11. Valway SE, Sanchez MPC, Shinnick TF, Orme I, Agerton T, Hoy D, *et al.* An outbreak involving extensive transmission of a virulent strain of *Mycobacterium tuberculosis*. *N Engl J Med* 1998;338:633–639.
12. Stucki D, Brites D, Jeljeli L, Coscolla M, Liu Q, Trauner A, *et al.* *Mycobacterium tuberculosis* lineage 4 comprises globally distributed and geographically restricted sublineages. *Nat Genet* 2016;48:1535–1543.
13. Domenech P, Zou J, Averback A, Syed N, Curtis D, Donato S, *et al*. Unique regulation of the DosR regulon in the Beijing lineage of *Mycobacterium tuberculosis*. *J Bacteriol* 2016;199: e00696-16.
14. Reed MB, Gagneux S, Deriemer K, Small PM, Barry CE III. The W-Beijing lineage of *Mycobacterium tuberculosis* overproduces triglycerides and has the DosR dormancy regulon constitutively upregulated. *J Bacteriol* 2007;189:2583–2589.

New Tricks for an Old Drug: Prostacyclins and Right Ventricular Contractility in Pulmonary Arterial Hypertension

Prostacyclin analogs are the cornerstone medical therapy for pulmonary arterial hypertension (PAH), a disease characterized by progressive pulmonary endothelial dysfunction and remodeling of distal pulmonary arterioles, which can lead to right ventricular (RV) failure (1). Prostacyclins improve cardiac output (CO), functional status, and survival in PAH—effects classically attributed to vasodilatory, antithrombotic, and antiproliferative properties at diseased pulmonary arterioles (2–5). In this model, prostacyclins target PAH vasculopathy to reduce RV afterload and restore ventriculoarterial coupling, a metric of mechanical efficiency. Conversely, approved therapies for RV contractile dysfunction in PAH, a key determinant of survival, do not exist currently. In this issue of the *Journal*, Tello and colleagues (pp. 111–114) challenge this contemporary paradigm of prostacyclin pharmacology in PAH. Through high-fidelity hemodynamic analysis, they conclude that inhaled iloprost enhances CO not only through effects on the pulmonary circulation but also through enhanced RV contractility (6).

To disentangle the relative contributions of afterload and contractility to RV performance, effective arterial elastance (Ea) and end-systolic ventricular elastance (Ees), respectively, can be quantified through analysis of RV pressure waveforms (single-beat method) or pressure–volume loops (multibeat method). When the Ees/Ea ratio is approximately 1.5–2, RV contractility is matched to afterload, and blood is ejected from the RV into the pulmonary circulation with optimal efficiency (7, 8). It follows that decreases in afterload (Ea), mediated by pharmacologic (or surgical) intervention, may lead to a decrease in contractility (Ees) to spare the RV from inefficient energy consumption. Indeed, in patients with PAH initiated on continuous intravenous treprostinil, it has been shown that Ees declined together with Ea after days to months of pulmonary vasodilator therapy (9). This observation would appear to validate the classical model that prostacyclins improve CO in PAH through effects on the pulmonary circulation and RV afterload (9). Importantly, this prior work did not profile the real-time Ees/Ea response to prostacyclin administration, opening a path forward to clarify the acute RV response to prostacyclin therapy.

To understand the acute effects of prostacyclin on RV function, Tello and colleagues administered inhaled iloprost to 32 patients with PAH undergoing high-fidelity conductance catheterization. This approach enabled real-time assessment of RV pressure–volume loops and, thus, direct Ees/Ea measurement through the multibeat method. As a comparator to iloprost, inhaled nitric oxide (NO) or oral riociguat, which stimulates the NO effector, soluble guanylyl cyclase, was administered to a comparator group. Full methodologic details, critically important to the interpretation of sophisticated hemodynamic analysis, are provided in an online supplement. The authors observed that iloprost improved CO and RV ejection fraction versus the pretreatment baseline, but through an unexpected mechanism: lower Ea and increased Ees, leading to a net increase in Ees/Ea from 0.93 ± 0.44 to 1.46 ± 0.70. Conversely, patients treated with inhaled NO/riociguat demonstrated decreased Ea, decreased Ees, and unchanged Ees/Ea. Collectively, these findings suggest that the acute benefits of inhaled iloprost are mediated by afterload reduction and positive inotropy, in contrast to the purely vasodilatory effects of NO/riociguat. The investigators went on to validate the effect of intravenous iloprost using a rodent pulmonary arterial banding model, a system used to study RV performance under conditions of fixed afterload. They observed directionally similar findings for increased Ees and CO with iloprost administration, adding additional plausibility to the concept that iloprost improves RV contractility.

