Progress in Cardiovascular Diseases 55 (2012) 180–186
www.onlinepcd.com

Arrhythmias in Pulmonary Arterial Hypertension

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Abstract Cardiac arrhythmias are important contributors to morbidity and mortality in patients with pulmonary arterial hypertension (PAH). Such patients manifest a substrate resulting from altered autonomics, repolarization abnormalities, and ischemia. Supraventricular arrhythmias such as atrial fibrillation and flutter are associated with worsened outcomes, and maintenance of sinus rhythm is a goal. Sudden death is a relatively common issue, though the contribution of malignant ventricular arrhythmias versus bradyarrhythmias differs from non-PAH patients. Congenital heart disease patients with PAH benefit from catheter ablation of medically refractory arrhythmias. Clinical studies of defibrillator/pacemaker therapy for primary prevention against sudden death in PAH patients are lacking. (Prog Cardiovasc Dis 2012;55:180-186)

Keywords: Arrhythmia; Pulmonary artery hypertension; Supraventricular tachycardia; Ventricular tachycardia

Cardiac arrhythmias are important contributors to morbidity and mortality in patients with pulmonary arterial hypertension (PAH). This review will primarily focus on arrhythmias in patients with Group 1 PAH, which includes idiopathic PAH (formerly called primary pulmonary hypertension), hereditary PAH, or PAH due to diseases that localize to small pulmonary arterioles, such as connective tissue disorders, human immunodeficiency virus infection, portal hypertension, congenital heart disease (CHD) and drug use.[1] All these apparently heterogeneous conditions share a comparable clinical and hemodynamic picture with similar pathological changes of the pulmonary microcirculation. The increase in pulmonary vascular resistance (PVR) is related to different mechanisms, including vasoconstriction (related to smooth muscle and endothelial cell dysfunction), proliferative and obstructive remodeling of the pulmonary vessel wall, inflammation and thrombosis.[2,3] The subsequent increase in PVR leads to increased afterload of the right ventricle (RV), resulting in RV hypertrophy and dilatation as well as upstream dilatation of the right atrium. In addition to autonomic system modulations present in patients with PAH, these factors combine to form the foundation for initiation and maintenance of atrial and ventricular tachyarrhythmias.

Historical perspective

Awareness of arrhythmias as a cause of morbidity and mortality in pulmonary hypertension patients has existed for decades. In 1962, James described the postmortem findings of sinoatrial and atrioventricular nodal artery disease in three patients with severe PAH and syncope who died suddenly.[4] In 1979, Kanemoto et al examined electrocardiograms (ECGs) from patients with PAH and found that sinus tachycardia, sinus bradycardia and first degree A-V block occurred in 70% of the patients, whereas ventricular arrhythmias were rare.[5] Although these early studies highlighted the need to investigate the incidence of arrhythmias in this patient population further, there remains a relative paucity of data regarding the incidence, mechanism, prognostic significance, and treatment of arrhythmias in patients with PAH.

Statement of Conflict of Interest: see page 185.

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http://dx.doi.org/10.1016/j.pcad.2012.06.002

Abbreviations and Acronyms

AF = atrial fibrillation

AFL = atrial flutter

AV = atrioventricular

AVNRT = atrioventricular nodal reentry tachycardia

CHD = congenital heart disease

CPR = cardiopulmonary resuscitation

CRT = cardiac resynchronization therapy

ECG = electrocardiogram

PAH = pulmonary artery hypertension

PVR = pulmonary vascular resistance

RV = right ventricle

SVT = supraventricular tachycardia

VF = ventricular fibrillation

VT = ventricular tachycardia

Predisposing factors for arrhythmias in PAH

Remodeling of the right ventricle and the right atrium in response to longstanding pressure and volume overload appears to generate the underlying arrhythmogenic substrate in patients with PAH. Factors involved in such remodeling include the following:

