino et al. 2003; Carrio et al. 2010; Cohen-Solal et al. 1999). The uptake of 123I-mIBG, a modified form of guanethidine, reflects sympathetic nerve activity through the uptake-1 mechanism, which normally transports norepinephrine (Morimitsu et al. 1996). By comparing activity at 3-h scans to that at 30 min, one can gauge the washout of mIBG, indicating the retained norepinephrine within sympathetic neurons. Activation of the sympathetic system leads to
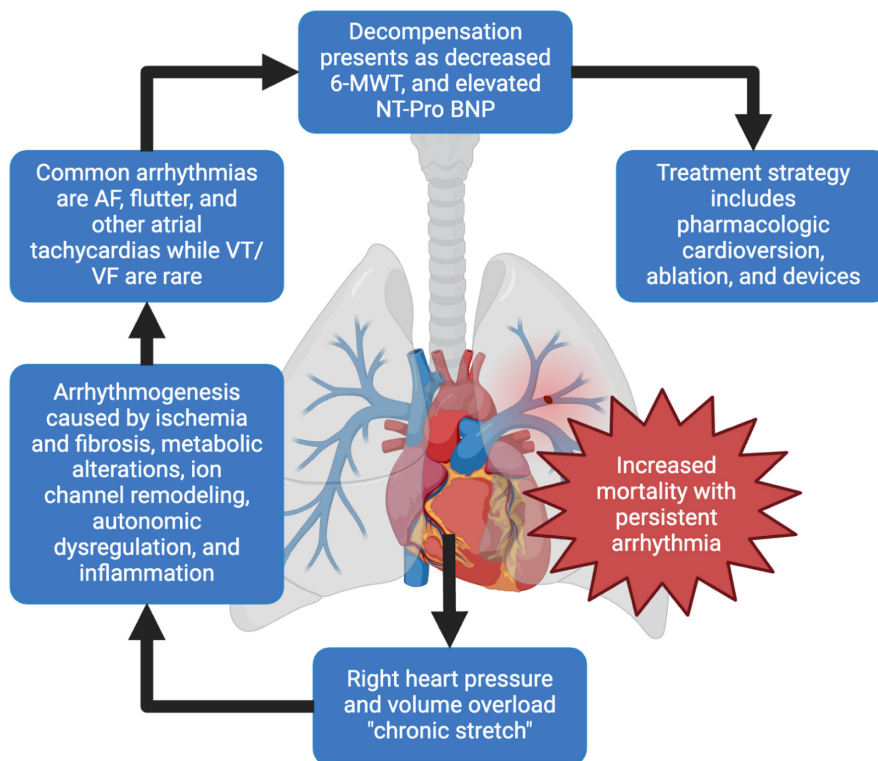
FIGURE 1 | A schematic representation depicting the progression and impact of arrhythmias in pulmonary hypertension (PH).

reduced presynaptic norepinephrine uptake, resulting in lower retention of mIBG. A low heart-to-mediastinal (HMR) ratio of mIBG (<1.2) in later images predicts event-free survival in left heart failure (Sakamaki et al. 2000; Maron and Leopold 2015).

Increasing mPAP correlates with decreased mIBG activity in the right ventricle (RV), indicating heightened RV sympathetic activity. This reduced mIBG activity is associated with poorer cumulative survival in PAH patients. Furthermore, there is evidence of adrenergic remodeling in the RV, including downregulation and desensitization of β1-adrenergic receptors, as well as downregulation of α-adrenergic and dopaminergic receptors (Ryan and Archer 2014). In PAH patients with RV failure, there is also decreased responsiveness of adenylyl cyclase to β-agonists and depletion of norepinephrine, resulting in an inability to augment catecholamine levels during exercise (Ryan et al. 2015).

Both the intrinsic and extrinsic cardiac nervous systems have been implicated in the susceptibility to supraventricular arrhythmias (SVA) in PAH (Piao et al. 2012; Bristow et al. 1992; Nootens et al. 1995). In a recent study conducted by Huang et al., atrial arrhythmias were investigated using a canine model where PAH was induced in beagles through a single injection of 2 mg/kg of dehydromonocrotaline, followed by an 8-week observation period during which PAH developed (Zhao et al. 2015). Dogs with PAH exhibited increased vulnerability to induced AF/AFl compared to controls.

Histopathological analysis revealed higher densities of sympathetic nerves and β1 autonomic receptors in the right atrium of PAH dogs, contrasting with the downregulation of β-adrenergic receptors in the failing RV (Bristow et al. 1992; Nootens et al. 1995). By selectively ablating the ganglionic plexi, which contain cholinergic and adrenergic neurons influencing the atrial myocardium, susceptibility to atrial arrhythmias was reduced, highlighting the crucial role of the adrenergic component of the autonomic nervous system in regulating vulnerability to atrial arrhythmias in PAH.

