Commentary: Mitochondrial targets in the failing right ventricle—multiple opportunities to rescue the right heart in pulmonary hypertension

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Diagram of mitochondrial structure.¹

Central Message

Mitochondria offer multiple therapeutic targets in right ventricular failure. Future trials should explore multimodal interventions for right ventricular rescue in pulmonary hypertension.

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Because right ventricular failure with concomitant mitochondrial dysfunction has significant consequences, therapeutic targets to rescue the right side of the heart are important.²⁻⁴ Mitochondria generate adenosine triphosphate through the oxidative phosphorylation of fatty acids and carbohydrates.⁵ Although fatty acids are their preferred substrate, carbohydrates are more efficient and likely improve cardiac performance in pulmonary hypertension.⁵ Consequently, trials have approached mitochondria as therapeutic targets, including through manipulation of their bioenergetics.²⁻⁵

The study by Noly and colleagues⁶ in this issue of the *Journal* highlights the central roles of mitochondria and suggests new therapeutic alternatives in right ventricular failure. In their piglet model of chronic pulmonary hypertension, these investigators demonstrated that mitochondria had impaired oxidative phosphorylation and significant structural damage.⁶ These findings suggest that mitochondrial functional and structural quality together play an important part in right heart failure resulting from pressure overload.⁶

Targeted therapies for the failing right ventricle in pulmonary hypertension must therefore extend beyond metabolic manipulation to address the structural integrity of the mitochondria.⁵⁻⁷ Autophagy may be a possibility, because it is a continuous cellular process that recycles cellular components such as mitochondria to maintain homeostasis.^{5,7} Because it also influences the choice of metabolic substrate by myocardial mitochondria, therapeutic manipulation of autophagy in pulmonary hypertension may facilitate not only structural restoration of damaged mitochondria but also a favorable metabolic shift in the failing right ventricle.^{5,7} Autophagy therefore offers the therapeutic potential to address the functional and structural quality of failing mitochondria⁵⁻⁷ that has

been elucidated in the important work by Noly and colleagues.⁶

Furthermore, mitochondrial dynamics should also be considered.⁸⁻¹⁰ Mitochondrial dynamics include activities such as migration, division (also known as fission), and joining together (also known as fusion).⁸⁻¹⁰ Multiple disorders of mitochondrial dynamics have been implicated in pulmonary hypertension, thereby offering further therapeutic targets for the failing right ventricle.^{10,11} The study by Noly and colleagues⁶ did not address mitochondrial dynamics.

So, where are we, and where do we go from here? Clearly, mitochondrial structure, function, and dynamics are important in right ventricular adaption and subsequent failure.²⁻¹¹ These multiple mechanisms suggest a multimodal therapeutic approach to mitochondrial processes for rescue of the right side of the heart in pulmonary hypertension. An intriguing therapeutic possibility might be mitochondrial transplantation.^{1,12} The injection of autologous healthy mitochondria from skeletal muscle into the failing myocardium may restore mitochondrial quality and provide a multimodal molecular intervention for right ventricular rescue.^{1,12}

In conclusion, Noly and colleagues⁶ are to be congratulated for highlighting mitochondrial metabolism and structure in the pathogenesis of right ventricular failure from

pulmonary hypertension. Their observations add to our understanding of the mitochondrial roles in this pathologic cascade. Future trials will likely focus on interventions to optimize both metabolic and structural processes in the mitochondria of the failing right ventricle. The potential of autophagy and mitochondrial transplantation in this setting merits further investigation. These therapeutic investigations should also consider the mitochondrial dynamics of migration, fission, and fusion.

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