1. *Modulation in autonomic activity* has been considered to be a factor predisposing to cardiac arrhythmias in pulmonary hypertension patients. Folino et al studied cardiac arrhythmias by ambulatory ECG monitoring in nine patients with PAH.[6] Four patients were noted to possess high density ventricular ectopy (ie, premature ventricular contraction burden >700/24 h.) and a reduced heart rate variability, correlating with a higher right ventricular systolic pressure. In addition to reduced heart rate variability, elevated levels of plasma norepinephrine and selective down-regulation of beta-adrenergic receptors in the right ventricle in PAH patients were indicators of increased sympathetic activity affecting the RV. Moreover, these findings correlated positively with disease severity.[7] Thus, the increase in pulmonary pressure and resultant reduction in cardiac output may induce changes in autonomic activity resulting in an increase in sympathetic drive, well known for its pro-arrhythmic effects.
2. *Delayed cardiac repolarization* leading to enhancement of QT dispersion is a well characterized precursor of arrhythmias and has been shown to be a predictor of all- cause mortality.[8] In a study of 201 patients with severe PAH, mean QTc (cycle length corrected QT) and QTcd (QTc dispersion) correlated positively with mean pulmonary artery pressure in women with PAH.[9] The underlying mechanisms of prolonged QTc and QTcd and their potential for predisposing to clinical arrhythmias in PAH patients have not yet been studied in depth. In addition, the potential additive role of electrolyte abnormalities due to diuretic treatment in the background of already-altered cardiac repolarization has not been well-established.
3. *RV myocardial ischemia* has been suggested as a mechanism of ventricular arrhythmia in patients with PAH. This may be attributable to a number of factors, including RV subendocardial ischemia resulting from intra-myocardial arteriolar compromise, decrease in coronary perfusion pressure gradient, and increase in myocardial oxygen demand due to RV overload.

Supraventricular tachyarrhythmias

Supraventricular tachycardias (SVT) may compromise cardiac function and worsen the prognosis of patients with PAH, but information about their incidence and clinical role is based on a small number of retrospective studies. Nevertheless, these studies provide important insight into the clinical impact and management of SVT in patients with PAH in whom structural changes in the right atrium secondary to chronic pressure overload of the RV and alteration in autonomic tone may pose significant risk factors for arrhythmogenesis.

In a 6-year retrospective analysis of 231 patients with PAH and chronic thromboembolic pulmonary hypertension, Tongers et al noted a cumulative 11.7% incidence of SVT and an annual risk of 2.8% per patient.[10] The most common types of arrhythmia were atrial flutter (AFL) and atrial fibrillation (AF), followed by atrioventricular (AV) nodal re-entry tachycardia (AVNRT). However, this cohort of PAH patients was not entirely homogeneous and the relative incidence of various types of SVT may vary based on the etiology of pulmonary hypertension. The average interval from the diagnosis of PAH to arrhythmia documentation was 3.5 years, suggesting that these arrhythmias are a manifestation of longer-standing PAH. In most cases, onset of atrial tachyarrhythmias was related to clinical deterioration, including RV failure, marked deterioration in exercise capacity by one functional class or more, and development of ascites and/or edema refractory to diuretic therapy. Restoration of normal sinus rhythm was invariably associated with clinical improvement and recovery from right heart failure.

Although it can be postulated that SVT may be the consequence and not the cause of RV failure, the observation that sinus rhythm restoration was followed by marked and rapid clinical improvement suggests some degree of causal role of SVTs in precipitating and/or worsening RV failure. Such clinical deterioration appeared to be related to the deleterious hemodynamic effects of the loss of atrial transport mechanism and/or compromise in diastolic filling time resulting from rapid heart rates in the presence of ventricular dysfunction. With regard to

mortality, whereas AVNRT and AFL were invariably converted to sinus rhythm and were not associated with an increased risk of death (cumulative mortality <6%), the presence of persistent atrial fibrillation and failure to restore sinus rhythm were associated with a cumulative mortality of >80%. Although it is a matter of debate whether AF serves as an independent predictor of poor prognosis in chronic left heart failure patients, AF may be a particularly malignant arrhythmia in patients with chronic PAH and right heart failure.