3 | Electrical Remodeling

Stretch and fibrosis of the right atrium create an arrhythmogenic environment, which, when combined with electrical remodeling resulting from alterations in the expression and function of ion channels in cardiomyocytes, heightens susceptibility to and propagation of arrhythmias (Medi et al. 2012; John et al. 2008; Sanders et al. 2003; Morton et al. 2003). An electrophysiology study comparing the right atrium of eight patients with long-standing IPAH to 16 matched controls revealed prolonged sinus node recovery time, reduced tissue voltage with electrically inactive areas in the atrium, slowed atrial conduction and activation times, and an increase in areas exhibiting complex fractionated activity, known as critical sites for sustaining AF (Medi et al. 2011; Oral et al. 2006). These factors contribute to an elevated susceptibility to AF induction, triggered by increased automaticity (ectopy) or single and multiple reentrant pathways (Nattel, Burstein, and Dobrev 2008).

Patients with PAH or chronic thromboembolic PH (CTEPH) often exhibit right ventricular hypertrophy (RVH) and

fibrosis, which are linked to increased overall mortality (Ozawa et al. 2013). RVH is characterized by the downregulation of inward rectifying potassium channels and slowed ventricular conduction, stemming from reduced expression of gap junctions, particularly connexin-43, as well as fibrotic changes (Piao et al. 2010). These alterations impair both depolarization and repolarization processes in RVH, leading to arrhythmogenic early and late after-depolarizations and heightened susceptibility to spontaneous or induced ventricular arrhythmias, observed in models of RVH and left ventricular hypertrophy (LVH) (Fischer et al. 2007; Tanaka et al. 2013; Umar et al. 2012).

Changes in calcium handling have also been implicated in the prolongation and dispersion of action potential duration in rat models of PH (Benoist et al. 2011, 2012). Collectively, these dynamic alterations in the electrical system of the RV predispose individuals to the formation of reentrant circuits and subsequent arrhythmias (Keldermann et al. 2008; Wickenden et al. 1998). Structural remodeling, such as myocyte fiber angle disarray, can further disrupt electrical conduction, resulting in prolonged action potential duration and increased vulnerability to arrhythmias, as demonstrated in the monocrotaline-PAH rat model (Benoist et al. 2014).

3.1 | Ischemia

Ischemia is a well-recognized pro-arrhythmic factor in the left ventricle, and similarly, it is believed that RV ischemia contributes to arrhythmia vulnerability in patients with PAH/CTEPH (Sedlis 1992; Luqman et al. 2007). Elevated levels of troponin in PAH patients indicate this ischemic state and are linked to increased mortality, although not specifically tied to arrhythmias (Torbicki et al. 2003). The development of ischemia in RVH is multifaceted, stemming from a combination of factors affecting epicardial coronary artery perfusion pressure (including reduced perfusion pressure in the right coronary artery due to elevated right ventricular systolic pressure [RVSP] and compression of the left main coronary artery) as well as microvascular abnormalities (such as impaired angiogenesis resulting in capillary rarefaction due to decreased expression of angiogenic genes) (van Wolferen et al. 2008; Galie et al. 2017; Bogaard, Abe, et al. 2009; Bogaard, Natarajan, et al. 2009; Archer et al. 2013). Additionally, secondary metabolic changes related to ischemia in the maladaptive RV, such as increased rates of uncoupled glycolysis, are thought to perpetuate the cycle of ischemia (Archer et al. 2013).

4 | ECG Abnormalities

Changes in electrocardiogram (ECG) patterns are frequent among patients with PAH and CTEPH. However, there is ongoing debate regarding the clinical significance of these abnormalities, leading to uncertainty regarding the usefulness of screening ECGs. In a study by Kanemoto and Sasamoto (1979), 171 ECGs from 101 PAH patients were reviewed, revealing "arrhythmia" in 17.8% of cases, with a notably higher prevalence (33.9%) among those who had passed away. Three main abnormalities constituted 70% of all observed arrhythmias: sinus tachycardia (38%), sinus bradycardia (18%), and first-degree

AV block (15%). Sinus tachycardia was notably associated with increased mortality. A more recent investigation tracked the progression of ECG changes in 50 PAH patients, showing a significant increase in median heart rate, PR interval, QRS duration, R/S ratio in lead V1, and QTc duration in the ECG closest to death compared to the initial diagnosis. None of the PAH patients retained a normal ECG close to death (Tonelli et al. 2014).

