Initium novum?

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It is a chilling reality that naturally progressive, irreversible cardiovascular processes such as atherosclerotic heart disease and heart failure exceed the capabilities of our current pharmacologic interventions.¹ Our surgical dogma has also taught us that fixed pulmonary hypertension is by its very nature immutable. This has implications in the care of our patients, especially those with congenital heart disease. In this issue of the *Journal*, Roan and colleagues² describe a remarkable cardiovascular benefit with the glucagon-like peptide-1 analog, exendin-4 (Ex4), in a model of pulmonary arterial hypertension (PAH). Ex4 is a new-generation antidiabetic agent approved for type 2 diabetes. Early benchtop studies demonstrated an intriguing extraglycemic effect.³ The authors explored this potential with a rodent model of PAH and right heart failure.

Study animals were injected with 60 mg/kg monocrotaline, a pneumotoxic alkaloid, which damages pulmonary artery endothelial cells, inciting vascular inflammation, hyperplasia, and fibrosis. A week later, they underwent aortocaval shunting, which accelerates flow-induced PAH and right heart failure. The authors should be recognized for executing a very thorough and intricate small-animal study. Understandably, this is a challenging clinical entity to replicate, but they used, arguably, the most effective PAH model to test their hypothesis. The sample size, albeit limited, had more than a 75% completion rate with 11 control and 14 treated animals.

Furthermore, the authors demonstrated a variety of compelling hemodynamic, functional, morphologic, histologic, and biochemical endpoints. Not only did Ex4 improve survival, it also improved right ventricular function, pulmonary tensile strength and relaxation responses, inflammatory biomarkers, and gene expression profiles. Many of the results were statistically significant and, overall, their hypothesis was reasonably substantiated.

So how do we translate this finding? Should we be exchanging pulmonary vasodilators for antidiabetic agents? Is this the tip of a revolutionary transformation? Or, are we chasing fumes? Small-animal models are inherently plagued by their inability to recapitulate the complexities of human

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Central Message

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pathophysiology. Drug susceptibility can also be quite variable.⁴ Furthermore, a recent study demonstrated reverse remodeling in the rodent monocrotaline model beyond 4 weeks, thus undermining any potential benefit.⁵ Perhaps reproducing the findings in a large-animal model can add credibility and bridge the gap to a clinical trial. Two unanswered questions that can further facilitate clinical translation are (1) an exploration of the untoward side effects from therapeutic usage of Ex4 for PAH and (2) an analysis of patients with PAH who are already on glucagon-like peptide-1 analogs; are they already receiving a secondary gain?

PAH management has had but modest gain since the introduction of pulmonary vasodilators. The potential for PAH reversal is intriguing. The present study gives us a glimpse of a novel therapy early in the investigative phase. Could this be a new beginning, or more emphatically, the beginning of the end for pulmonary hypertension?

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