Similar findings of clinical decompensation were noted in another retrospective analysis of 282 patients with PAH, during which most of the SVT episodes led to clinical deterioration or worsening right heart failure. Restoration of sinus rhythm led to improvement in clinical status measured objectively by the 6-minute walk test.[11] However, after the occurrence of the first episode of SVT, 46.4% of patients required an increase in the specific therapy for PAH due to progressive clinical deterioration or right heart failure despite restoration of sinus rhythm or control of ventricular rate. Thus, the onset of these arrhythmias could be a warning sign for deteriorating RV function and hence the need for increasing specific therapy for PAH, including even consideration of lung transplantation in the most severe cases. Although prospective and controlled data are lacking, these findings suggest that maintenance of sinus rhythm is an important treatment goal in patients with PAH, which contrasts with the clinical experience in left heart failure in non-PAH patients, where the rhythm control strategy seems to offer no mortality benefit compared to the rate control and systemic anticoagulation strategy.[12]

With regard to therapies for SVTs in PAH patients, medical treatment includes rate control (eg, digoxin, calcium-channel blockers) versus rhythm control (ie, antiarrhythmic agents) for AF and AFL, and AV-nodal blocking agents such as calcium-channel blockers for SVTs including AVNRT. The need for systemic anticoagulation in the setting of AF/FL should be considered in all patients. With regard to AV nodal blockade, although digoxin is used for control of ventricular response in SVT in patients with pulmonary hypertension in the setting of chronic obstructive pulmonary disease,[13] its role in pulmonary hypertension due to other causes is not well established. Even when calcium blockers are used as part of the PAH treatment regimen, up-titration for arrhythmia management can be problematic due to their negative inotropic effects. The use of beta-blocker therapy for the treatment of SVTs in patients with PAH is also considered to be deleterious due to their negative inotropic effects.

Because of the significant side effect profile of many antiarrhythmic agents in the PAH population, their role is unfortunately limited. For example, sodium-channel blockers such as propafenone and flecainide are not indicated in patients with structural heart disease, and Class III agents such as sotalol prolong the QT interval and possess negative inotropic effects. In the acute setting, while amiodarone has been used for control of hemodynamically significant arrhythmias, the role of chronic, prophylactic antiarrhythmic drugs to maintain sinus rhythm remains questionable given significant potential side-effects (eg, development of pneumonitis/fibrosis with long term amiodarone use). Nevertheless, the recurrent development of poorly tolerated arrhythmias in the absence of more suitable alternatives may require its use on a long-term basis; in such cases, the use of the lowest possible effective dose is encouraged. The safety and efficacy profiles of newer antiarrhythmics such as dronedarone have not been established in this subgroup. Finally, interactions of medications used for arrhythmia treatment and other PAH agents must be carefully considered. For example, amiodarone may increase levels of bosentan, requiring close monitoring and adjustment.

In a retrospective analysis of 22 patients with AFL and PAH due to pulmonary artery hypertension and chronic thromboembolic pulmonary hypertension, Showkathali et al. demonstrated that AFL cavotricuspid isthmus ablation can be performed successfully and without complications, and was accompanied with a statistically significant improvement in functional class after ablation. In addition, there were no observable changes in echocardiographic parameters before versus after ablation, suggesting that acute improvement in clinical status was secondary to restoration of sinus rhythm rather than cardiac remodeling.[14] The site of origin of these arrhythmias is in the right atrium and the catheter ablation procedure does not require other interventions such as transseptal puncture followed by long left atrial procedures under general anesthesia. Thus, according to available limited data, treatment of AFL or AVNRT by catheter ablation is feasible, relatively safe, and effective in patients with PAH, though they may need to be extensive and repeated due to the severe right atrial enlargement/hypertrophy as well as multiple sites of origin.[10,14] Cardioversion was also found to be safe in these patients, although the sample size was too small to allow definite conclusions.