As mentioned earlier, sinus tachycardia is likely a consequence of autonomic dysregulation in patients with RV failure and PH (Ciarka et al. 2010). Moreover, in these patients, stroke volume may be fixed at a low level, and sinus tachycardia serves as a compensatory mechanism to maintain cardiac output. The reduction in heart rate variability, indicative of autonomic dysfunction, reflects constant activation of the autonomic nervous system and may also represent an effort to stabilize cardiac output. During exercise testing of PAH patients, heart rate variability diminishes, and a decline in resting heart rate variability corresponds with the severity of PH as measured by mPAP (Wensel et al. 2009; Yi et al. 2014). Sinus tachycardia and diminished heart rate variability could serve as valuable indicators of susceptibility to SVA.

In conditions affecting the left heart and other noncardiac ailments, the prolongation of the QT interval on an ECG is recognized as a precursor to ventricular arrhythmias and is associated with heightened mortality and sudden death (Barr et al. 1994; Bluzaite et al. 2006; Pye, Quinn, and Cobbe 1994; Zareba, Moss, and le Cessie 1994; Algra et al. 1993, 1991; Malik and Batchvarov 2000; Okin et al. 2000). In PAH, longer QTc (corrected QT) intervals and QTc dispersion correlate with increasing mPAP (Hong-Liang et al. 2009). In a study matching patients receiving PAH-specific therapy by age and sex, both QRS duration and QTc interval were extended in 202 PAH patients compared to 100 controls. A QTc duration ≥480 ms emerged as an independent predictor of mortality, even within the subgroup encompassing PAH and CTEPH (Rich et al. 2013). Notably, there was no discernible difference in serum potassium levels to account for the QTc prolongation, as might be expected with aggressive diuretic use. Instead, QTc prolongation correlated with impaired right ventricular (RV) function, increased RV mass (determined via cardiac MRI), and a bleak prognosis.

In animal models of PAH, the prolongation of QT interval is linked to an extended action potential duration, creating a proarrhythmic condition (Benoist et al. 2012). In the monocrotaline-induced rodent PAH model, QT prolongation is correlated with reduced expression of repolarizing voltage-gated potassium channels (Kv) such as Kv1.2, Kv1.5, and Kv4.2 in right ventricular (RV) myocytes. This effect can be reversed by metabolic therapies like the pyruvate dehydrogenase kinase inhibitor dichloroacetate (Piao et al. 2010). The precise cause of prolonged QTc in patients with PH remains unclear but may result from chronic ischemia in RVH and/or alterations in the sympathetic nervous system, as discussed previously (Piao et al. 2010; Zhou et al. 2001). While extrapolation from other disease processes suggests that such ionic remodeling and QTc prolongation may increase susceptibility to ventricular arrhythmias, direct investigation in PAH/CTEPH patients has yet to be conducted, presenting an avenue for future research. QRS

prolongation has also been under active investigation in PAH. Studies have revealed longer QRS duration in patients with PH compared to controls, and this is associated with markers of reduced RV function. Specifically, prolonged QRS duration may contribute to RV dyssynchrony, a common occurrence in PAH that independently predicts clinical deterioration (Badagliacca et al. 2015; Kalogeropoulos et al. 2008).

5 | Supraventricular Tachycardias

SVAs are the most common rhythm disturbances observed in patients with PAH and CTEPH, occurring more frequently than in the general population (Galie et al. 2015; Orejarena et al. 1998; Heeringa et al. 2006; Lloyd-Jones et al. 2004). In this context, SVAs refer specifically to AF, AFl, AV nodal reentrant tachycardia (AVNRT), or atrial tachycardia, excluding sinus tachycardia. The onset of SVA often indicates progressive right-sided cardiac dysfunction and can lead to clinical decompensation by disrupting the atrial kick, crucial for diastolic right ventricular filling in the hypertrophied RV (Rajdev, Garan, and Biviano 2012; Goldstein et al. 1990; Gaine, Naeije, and Peacock 2014). Several retrospective and prospective studies have investigated the incidence and clinical significance of SVA in PAH, some including patients with CTEPH, and one involving patients with Group 3 PH (Malaczyn′ska-Rajpold et al. 2016; Olsson et al. 2013; Rottlaender et al. 2012; Wen et al. 2014; Cannillo et al. 2015). While these studies are small and have significant methodological limitations, collectively, they underscore six key points regarding SVA and PAH/CTEPH.