How did the present study detect inotropic effects which have not been demonstrated in patients with PAH before? First, although the efficacy of prostacyclin analogs is generally regarded to be similar, it is conceivable that iloprost may have unique inotropic properties relative to previously studied agents such as treprostinil (10). This study did not compare the effects of iloprost to other prostacyclin formulations. Second, the study by Tello and colleagues was the first to use multibeat determination of Ees and Ea during the acute initiation of prostacyclin therapy. As the multibeat approach may predict PAH outcomes better than the single-beat method, it is possible that multibeat analysis is a more sensitive measure of load-independent RV function (11). Last, the study by Tello and colleagues was designed to test only the short-term hemodynamic effects of iloprost; taken together with prior data collected over a longer period, prostacyclin enhancement of RV contractility may wane during

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prolonged treatment, perhaps as the RV adapts to improved loading conditions (9).

This study is a valuable contribution to the literature on prostacyclin pathophysiology in PAH. Nonetheless, there are a few points left unanswered. The authors present a combined comparator group of patients treated with NO and/or riociguat; the use of disparate agents, although rooted in the premise that both drugs act at least partially on the same signaling pathway, is a puzzling choice, as inhaled NO and oral riociguat differ in their PAH pharmacology. The decision to pool distinct medications into one group may reflect the challenge of enrolling sufficient patients for a multi-arm invasive hemodynamic study. To this point, the study was underpowered to meaningfully assess for differences in hemodynamic pharmacology between iloprost, NO, and riociguat individually. This may explain why the latter agents did not increase CO, as has been shown in other studies before (11, 12). Furthermore, pressure–volume loop analysis, although considered a gold-standard load-independent assessment of RV function, involves assumptions and analysis approaches that contribute to intrastudy and interstudy variability (13, 14). For example, in this study, inhaled iloprost improved median CO by about +0.8 L/min despite an incremental +6 ml/beat increase in stroke volume and no meaningful change in heart rate. A direct Fick determination of CO might have added confidence in the CO measurements, a practice warranting greater emphasis in clinical practice as well (15).

Overall, Tello and colleagues present compelling evidence that iloprost improves RV contractile function in both human and experimental PAH. Further study of the biological mechanism, duration, and generalizability of prostacyclin-dependent inotropy may ultimately improve treatment strategies for patients with PAH with RV contractile dysfunction. ■

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References

1. Maron BA, Abman SH, Elliott CG, Frantz RP, Hopper RK, Horn EM, *et al.* Pulmonary arterial hypertension: diagnosis, treatment, and novel advances. *Am J Respir Crit Care Med* 2021;203:1472–1487.
2. Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, *et al.*; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347: 322–329.
3. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, *et al.*; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334: 296–301.
4. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 1998;338:273–277.
5. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann XJ, Georgiou D, *et al.* Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol* 1997;30:343–349.
6. Tello K, Kremer N, Richter MJ, Gall H, Muenks J, Ghofrani A, *et al.* Inhaled iloprost improves right ventricular load–independent contractility in pulmonary hypertension. *Am J Respir Crit Care Med* 2022;206:111–114.
7. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circ Res* 1985;56:586–595.
8. Sagawa K, editor. Cardiac contraction and the pressure-volume relationship. New York: Oxford University Press; 1988.
9. Vanderpool RR, Desai AA, Knapp SM, Simon MA, Abidov A, Yuan JX-J, *et al.* How prostacyclin therapy improves right ventricular function in pulmonary arterial hypertension. *Eur Respir J* 2017;50:1700764.
10. Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2008;31: 891–901.
11. Bhorade S, Christenson J, O'connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. *Am J Respir Crit Care Med* 1999;159:571–579.
12. Ghofrani H-A, Galiè N, Grimminger F, Grünig E, Humbert M, Jing Z-C, *et al.*; PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013;369:330–340.
13. Kass DA, Kelly RP. Ventriculo-arterial coupling: concepts, assumptions, and applications. *Ann Biomed Eng* 1992;20:41–62.
14. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;289:H501–H512.
15. Opotowsky AR, Hess E, Maron BA, Brittain EL, Barón AE, Maddox TM, *et al.* Thermodilution vs estimated Fick cardiac output measurement in clinical practice: an analysis of mortality from the Veterans Affairs clinical assessment, reporting, and tracking (VA CART) program and Vanderbilt University. *JAMA Cardiol* 2017;2:1090–1099.