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LETTER TO THE EDITOR

Maladaptive right ventricular electrical remodeling in PAH: bridging preclinical, sex-specific, and clinical monitoring perspectives

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TO THE EDITOR: We read with great interest the study by El-Rabahi et al. (1), who provide a detailed characterization of maladaptive right ventricular (RV) functional and electrical remodeling in male Fischer CDF rats during progressive monocrotaline-induced pulmonary arterial hypertension (PAH). By combining echocardiography, ECG, cardiac catheterization, and optical mapping, the authors show a transition from adaptive RV hypertrophy at 4 wk to maladaptive remodeling at 5 wk, accompanied by reduced potassium and sodium channel expression, reduced RV vascular density, and elevated markers of RV ischemia. This work meaningfully advances our mechanistic understanding of why PAH patients remain at increased risk of sudden cardiac death, a phenomenon whose electrophysiological basis has so far been incompletely defined.

The electrical remodeling described by El-Rabahi et al. (1) resonates strongly with clinical data linking ECG abnormalities to RV dysfunction in human PAH. Rich et al. (2) showed that QTc prolongation, plausibly reflecting altered ventricular repolarization related to ion channel remodeling, is independently associated with impaired RV function and predicts mortality in patients with pulmonary hypertension . Read together, these preclinical and clinical datasets support a coherent pathophysiological continuum, in which structural ion channel downregulation in the failing RV translates into a measurable, prognostically relevant electrocardiographic signature in patients, reinforcing the clinical relevance of the mechanisms identified by the authors.

We would also like to highlight the sex-specific design of this study. The authors deliberately used only male rats, consistent with the well-established observation that the male RV is more prone to maladaptive remodeling under chronic pressure overload. This is in line with our own clinical findings in systemic sclerosis-associated pulmonary hypertension, where we showed that men experience a distinctly worse cardiovascular course than women, with differences that appear to extend beyond hormonal status alone (3). Given the electrical findings reported here, it would be of considerable interest to determine whether female rats, which typically show more adaptive RV remodeling, are relatively protected from the ion channel downregulation and arrhythmic substrate described in males, a comparison that could help clarify the biological basis of the sex disparity we and others have observed clinically.

From a translational standpoint, we also note that the transition from adaptive to maladaptive RV remodeling described by El-Rabahi et al. (1) conceptually mirrors the deterioration in RV-pulmonary arterial (PA) coupling that noninvasive markers aim to capture in patients. In a cohort with idiopathic pulmonary fibrosis, we recently found that DLCO correlated with echocardiographic RV-PA coupling, supporting the broader principle that simple, noninvasive parameters can meaningfully track the same underlying maladaptive transition identified at the tissue level in this rat model (4).

Finally, translating these mechanistic insights into long-term arrhythmic risk surveillance in patients will require robust longitudinal monitoring protocols. In our own real-world 12-mo cardiac rehabilitation program, we observed substantial patient attrition over follow-up, driven by factors that are rarely accounted for in structured monitoring studies (5). We believe this is a relevant consideration for any future clinical protocol aiming to serially track electrocardiographic or echocardiographic correlates of the maladaptive RV remodeling process described here.

We congratulate the authors on an elegant and mechanistically rigorous study that meaningfully advances our understanding of arrhythmic risk in PAH, and we look forward to future work exploring its sex-specific and clinical translational dimensions.

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DISCLOSURES

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