1. There is not a clear distinction in baseline characteristics that can reliably predict susceptibility to SVAs. However, certain findings are more closely associated with the development of SVA, such as elevated right atrial pressure (RAP) and indicators of overall cardiac dysfunction, including decreased cardiac index/output, increased right ventricular (RV) diameter, and elevated NT-proBNP levels (Malaczyn′ska-Rajpold et al. 2016; Olsson et al. 2013; Rottlaender et al. 2012; Wen et al. 2014; Cannillo et al. 2015; Mercurio et al. 2018). In some studies, pulmonary vascular resistance (PVR) and mPAP were only minimally associated with the incidence of SVA, suggesting that it is the heart's response to increased afterload rather than the afterload itself that predicts SVA development (Olsson et al. 2013; Wen et al. 2014). This finding is biologically plausible, considering that the maladaptive response of the right heart is believed to predispose to atrial arrhythmias (Zhao et al. 2015; Medi et al. 2012).

   Noninvasive measures of disease severity, such as the 6-min walk distance (6MWD) and World Health Organization (WHO) functional class (FC), did not consistently predict the development of SVA across the studies. This unexpected outcome might be due to the overall homogeneity of the included cohorts, which mainly comprised patients with poor functional status, or the relatively small sample size with less sensitive and more subjective measures.

   Similarly, most studies did not find significant differences in baseline PAH therapy or comorbidities between PAH/CTEPH patients with SVA and those without. One exception is the study by Mercurio et al. (2018), which noted

a significantly higher prevalence of thyroid disease (defined as hypo- or hyperthyroidism, or radiographic thyroid nodules) in the SVA group compared to those without SVA. The clinical relevance of thyroid disease, which is common in PAH, was not thoroughly explored in other studies and could be an overlooked contributing factor to arrhythmia development (Vakilian et al. 2016).

2. The onset of SVA often coincides with clinically significant decompensation. It is not always clear whether the SVA triggers the decompensation or is a consequence of right heart failure; however, in many instances, clinical decompensation occurs abruptly alongside an episode of SVA and, conversely, resolves with the restoration of sinus rhythm. The majority of patients experience symptoms at the onset of SVA, ranging from 59% to 98% across studies. Objective and standardized measures of disease severity consistently worsen after the development of SVA. These measures include deteriorating New York Heart Association (NYHA) functional class and a decrease in 6MWD (Ruiz-Cano et al. 2011). In one study, 46% of patients with SVA experienced an escalation in PAH-specific therapy, while another study noted that approximately 30% of SVA episodes led to admission to the intensive care unit and necessitated vasopressor use (Mercurio et al. 2018).

3. Although most patients experience symptoms at the onset of SVAs (approximately 80% on average), up to 41% of episodes are asymptomatic, and the arrhythmia is only detected through screening ECGs or ambulatory monitors. Given the association between SVA and increased mortality in patients with PAH or CTEPH, there is a need for further investigation into the role of routine surveillance of PAH/CTEPH patients using methods such as routine ECGs, Holter monitors, or loop recorders.

4. The reversal of adverse effects accompanying an episode of supraventricular arrhythmia (SVA) coincides with the restoration of sinus rhythm. AV synchrony in sinus rhythm enhances cardiac output, which is particularly crucial in the presence of diastolic dysfunction. Therefore, it is likely that the active, synchronized loading of the ventricles by the atria during sinus rhythm contributes to increased cardiac output in patients with PAH. Consequently, restoring sinus rhythm should be strongly considered in patients with PH. However, as discussed in the management section, there is a lack of randomized clinical trial data comparing rate control versus rhythm control in PAH/CTEPH patients. Nevertheless, reported cases indicate that the restoration of sinus rhythm is associated with objectively confirmed clinical improvement. For instance, in one study, the 6MWD decreased from 362 ± 114 m at the time of SVA onset to 258 ± 147 m, returning to a value near baseline (345 ± 137 m) 6–12 weeks after sinus rhythm restoration. Concurrently, the NT-proBNP levels decreased from 5926 ± 4648 ng/L at the time of SVA onset to 3360 ± 2804 ng/L after correction over the same time period (Olsson et al. 2013).

