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EDITORIAL COMMENT

Shielding the Heart

Preload Reduction Therapies in Heart Failure*

Muhammad Shahzeb Khan, MD, MSc,[a] Ryan J. Tedford, MD,[b] Marat Fudim, MD, MHS[a,c]

Preload reserve relates to the capability to raise cardiac output (CO) through increased venous return to fulfil the body's fluctuating metabolic requirements. Compared to arteries, which carry only approximately 30% of the total blood volume, veins serve not just to return the blood to the heart but also as functional reservoirs of blood, storing approximately 70% of the total blood volume. The augmentation of preload to enhance CO is beneficial for exercise performance in healthy individuals.[1] With little variations in pulmonary artery pressures, healthy individual may improve CO by 5-fold during exercise. However, patients with heart failure (HF) have a substantial elevation in right atrial pressure and pulmonary capillary wedge pressure during exercise.[2] This aggravates exercise intolerance and worsens HF symptoms due to an elevation in filling pressures at rest and during exercise. Therefore, restricting preload via pharmaceutical approaches or splanchnic nerve modulation or can possibly assist in unloading the heart by increasing the unstressed blood volume and decreasing the stressed blood volume (**Figure 1**).[1]

Additionally, preload restriction can also be achieved by blocking the inflow to the superior vena cava or inferior vena cava (IVC). In patients who have heart failure with preserved ejection fraction, balloon infiltration in the IVC for preload restriction led to a 25% reduction in pulmonary artery pressure during exercise, without any reduction in CO.[2,3] Caval flow occlusion relocates blood out of the thoracic compartment by preventing the return of venous blood without a change in vascular compliance. This reduces ventricular filling pressures and cardiac workload, and subsequently enhances cardiac function. Short-term caval restriction also enhances urine production and diuretic sensitivity as a result of central venous pressure reduction.[1] Therefore, a strategy that efficiently lowers volume overload and diuretic intolerance, while maintaining renal function, seems attractive for patients with acute HF (AHF).

The Doraya pilot clinical trial which is published in this issue of *JACC: Basic to Translational Science*,[4] is a nonrandomized, open-label, single-arm, prospective study that sought to evaluate the safety, feasibility, and hemodynamic and renal effects of a temporary (<12 hours) Doraya catheter procedure as an add-on to the usual diuretic therapy in patients with AHF.[3,4] The patients were required to have a primary diagnosis of congestive AHF, a poor response to diuretic therapy, and evidence of fluid overload. Patients with a history of deep venous thrombosis or pulmonary embolism, systolic blood pressure <90 mm Hg, and severe renal dysfunction (estimated glomerular filtration rate <18 mL/min/1.73 m^2) were excluded. Nine patients were included and were followed up until 60 days after catheter deployment. Because each patient was maintained on standard care for 24 hours and assessed before the procedure as well, each patient served as their own control. The primary endpoint was incidence of serious adverse events (SAEs). All surgeries were declared technically successful based on the capacity to put the catheter under the renal veins, control flow in the IVC, and establish a pressure difference of minimum 2 mm Hg.

