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EDITORIAL COMMENT

Turning Pressure Into Success

Preload Restriction in HFpEF?*

Jessica Atkins, MD,[a] Marat Fudim, MD, MHS,[b,c] Ryan J. Tedford, MD[a]

"When you start thinking of pressure, it's because you've started to think of failure."
—Tommy Lasorda (1)

The late, great Los Angeles Dodgers manager Tommy Lasorda once remarked that the word "pressure" is misused in our vocabulary, because it is often associated with thoughts of failure. Instead, he believed, pressure should represent an opportunity for success. Heeding the wisdom of Mr. Lasorda, in this issue of *JACC: Basic to Translational Science* Kaiser et al. (2) have performed a first-in-human study with the idea that "pressure," in this case, targeting pulmonary pressure in heart failure with preserved ejection fraction (HFpEF) with preload reduction during exercise, may represent 1 such opportunity.

The authors enrolled 6 subjects with New York Heart Association functional class II-III heart failure symptoms, left ventricular ejection fraction >40%, and moderate diastolic dysfunction on echocardiogram (defined as e/e` >9). Important exclusion criteria included significant valve disease, significant resting pulmonary hypertension, lung disease, and more than moderate right ventricular dysfunction. Subjects underwent invasive, supine, symptom-limited cardiopulmonary exercise testing twice, with a 20-min rest period in between. During 1 of the studies, partial inferior vena cava (IVC) balloon occlusion was performed with a goal of maintaining pulmonary artery diastolic pressure (PAD) at 25 mm Hg. Partial IVC balloon occlusion was reportedly successful in maintaining PAD, and this was associated with reduced right atrial and pulmonary pressures, minute ventilation, and respiratory rate without a significant reduction in cardiac output. There was no statistical difference in exercise time or peak oxygen consumption, although there were trends toward longer exercise time during occlusion therapy.

HFpEF is not just a disease without therapies known to impact mortality, but just as important, also one without effective strategies to relieve symptoms and improve functional capacity. Thus, the authors are to be congratulated on this novel concept and forward-thinking approach that targets 2 relevant and underappreciated pathophysiologic mechanisms of exertional intolerance in HFpEF: preload reserve and pericardial restraint. Humans depend on the recruitment of blood volume toward the heart from the legs and the abdominal compartment to augment cardiac output with exercise. In accordance with the Frank-Starling relationship even a small augmentation in preload (venous return) can lead to marked increases in cardiac output (3). The increase in preload (preload reserve) manifests itself as an increase in thoracic blood volume (>30%) (3). Although healthy adults are able to translate an increased preload into increased cardiac output, patients with HFpEF cannot. Diastolic impairment and pericardial restraint explain why the physiological preload reserve leads to intracardiac pressure elevations in HFpEF (4). With the elevation of the right atrial volume and pressure (RAP), a septal shift occurs and pericardial pressure increases to a similar degree as RAP. This external pressure contributes to the rise in measured left ventricular and

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From the [a]Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA; [b]Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA; and the [c]Duke Clinical Research Institute, Durham, North Carolina, USA.

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pulmonary arterial pressures but actually reduces the effective left ventricular distending pressure (i.e., true preload), limiting cardiac output. By limiting the rise in RAP with preload restriction, the effect of pericardial restraint and diastolic ventricular interaction are therefore also reduced. Unfortunately, pulmonary artery wedge pressure (PAWP) was not measured during exercise in this study, and therefore determining the contribution of pericardial restraint is not possible. It is worth noting, however, that preload reduction therapy with superior vena cava occlusion and through splanchnic nerve modulation have been reported, seem promising, and are in various phases of clinical trials (5,6).

Although the perceived dyspnea of subjects is not reported, the reduction of respiratory rate and minute ventilation at paired exercise points is indeed interesting, and may hint at the notion that the elevations in (potentially modifiable) pulmonary pressure may directly contribute to symptomatology in HFpEF. Finally, a particularly intriguing idea proposed by the authors is coupling the technology to pulmonary artery monitoring devices, which could offer a direct feedback mechanism to determine the degree of required occlusion pressure to maintain goal pulmonary pressures.

Several additional considerations merit discussion as this technology moves past first-in-human studies. First, despite the rather broad inclusion criteria and exclusion of subjects with more than moderate right ventricular dysfunction, the current small cohort may be enriched for those with favorable, yet uncommon, physiology to benefit from this type of therapy. For example, the average resting central venous pressure (similar to RAP) was reported at 18 $\pm$ 6 mm Hg, not consistent with a typical HFpEF population. Although resting PAWP is not reported, the average resting PAD was 24 mm Hg. By assuming the average PAWP was less than 24 mm Hg, the RAP/PAWP ratio approaches 1. These hemodynamics are consistent with either significant right ventricular failure or restrictive/constrictive physiology. Similarly noteworthy, 1 of the 6 subjects achieved a cardiac output of 25 l/min during exercise and did not reach a PAD of 25 mm Hg during exercise, both inconsistent with diagnosis of HFpEF.

Another area that requires further evaluation is the PAD target during exercise. Accurately assessing PAD during exercise can be complex. Accentuated changes in intrathoracic pressure can lead to significant respiratory swings and fluid-filled catheters may show catheter ringing artifact. Targeting either mean pulmonary artery pressure or even a "mean" PAD may be more appropriate, yet this requires averaging over several cardiac and respiratory cycles. The delay with this approach may not provide the instant feedback necessary to safely regulate preload. Additionally, a "1 size fits all" pressure target may not be appropriate. As previously noted, 1 patient did not achieve a PAD of 25 mm Hg during exercise. Limiting the PAD to 20 mm Hg in this subject limited cardiac reserve. HFpEF patients with combined post- and precapillary PH, who have a significant gradient between PAWP and PAD, may be another group requiring a more personalized threshold.

Finally, if any occlusion occurs in any continuous circuit, upstream and downstream effects must be considered. Although the downstream effects seem to be beneficial in this pilot study, one must also remember that these subjects exercised in the supine position. Because approximately 70% of the heart's venous return comes from the IVC, any overrestriction of venous return, even transiently, could precipitate hypotension or even syncope. This may be even more likely while in the upright position of normal exertion, and these series of experiments should be repeated in the upright position before optimization of the technology and feedback mechanisms. The upstream effects of balloon occlusion of the IVC could lead to venous pooling in the abdominal organs and lower extremities, especially with sustained reduction of flow. Monitoring for development of lower extremity edema, ascites, renal congestion and insufficiency, or even hepatic fibrosis is required.

In summary, the paper by Kaiser et al. (2) offers a first look at mechanical preload control during exercise in HFpEF patients. The results are intriguing and provocative, although there is still much to consider as the next steps are taken. It also highlights the importance of understanding the hemodynamic and pathophysiologic basis for symptomatology in heart failure as new therapeutic approaches are developed. As in this case, redefining "pressure" as an opportunity may bring about success in a disease of failure.

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ADDRESS FOR CORRESPONDENCE: Dr. Ryan J. Tedford, Division of Cardiology, Department of Medicine, Medical University of South Carolina, 30 Courtenay Drive, BM215, MSC592, Charleston, South Carolina 29425, USA. E-mail: TedfordR@musc.edu. Twitter: @RyanTedfordMD.

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