5. SVA are linked to elevated mortality rates, particularly when the arrhythmia becomes permanent rather than transient. In four retrospective studies, mortality rates ranged from 22% to 53% among patients with SVA, compared to 0% to 13% among those without SVA (Tongers et al. 2007;

Malaczyn'ska-Rajpold et al. 2016; Cannillo et al. 2015; Vakilian et al. 2016; Ruiz-Cano et al. 2011). Similarly, two prospective studies reported increased hazard ratios (HR) for mortality among patients who developed SVA, ranging from 1.75 to 2.15 (Olsson et al. 2013; Wen et al. 2014). Another study noted a mortality rate of 69% in the SVA group compared to 51% in those without SVA, though this difference was not statistically significant on survival analysis. Notably, the impact of permanent SVA on mortality is particularly notable. The majority of the increase in mortality was attributed to the development of permanent SVA, with HR ranging from 2.3 to 3.8, compared to transient or no occurrence of SVA (Olsson et al. 2013; Wen et al. 2014).

6. AF stands as the predominant cause of permanent supraventricular arrhythmia (SVA) in patients with PAH or CTEPH, accounting for 42%–70% of all cases. Additionally, AFl is also prevalent, occurring in 12%–50% of the reviewed series. Less common SVAs include AVNRT and atrial tachycardia. The high incidence of AF holds clinical significance, as restoring sinus rhythm is typically more challenging in AF compared to other SVAs, and permanent SVA is linked with increased mortality (Benza et al. 2012, 2010; Sitbon et al. 2015; Hoeper et al. 2017). Clinicians should consider the development of permanent AF as a serious adverse event in patients with PAH/CTEPH. Integrating permanent SVA into contemporary mortality prediction models, such as the REVEAL registry risk assessment, may aid in prognostication, as it indicates a substantial decline in survival. Further large-scale investigations are warranted to prospectively characterize the incidence of SVA in PH. While the onset of SVA appears to correlate with increased mortality, it remains unclear whether SVA causally contributes to deterioration or simply reflects worsening clinical condition. Unfortunately, due to the nature of the disease process and the invasiveness required to obtain hemodynamic data, frequent monitoring necessary to address this question may need to be conducted as part of large clinical trials or international registries. To date, the incidence and prevalence of SVA have not been reported in prospective or large-scale studies (Benza et al. 2010; Olsson et al. 2014; Delcroix et al. 2016).

5.1 | Management Strategies

5.1.1 | Guidelines

There is currently no standardized guidance for managing SVA in PAH or CTEPH, although various options exist, including both pharmacologic and non-pharmacologic interventions (Tables 1 and 2). Despite the observed improvements in hemodynamics and functional status associated with restoring sinus rhythm, the guidelines from the European Society of Cardiology (ESC) and European Respiratory Society (ERS) suggest that maintaining a stable sinus rhythm after cardioversion should be considered an important treatment objective in PAH patients, albeit without prospective and controlled data to support this recommendation (Galie et al. 2015; Tongers et al. 2007; Olsson et al. 2013; Wen et al. 2014; Cannillo et al. 2015; Ruiz-Cano et al. 2011). These guidelines also indicate that SVAs warrant consideration for oral anticoagulation to prevent stroke,

TABLE 1 | Recommendations for the management of SVAs in PAH and CTEPH.

Recommendation	Description
Rhythm control	Rhythm control should be prioritized over rate control as the initial first-line therapy for supraventricular arrhythmias in PAH/CTEPH.
Pharmacologic options	Options for pharmacologic rhythm control include amiodarone, sotalol, dronedarone, and Class 1C anti-arrhythmics. However, potential drug–drug interactions with PAH/CTEPH medications should be carefully assessed.
Short-acting beta blockers or calcium channel blockers	Consideration can be given to using short-acting beta blockers or calcium channel blockers for rate control in acute supraventricular arrhythmias, especially in patients with acute decompensated right ventricular failure (RVF). Long-term use for maintaining rate control in RVF requires further investigation.
Catheter ablation	Electrophysiology studies with catheter ablation are a safe alternative to pharmacologic therapy, particularly in patients with atrial flutter.
Left atrial interventions	The safety and efficacy of left atrial interventions, such as pulmonary vein isolation or the "maze" procedure, have not been studied in PAH/CTEPH.
Anticoagulation	Anticoagulation can be considered in patients with PAH, especially those with permanent atrial fibrillation. However, the risks and benefits should be carefully evaluated, as certain subgroups of PAH may experience harm with anticoagulant use, and current risk stratification models may not accurately represent this population.

although the stroke risk in PAH patients with AFl remains uncertain. However, due to the lack of prospective and controlled data, the guidelines do not provide a specific level of recommendation or strength of evidence for maintaining sinus rhythm or administering anticoagulation. Additionally, the 2009 expert consensus document from the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) on PH management does not explicitly address the management of SVAs (McLaughlin et al. 2009).