Ventricular arrhythmias and sudden cardiac death

In the modern era of PAH management, RV failure (36%) and sudden cardiac death (28%) together account for the majority of deaths in patients with PAH.[15,16] However, in contrast to patients with advanced left heart disease, malignant ventricular arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) are relatively rare in patients with PAH. In patients with PAH, pulseless electrical activity is often heralded by bradycardia. The natural history of pulmonary hypertension indicates that the major determinant of prognosis is RV function and sudden death is more likely to occur in

such patients with severe hypoxia.[17] Less common non-arrhythmogenic etiologies of sudden death should also be considered, including rare cases of dissection or rupture of the pulmonary artery.[18]

Hoeper et al reported the outcome after cardiopulmonary resuscitation (CPR) in patients with PAH at 17 centers in Europe and in the USA.[19] Of the 3,130 reported patients, 513 (16%) experienced circulatory and respiratory arrest over a 3-year period. CPR was attempted in 132 (26%) of 513 patients of these patients. The initial ECGs at the time of cardiopulmonary arrest showed bradycardia in 58 cases (45%), electromechanical dissociation in 37 cases (28%), asystole in 19 cases (15%), ventricular fibrillation in only 10 cases (8%), and other arrhythmias in 6 cases (4%). Thus, bradycardia that is inappropriate relative to the clinical scenario is an ominous sign. These findings are quite different from the higher incidence of VT/VF recorded in patients having a cardiac arrest in the setting of advanced left heart disease. In approximately 50% of the patients in this study, an intercurrent illness contributed to death. These intercurrent diseases were often minor abnormalities such as simple respiratory tract infections or gastrointestinal infections, which underscores the notion that patients with pulmonary hypertension are clinically tenuous with little or no compensatory reserve in the setting of concomitant illnesses. Unfortunately, survival after CPR in this group of patients is quite poor. In this survey of 132 patients with PAH in whom CPR was instituted, only 8 patients (6%) survived for more than 90 days. Seven of these patients had correctable causes of cardiopulmonary arrest, such as vasovagal episodes, digitalis toxicity, or pericardial tamponade. Thus, the single most important factor that seems to influence success of CPR in PAH patients is the presence and discovery of an identifiable trigger/condition for cardiopulmonary arrest and its prompt correction.

It is believed that rest and exercise RV myocardial ischemia resulting from reduced coronary driving pressure in hypertrophied RV myocardium occurs in a majority of the patients with PAH and is acutely worsened during cardiac arrest.[20] Based on these pathophysiologic considerations, measures to improve the results of CPR for arrhythmic-mediated cardiac arrests in PAH patients may need to focus on lowering the PVR (and thus decreasing overall RV ischemia). In this context, it is noteworthy that successful CPR attempts have included the intravenous bolus administration of iloprost, a prostacyclin analogue, although these are preliminary observations.[21] However, in cases where the cardiac arrest is due to a vasovagal reaction, systemic hypotension could be aggravated by acute administration of prostanoids and improved by the use of atropine and adrenergic drugs. The role of pacing PAH patients for relative bradycardia is not well established. These issues highlight the inherent difficulties of clinical management of PAH patients during cardiac arrest.

Although the reported percentages of death attributable to ventricular tachyarrhythmias vary widely (from 8% to 26%),[22] the actual numbers might be significantly different from one PAH subgroup to the next. Moreover, these estimates are based on retrospective studies which preceded the introduction of medical therapy for modern management for PAH. Systemic prospective clinical trials are necessary to determine the current incidence of sudden death in different subgroups of PAH, which in turn may allow a more accurate assessment of the clinical role of implantable cardioverter/defibrillators in PAH patients. However, the relative paucity of patients with such end stage arrhythmias makes systematic research difficult to pursue.

ACC/AHA/ESC guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death emphasize that prophylactic anti-arrhythmic therapy is not indicated for primary prevention of sudden cardiac death in patients with PAH.[23] In the absence of clinical trials showing any benefit from prophylactic antiarrhythmic therapy in such patients, one must rely on individualized, conservative clinical judgment in the management of asymptomatic arrhythmias such as non-sustained ventricular tachycardias, as they may be prone to pro-arrhythmic and other side-effects of anti-arrhythmic agents. In contrast, implantable cardioverter defibrillator implantation is offered to PAH patients who manifest either syncope or cardiac arrest in the setting of documented VT/VF.

