EDITORIAL COMMENTARY

New insights into ventricular arrhythmogenesis in a pure model of pulmonary arterial hypertension

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Pulmonary arterial hypertension, defined as a resting mean pulmonary arterial pressure over 25 mm Hg, is characterized by extensive vasoconstriction, adverse vascular remodeling, and vascular noncompliance due to extensive fibrosis and vascular stiffening.[1–3] Pulmonary arterial hypertension (PAH) is further characterized by progressive endothelial damage, significant neointimal proliferation, and complex plexogenic arterial lesions.[1,3] As PAH progresses, increased afterload on the right ventricle (RV) results in ventricular hypertrophy and eventual RV failure and death. Despite significant advances in pharmacotherapies to treat PAH, there is no cure and 5-year mortality remains high.[1,3]

RV failure is often cited as the primary cause of death in patients with end-stage PAH; however, arrhythmias are common comorbidities that significantly contribute to mortality.[3,4] The most common rhythm disturbances observed in patients with PAH are supraventricular arrhythmias.[5] Nevertheless, ventricular arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF), have been described in patients with PAH. While these have been seen less frequently that supraventricular arrhythmias, it is important to note that sudden cardiac death is common in PAH. As sudden cardiac death often occurs for unknown reasons outside the hospital, VT/VF may be occurring more frequently in PAH than is currently recognized.[3] Arrhythmias in PAH are thought to occur in association with changes in autonomic nervous system activity, electrical and structural remodeling in the RV, and ischemia in the RV[3]; however, many of the mechanisms are poorly understood, which contributes to disease severity and mortality.

Capturing the complex nature of human PAH in animal models has proved challenging. Notably absent in most models are the neointimal fibrosis and plexogenic arteriopathic lesions that are prevalent in the human clinical presentation of PAH. Moreover, species type, strain, age, and sex affect the extent and progression of PAH as well as the accompanying arrhythmias in animal models. Importantly, animal PAH has often proved to be more reversible than the clinical presentation; thus, clinical translation of therapeutics designed using these models has been limited. The 2 most characterized models of PAH are the chronic hypoxia and monocrotaline (MCT) models.[6,7]

The chronic hypoxia model of PAH involves the application of normoxic and hypobaric oxygen conditions and has demonstrated reliable and reproducible results in rodent models; however, this model tends to produce a less severe form of PAH.[6] Thus, it may be considered a model of less severe or less advanced forms of PAH. Conversely, use of the pyrrolizidine alkaloid MCT leads to more extensive vascular endothelial damage after hepatic activation of the cross-linking agent monocrotaline pyrrole.[6] While this method of injury is popular for its ease of application and simplicity, responses to MCT can be highly variable. Furthermore, off-target toxicity leading to myocarditis and liver failure is common. Thus, while MCT injection induces significant RV hypertrophy and dysfunction common in PAH, the off-target effects and lack of neointimal damage suggest MCT may function more as an acute toxicity model of PAH. The MCT model also causes an injury more improvable upon treatment with pharmacotherapies, which is not the case with the clinical presentation of PAH in which pharmacotherapy is difficult and complex. Nevertheless, MCT is easy to deliver and does reproduce many features of PAH, including arrhythmias. As a result, MCT is a commonly used model that has provided valuable information.

Endothelial cell maintenance and differentiation greatly affect the progression of vascular damage in human PAH. Accordingly, models of PAH using endothelial cell receptor inhibitors have been developed. The most well characterized of these targets is Sugen-5416 (Su-5416), a tyrosine kinase inhibitor of the vascular endothelial growth factor receptor previously used in cancer research. When combined with chronic hypoxia, administration of Su-5416 elicits endothelial proliferation and recapitulates the chronic progression of pulmonary vascular damage, including plexiform lesions, and RV dysfunction seen clinically in patients with severe

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PAH.[6,8,9] As a result, combining Su-5416 with left pneumonectomy (Su/Pn) has emerged as an important animal model of PAH. Left pneumonectomy is used to induce changes in pulmonary vascular resistance and pressure that ultimately leads to RV hypertrophy and dysfunction. The Su/Pn model is advantageous as it produces many of the major features of human PAH without the limitations and off-target effects seen in other models. Thus, the Su/Pn model has been viewed a more pure model of PAH.

In their recent elegant study, Strauss et al[10] used the Su/Pn model in rats to effectively recapitulate many of the clinical features of PAH and investigate ventricular arrhythmogenesis.[10] Su/Pn rats exhibited clear increases in pulmonary arterial pressure and increased medial wall thickness in the pulmonary arteries. In association with these changes, Su/Pn rats displayed RV hypertrophy, RV hemodynamic dysfunction, and increased expression of B-type natriuretic peptide. These changes occurred more extensively in the RV compared to the left ventricle.

Importantly, the authors demonstrated that hearts from Su/Pn rats were highly susceptible to pacing-induced VT/VF in association with slow conduction and the occurrence of conduction block (assessed by optical mapping). In addition, Su/Pn rats were characterized by preferential increases in RV action potential (AP) duration and the occurrence of RV AP duration alternans. Overall, the wavelength of reentry before the induction of VT/VF was shorter in Su/Pn hearts. Using molecular biology and histological approaches, the authors investigated the basis for VT/VF and conduction impairments in Su/Pn rats. These studies showed reductions in phosphorylated connexin 43 and reduction in messenger RNAs for Kv4.2/Kv4.3 (which underlie expression of the transient outward K^+ current). In addition, RV fibrosis and collagen gene expression were increased in Su/Pn hearts. Collectively, these important data provide insight into the basis for electrical and structural remodeling in the RV of Su/Pn rats, which could explain the occurrence of ventricular arrhythmias in PAH.

Follow-up studies are warranted to advance the intriguing findings of the present study. For example, it will be important to determine the impacts of the changes in ion channel gene expression by directly assessing ion channel properties in isolated RV myocytes from Su/Pn rats. Additional studies will be required to determine the roles of connexin 43 phosphorylation and fibrosis in conduction impairments. Similarly, the role of AP duration alternans in arrhythmogenesis, and whether these arise from changes in Ca^{2+} handling or other mechanisms, remains to be determined. The Su/Pn model will also serve as a valuable tool for investigating supraventricular arrhythmias in PAH. As noted above, ventricular arrhythmias have been thought to be somewhat rare in PAH; however, the present study demonstrates substantial RV remodeling and changes in electrophysiology, suggesting that ventricular arrhythmias in PAH may be underrecognized clinically. The present study serves as an important indicator that this should be investigated in patients with PAH in greater detail.

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