5.1.2 | Rate Versus Rhythm Control

Several studies have examined treatment practice patterns, revealing considerable heterogeneity in real-world approaches and outcomes (Tongers et al. 2007; Malaczyn'ska-Rajpold et al. 2016; Olsson et al. 2013; Wen et al. 2014; Cannillo et al. 2015; Ruiz-Cano et al. 2011). In three of the seven studies, all patients with SVA underwent initial attempts at rhythm control using methods such as direct current cardioversion, radiofrequency ablation, or anti-arrhythmic drug therapy (Tongers et al. 2007; Olsson et al. 2013; Wen et al. 2014). A rate control strategy was employed in a minority of patients, typically those with permanent AF. Rhythm control strategies were more successful in treating AFl (with success rates ranging from 46.2% to 100%) compared to AF (with success rates ranging from 16.7% to 67.0%) (Malaczyn'ska-Rajpold et al. 2016; Cannillo et al. 2015). Ruiz-Cano et al. (2011) did report that patients with AVNRT, referred to as INRT, underwent catheter ablation of the slow pathway, while those with typical AFl had cavotricuspid isthmus ablation. The management of AF was not discussed, and outcomes were simply noted to be "similar to that of the general population" (Ruiz-Cano et al. 2011).

A variety of pharmacologic strategies have been employed for treating SVAs in PAH or CTEPH. These strategies include the use of medications such as digoxin, amiodarone, sotalol, dronedarone, and Class 1C anti-arrhythmic agents (flecainide and propafenone). However, medical therapy for SVA in PAH/CTEPH is constrained by concerns about potential drug interactions with anti-arrhythmic agents and PAH-specific therapies, as well as adverse effects. For instance, bosentan, an endothelin receptor antagonist (ERA), is known to induce CYP3A4 and may decrease levels of amiodarone or dronedarone (Anon n.d.; Venitz et al. 2012). Additionally, many anti-arrhythmic drugs possess antihypertensive effects based on their mechanism of action and may induce systemic hypotension when used concurrently with phosphodiesterase inhibitors (such as sildenafil and tadalafil) or prostacyclins (like epoprostenol). The use of beta adrenergic blockers in PH remains a topic of debate due to the risk of precipitating heart failure or circulatory collapse, given their well-established negative inotropic and chronotropic effects (Peacock and Ross 2010; Provencher et al. 2006). While recent data have begun to explore the safety and efficacy of beta-blockers in PAH patients without congestion or heart failure, their use for improving right ventricular function and/or survival remains a subject of research and is not considered standard practice (Thenappan et al. 2014; Perros et al. 2017). Conversely, short-acting beta blockers may offer utility in restoring sinus rhythm or regulating heart rate during episodes of acute SVA.

Amiodarone, administered intravenously or orally, emerged as the most commonly utilized anti-arrhythmic agent for both medical cardioversion and maintenance of sinus rhythm. While generally well-tolerated in the short term, the prolonged use of

TABLE 2 | Management strategies and success rates of therapy for SVA in PAH/CTEPH.

Study	DCCV (%)	ABL (%)	ODP (%)	Pharmacologic	Sinus rhythm obtained (%)	Recurrence of SVA (%)
Tongers et al. (2007)	29.6	29.6	11.1	3.7% (digoxin)	59.3 (AF 16.7%; AFl 100%)	NR
Cannillo et al. (2015)	65.1	23.1	—	76.9% (sotalol, amiodarone, and 1C anti-arrhythmic)	65.0 (NR)	52.9
Malaczyn'ska-Rajpold et al. (2016)	18.8	25.0	6.3	25.0% (amiodarone and propafenone)	68.8 (AF 50.0%; AFl 60.0%)	56.3
Olsson et al. (2013)	56.3	33.3	2.1	85.4% (amiodarone, dronedarone, flecainide, and digitalis)	77.1 (AF 67.0%; AFl 88.0%)	27.1
Wen et al. (2014)	5.0	2.5	—	92.5% (amiodarone and digoxin)	52.5 (AF 25.0%; AFl 46.2%)	15.0
Mercurio et al. (2018)	31.0	31.0	—	NR (amiodarone, digoxin, metoprolol/carvedilol, verapamil/diltiazem, and flecainide)	NR	64.3

amiodarone may exacerbate morbidity in patients with PAH or CTEPH (Tongers et al. 2007; Olsson et al. 2013; Cannillo et al. 2015; Ruiz-Cano et al. 2011; Siddoway 2003).

In studies focusing on SVA in PAH/CTEPH, AFl and other atrial arrhythmias such as AVNRT were more effectively converted to and sustained in sinus rhythm with amiodarone during short- and intermediate-term follow-ups compared to AF.