The role of cardiac resynchronization therapy (CRT) in patients with right heart failure due to PAH is currently uncertain. In an experimental model of PAH and right heart failure, investigators found that pre-excitation of the RV free wall in the absence of baseline conduction disturbances resulted in improved RV systolic function and reduced adverse left ventricular diastolic interaction.[24] Another study demonstrated that resynchronization therapy acutely reduced ventricular dyssynchrony and enhanced RV contractility, left ventricular diastolic filling, and stroke volume in a patient suffering from right heart failure and ventricular dyssynchrony secondary to chronic thromboembolic pulmonary hypertension.[25] In addition, recent analysis notes that pediatric patients with PAH manifest abnormal mechanical as well as electrical RV activation when compared to patients without PAH.[26] These promising results warrant further investigations of CRT as a novel treatment for right heart failure secondary to PAH. However, without further data, the relative benefits versus risks of CRT in this setting remain unknown.

Arrhythmias related to PAH in specific subpopulations of PAH patients

1. *Congenital Disease and Eisenmenger Syndrome:* In contrast to patients with idiopathic PAH, which

represents a life-threatening disease with poor prognosis and a reported median survival of 2.8 years,[27] survival is better in patients with PAH associated with CHD. Two potential mechanisms may account for these superior survival prospects when compared to idiopathic PAH patients. First, in PAH associated with CHD, the right ventricle is subjected to high pressures from birth or from infancy and therefore may be better able to support systemic pulmonary pressures. Second, in patients with idiopathic PAH, pulmonary hypertension per se limits pulmonary as well as systemic blood flow during exercise. In contrast, those patients with CHD and associated intracardiac shunts are often able to maintain/increase their systemic cardiac output during exercise by shunting right to left, albeit at the expense of cyanosis.

Approximately 5% to 10% of patients with CHD develop PAH of variable severity, and cardiac arrhythmia is a major cause of morbidity and mortality in those patients who develop Eisenmenger syndrome.[28] The major supraventricular arrhythmias are atrial fibrillation and flutter, and are particularly associated with atrial septal defects with severe atrioventricular valve regurgitation.[29] Variables associated with a poor long-term outcome are syncope, elevated right heart filling pressure, and severe hypoxemia (systemic oxygen saturation less than 85%), which identify patients with advanced pulmonary vascular disease, severely impaired right ventricular function, decreased cardiac output, or inadequate oxygenation.[28] Accordingly, many patients with Eisenmenger syndrome die suddenly.[30,31] It would be reasonable to suspect that sudden death in the Eisenmenger population could be arrhythmic in origin as the arrhythmia (supraventricular or ventricular) may be the primary cause of death or produce acute worsening of cardiac performance and output.

Evaluation of arrhythmias in patients with Eisenmenger syndrome is of crucial importance. In addition to a careful history and physical examination, more sophisticated and comprehensive noninvasive and invasive investigation may be necessary. For example, ECG, QT and QTc dispersion, heart rate variability, and 24-hour Holter monitoring are noninvasive modalities for evaluating the predisposition to arrhythmias in patients with Eisenmenger syndrome. In a case-controlled, cross-sectional study, Semizel et al[29] investigated the tendency towards arrhythmia using non-invasive arrhythmia markers (QT dispersion and heart rate variability) in children with Eisenmenger syndrome. This study not only confirmed the well-known relationship between arrhythmias and Eisenmenger syndrome, but also showed that the patients with Eisenmenger syndrome have increased spatial dispersion of repolarization and reduced spectral indices of heart rate variability, which were correlated with their clinical and hemodynamic indices. Patients with higher pulmonary to systemic ratio were noted to have a higher incidence of arrhythmias on ambulatory ECG recordings, suggesting a relationship between increased arrhythmia risk and high pulmonary vascular resistance.

