AMERICAN JOURNAL OF PHYSIOLOGY
HEART AND CIRCULATORY PHYSIOLOGY

Am J Physiol Heart Circ Physiol 331: H1461–H1462, 2026.
doi:10.1152/ajpheart.90181.2026

LETTER TO THE EDITOR

From microvascular rarefaction to QT prolongation in PAH

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TO THE EDITOR: El-Rabahi et al. (1) provide compelling evidence that the transition from adaptive to maladaptive right ventricular (RV) remodeling in progressive monocrotaline-induced pulmonary arterial hypertension (PAH) is accompanied by a proarrhythmic electrical phenotype, characterized by QT and RV action potential duration (APD) prolongation, increased APD dispersion, downregulation of Kcnh2, Kcnk2, and Scn7a, and evidence of RV ischemia, including reduced vascular density, hypoxia-related gene activation, and ST-segment elevation. These findings reinforce the concept that maladaptive RV remodeling involves not only mechanical failure but also impaired angiogenesis, ischemia, and metabolic dysfunction, which may contribute to QT prolongation (2). Two additional experimental approaches could further clarify the relationship between this substrate and arrhythmic risk. First, continuous telemetry during the transition from adaptive to maladaptive remodeling, combined with standardized electrophysiological provocation, could determine whether progressive QT/APD prolongation and dispersion translate into spontaneous or inducible ventricular tachyarrhythmias. Previous optical mapping and electrophysiological studies in monocrotaline pulmonary hypertension demonstrated that increased RV repolarization heterogeneity is associated with pacing-inducible lethal arrhythmias (3). Second, intervention studies targeting the microvascular-metabolic axis could assess whether reversing ischemia also normalizes electrical remodeling. Notably, apelin analog therapy in severe PAH with RV failure reduced ST-segment elevation, nearly normalized QT intervals, and restored potassium-channel expression in RV cardiomyocytes (4). Mechanistically, the coexistence of reduced RV vascular density and hypoxia signatures provides a plausible upstream explanation for potassium-channel downregulation and APD prolongation. Loss of Kcnk3 (TASK-1) has been identified as a hallmark of RV hypertrophy and dysfunction in experimental and human pulmonary hypertension, suggesting that impaired outward potassium currents may contribute substantially to RV electrical remodeling (5). Hypoxia, metabolic stress, oxidative signaling, and altered intracellular pathways may simultaneously affect multiple potassium-channel systems, including TASK-1 and rapid delayed rectifier potassium current (IKr)/*Kcnh2*-related pathways, thereby amplifying repolarization abnormalities (6). A clinically relevant translational parallel may be found in primary Sjögren's syndrome, in which Coppi et al. (7) reported that a lower hemoglobin-to-red cell distribution width ratio (HRR) was associated with higher pulmonary artery pressures and impaired RV-pulmonary vascular coupling, particularly in the presence of vitamin D insufficiency. Although etiologically distinct, these findings suggest that systemic inflammation and impaired oxygen delivery may contribute to an "ischemia-prone" RV phenotype. An integrated cardiopulmonary framework combining microvascular dysfunction, oxygen-delivery biomarkers, RV mechanics, and electrophysiology may therefore help bridge preclinical evidence of electrical remodeling with patient-level risk stratification. Similar integrative approaches incorporating mitochondrial, microvascular, biomarker, and echocardiographic pathways have recently been proposed in systemic sclerosis cardiac disease (8).

DISCLAIMERS

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DISCLOSURES

No other conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

F.S.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing; G.P.: Conceptualization, Data curation, Formal analysis, Investigation; F.C.: Conceptualization, Data curation, Formal analysis, Supervision, Visualization.

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Submitted 2 September 2026 / Accepted 4 September 2026

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