Electrophysiology studies involving catheter ablation have demonstrated safety, feasibility, and success in patients with PH (Showkathali et al. 2011; Bandorski et al. 2014; Bradfield et al. 2012; Garlitski and Mark Estes III 2012; Luesebrink et al. 2012). For instance, in a retrospective analysis involving 22 patients with AFl and PAH/CTEPH, Showkathali et al. (2011) found that AFl ablation at the cavotricuspid isthmus was performed successfully without complications in all cases, leading to a statistically significant improvement in functional class. The favorable outcomes of this interventional approach can be attributed to the right-sided location of typical flutter or reentrant pathways, allowing for the avoidance of transseptal puncture and thereby reducing procedural risks associated with stroke and bleeding.

Left heart interventions in patients with PAH or CTEPH remain poorly understood, and the extent to which left-sided pathways contribute to arrhythmias in this population is uncertain. If pulmonary veins and left atrial pathways were found to play a significant role in SVA associated with PAH/CTEPH, caution would be warranted in terms of employing catheter-based therapeutic approaches. There is ambiguity regarding the impact of pulmonary vein manipulation on precapillary pulmonary pressures in patients with PAH/CTEPH (Hoeper and Granton 2011). Pulmonary vein isolation represents a more invasive procedure compared to interventions targeting the right heart, and concerns persist regarding the risks associated with anesthesia and intubation in this patient population. It is generally recommended to avoid intubation in PAH patients due to the potential adverse effects of sedation on cardiac function and vasodilation, which can lead to hemodynamic instability. In-hospital mortality rates for PAH patients requiring vasopressor support and mechanical ventilation for right ventricular failure are notably high, approaching 100% (Campo et al. 2011). Consequently, there is understandable reluctance to undertake more invasive and potentially low-yield ablation procedures in this vulnerable patient population.

5.1.3 | Anticoagulation

While anticoagulation is routinely used in the management of CTEPH, its role in treating SVAs may not significantly alter therapy. However, there is growing recognition of the lack of benefit and potential for harm associated with anticoagulation in certain forms of PAH (Cirulis and Ryan 2016; Thenappan et al. 2018). This underscores the importance of carefully evaluating the risks and benefits of anticoagulation for arrhythmias in PAH patients. Current guidelines suggest that oral anticoagulation may be harmful in patients with associated-PAH but may be warranted in idiopathic, heritable, or anorexigen-induced PAH. It remains uncertain whether these recommendations

should be adjusted in the presence of permanent AF, and it is unclear whether existing risk stratification models, such as CHA2DS2-VASc, are applicable to patients with PAH/CTEPH (Lip et al. 2010).

Regarding the frequency of anticoagulation therapy in PAH/CTEPH patients, only a few studies have provided specific commentary (Olsson et al. 2013; Wen et al. 2014; Mercurio et al. 2018). Differences in reported usage likely stem from variations in international practice patterns and study inclusion criteria (Olsson et al. 2014; Preston et al. 2015). However, there appears to be no discernible difference in the risk of developing SVA or subsequent morbidity or mortality based on the use of anticoagulation. Nonetheless, the impact of anticoagulation on vascular outcomes such as stroke remains unclear, as recent publications assessing the utility of anticoagulation in PAH have not specifically addressed atrial arrhythmias (Olsson et al. 2014; Preston et al. 2015). Given that a considerable proportion of patients with PAH experience asymptomatic atrial arrhythmias, conducting a study to evaluate the incremental benefit of anticoagulation in morbidity would necessitate screening with ECG or ambulatory monitoring to capture all potentially relevant SVAs.

6 | Ventricular Arrhythmias

Ventricular tachyarrhythmias (VT or VF) are believed to be the primary cause of SCD in adult patients, with registry data indicating that the majority of PAH patients succumb to progressive right heart failure or SCD (Katritsis, Gersh, and Camm 2016; Humbert 2010). The exact cause of sudden death in PAH patients remains incompletely understood, particularly as many instances occur outside the hospital. SCD in PAH patients is hypothesized to result from various factors, including arrhythmias, circulatory collapse, compression of the left main coronary artery, or pulmonary artery rupture or dissection (Zipes et al. 2006). Despite plausible changes in ventricular tissue such as fibrosis and QTc prolongation, malignant ventricular arrhythmias are not commonly observed in PAH, unlike advanced LV failure (Umar et al. 2012). While VF has been demonstrated in animal models of PAH, clinical investigations have found VT/VF in only a minority of PAH patients with SCD (8%) (Umar et al. 2012). Recent research has revealed that non-sustained VT (NSVT) is more prevalent than previously recognized in non-group two PH patients (Bandorski et al. 2015). However, subsequent studies have not found a correlation between NSVT and increased mortality in PAH/CTEPH patients. As routine and sustained rhythm monitoring is not standard practice in PAH/CTEPH, it remains possible that VT/VF may contribute to a higher proportion of SCD, highlighting the need for further investigation in this area (Bandorski et al. 2016).