Catheter ablation has been applied successfully to most form of tachyarrhythmias in CHD patients, particularly medically-refractory cases of atrial flutter and tachycardias. The major challenge during these cases is distorted anatomy that invalidates customary fluoroscopic landmarks and complicates catheter manipulation. The combination of improved imaging, mapping with 3-dimensional technology, and enhanced lesion creation has improved the acute success rates for intra-atrial reentrant tachycardia ablation from 60% more than a decade ago to nearly 90% in the present era.[32] Despite the effectiveness of catheter ablation therapy, however, invasive cardiac electrophysiology studies and catheter ablation therapy should be undertaken with great caution in patients with Eisenmenger syndrome. Electrically induced atrial tachyarrhythmias may precipitate acute right heart failure and increase right to left shunting, resulting in worsening cyanosis. Indications for pacemaker and defibrillator implantation in CHD patients have been published in the guidelines of the ACC/AHA/NASPE task force.[33] Important considerations surrounding device therapy in this population relate to lead placement (including the possibility of epicardial lead placement), which must take into account distorted anatomy and the risk for thromboembolic complications.

2. *Arrhythmias in Patients with PAH Secondary to Connective Tissue Disease:* in patients with connective tissue disorders such as systemic sclerosis, PAH is associated with an increased risk of sudden death. In addition to PAH, other arrhythmogenic mechanisms such as myocardial fibrosis and immunological autoantibody mechanisms also play a pivotal role.[34] Depending on the underlying cardiac involvement, increased numbers and frequency of ventricular ectopic beats (including episodes of ventricular tachycardia) can be seen in scleroderma. Other frequent abnormal findings include late potentials by signal averaged electrocardiography, decreased heart rate variability,[35] and greater QT dispersion.[36] Using signal averaged electrocardiography, Paradiso et al reported that 46% of the scleroderma patients (vs. 8% of control subjects) possessed late ventricular potentials.[37] Morelli et al noted an increase in late ventricular potentials in scleroderma patients (20%) who frequently had a septal infarct pattern on their ECG.[38]

Ambulatory electrocardiography is also useful for the risk stratification of patients with scleroderma. Ventricular ectopy and tachyarrhythmias found on ambulatory monitoring are associated with increased mortality. In a

study of 183 patients with systemic sclerosis studied with 24-hour ambulatory electrocardiography and followed for 33 months, the incidence of ventricular tachycardia was 7%.[39] Ventricular ectopy overall was common, occurring in 67% of patients. Ventricular tachycardia was associated with a 2-fold increase in the risk of death, whereas frequent ventricular ectopy defined as more than 100 premature ventricular contractions per 24 hours was associated with a 4-fold increase in the risk of death, and ectopy defined as more than 1000 premature ventricular contractions (PVCs) per 24 hours associated with a 6-fold increased risk of death. Bradyarrhythmias, on the other hand were uncommon. Reports of sustained VT are rare,[40] but patients with systemic sclerosis may die suddenly[41] and fatal ventricular arrhythmias have been reported. The mechanisms underlying ventricular arrhythmias in systemic sclerosis have not been well studied but likely include advanced age and fibrosis, compared to the relatively younger patients with other forms of PAH. Pathologic studies demonstrated diffuse myocardial fibrosis, which would provide a substrate for reentry, but automaticity as a possible mechanism has been reported. Unlike the VT of coronary artery disease, which often originates from the left ventricle, ventricular arrhythmias in patients with scleroderma without coronary artery disease are frequently recorded from the RV.[42]

Conclusion

Atrial tachyarrhythmias such as AFL and AF are common in patients with PAH, and often are associated with worsening heart failure and a decline in the clinical status of the patient. Despite an increased risk with invasive procedures in this patient population, catheter ablations carried out in the right atrium are relatively safe and quite effective for treating atrial arrhythmias, though they may need to be extensive and repeated due to the severe right atrial enlargement/hypertrophy as well as multiple sites of origin/maintenance present in PAH patients. Ventricular tachycardia is less common, and relative bradycardia is an ominous sign, with bradyarrhythmias frequently observed in the setting of cardiopulmonary arrest. Clinical studies of defibrillator/pacemaker therapy for primary prevention against sudden death in PAH patients are lacking.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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