6.1 | Device Therapy for SCD

Currently, there is a lack of evidence supporting the use of defibrillator implantation to prevent SCD in patients with PAH or CTEPH and right ventricular (RV) dysfunction. The guidelines and treatment approaches for managing arrhythmias in left heart failure may not be directly applicable to RV failure due to differences in the underlying disease processes. Similar

to how medications beneficial for one subgroup of PH may be harmful or ineffective in another subgroup, strategies for preventing and treating SCD may also vary. Practice guidelines for preventing SCD in PAH state that anti-arrhythmic therapy is not recommended for this purpose, and caution against high-risk procedures like implantable cardioverter-defibrillator (ICD) placement in PAH patients due to the absence of clinical trials demonstrating benefit in this population. While ICD implantation is commonly offered to non-PH patients who experience cardiac arrest due to documented VT or VF, decisions regarding the use of ICDs or prophylactic anti-arrhythmic agents in PAH/CTEPH patients should be made based on clinical judgment and individual patient factors, considering the lack of robust evidence supporting their efficacy in this specific population (Zipes et al. 2006; Priori et al. 2015).

The effectiveness of cardiac resynchronization therapy (CRT) in managing right heart failure due to PAH or CTEPH remains uncertain (Handoko et al. 2010; Rasmussen et al. 2014). In progressive RV failure associated with PAH, ventricular dyssynchrony is often observed, characterized by paradoxical septal movement resulting from RV pressure and volume overload compressing the left ventricle (Roeleveld et al. 2005; Tanaka et al. 1980). This dyssynchrony is believed to impede LV diastolic filling, leading to reduced LV stroke volume (Marcus et al. 2008). Studies have shown that RV free wall pacing with resynchronization improves RV function in computer simulation models of PAH, animal models of PAH, and in a small cohort of patients with CTEPH (Handoko et al. 2009; Lumens et al. 2009; Hardziyenka et al. 2011; Wanamaker et al. 2018). However, further research is necessary to validate whether CRT is a viable therapeutic approach in PAH/CTEPH patients with RV failure. It is worth noting that in left heart failure, CRT has not demonstrated benefit in patients with right bundle branch block or with QRS intervals of <160ms, both of which are common features in patients with RV failure due to PH. This raises questions about the potential efficacy of CRT in the context of PAH/CTEPH.

7 | Conclusion

In summary, arrhythmias pose a significant threat to patients with PAH and CTEPH, contributing to both morbidity and mortality. Despite ongoing research efforts, there are several knowledge gaps that hinder clinicians from effectively identifying and managing arrhythmias in PAH/CTEPH patients. SVAs, including AF and AFl, are more prevalent than ventricular arrhythmias. Sustained SVAs often signal clinical deterioration and are associated with increased mortality rates. Implementing improved screening methods and standardized management approaches for SVAs could potentially enhance outcomes in PAH patients. There is a pressing need for randomized trials to compare rhythm control versus rate control strategies and to explore the role of anticoagulation in this context. Although ventricular arrhythmias are less common, they can lead to SCD in PAH/CTEPH. Unlike in left heart failure, there is insufficient Grade I evidence supporting the use of implantable cardioverter-defibrillators (ICDs) for primary prevention of ventricular arrhythmias in PAH patients with right ventricular (RV) failure. A comprehensive surveillance study, possibly leveraging PH registries, could shed light on

the prevalence and etiology of sudden death related to arrhythmias, offering valuable insights for prevention and management strategies moving forward.

Author Contributions

Conceptualization: Jahanzeb Malik, Gulfam Ahmad, and Mansoor Ahmed. Methodology: Suniya Jatoi, Khansa Ali, Abdulrahman Abouzaid, Ahsan Nazim, and Amin Mehmoodi. Investigations: Gulfam Ahmad and Amin Mehmoodi. Validation: Jahanzeb Malik. First draft: Jahanzeb Malik, Amin Mehmoodi, Suniya Jatoi, Abdulrahman Abouzaid, Khansa Ali, Gulfam Ahmad, and Ahsan Nazim. Final draft: Suniya Jatoi, Ahsan Nazim, and Abdulrahman Abouzaid. Illustrations: Jahanzeb Malik.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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