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

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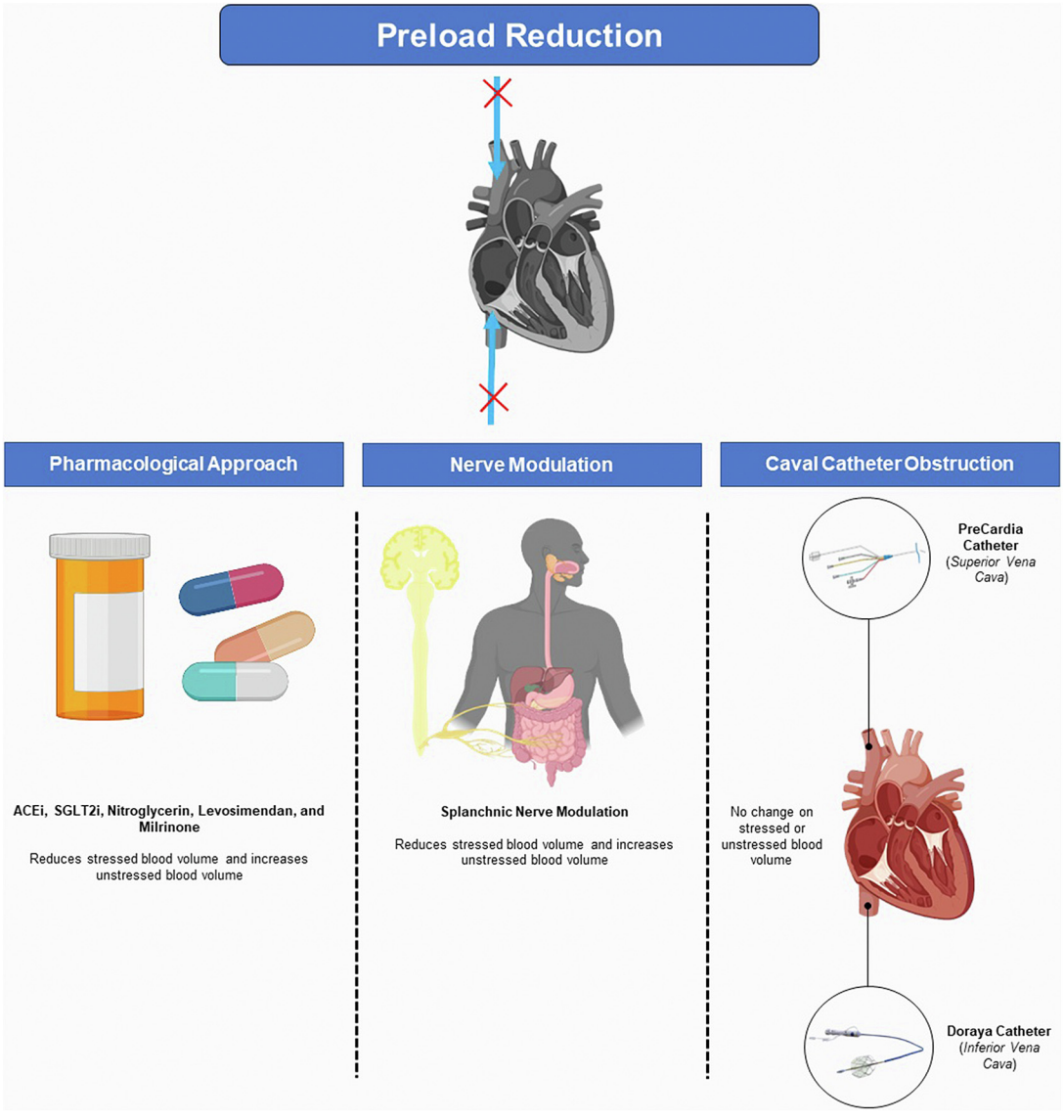
FIGURE 1 **Summary of Various Approaches for Preload Restriction**



ACEi = angiotensin-converting enzyme inhibitor; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

The Doraya catheter had no device-related SAEs during the procedure or at 30 days follow-up. One procedure-related SAE was observed 30 days post-procedure, but it was resolved without any consequences. During the 60-day follow-up period, 1 episode of Klebsiella infection, 1 episode of ventricular tachycardia, and 3 episodes of rehospitalization for worsening HF were observed. The Klebsiella infection and the ventricular tachycardia were treated without any complications by antibiotics and amiodarone, respectively. Two of 3 patients who had been rehospitalized were treated using diuretics and recovered without sequelae. However, 1 event of in-hospital mortality was observed who had several other comorbidities in addition to advanced HF. There were no instances of device failures or inadequacies, and no technical issues encountered during the device extraction. After the procedure, reduction in venous pressures was observed in all patients, where pressure above IVC significantly reduced from 18.4 $\pm$ 3.8 mm Hg to 12.4 $\pm$ 4.7 mm Hg ($P < 0.001$) from baseline. The average pressure

difference as a result of Doraya catheter was 4.6 ± 1.1 mm Hg. The mean diuresis improved in 7 patients, and signs of congestion, such as dyspnea and edema, improved at 48 hours after procedure.

Zymliński et al[4] are to be congratulated on conducting a novel study which supports the safety of Doraya catheter in patients with AHF and provides the groundwork for further study of clinical efficacy. However, some limitations, which are in keeping with first-in-human studies, should be appreciated. The study was conducted with a single-arm design, and provides preliminary data on the safety and feasibility of the Doraya catheter. The single-arm design makes it challenging to ascertain if the reported outcomes are attributable to the procedure, or if they were influenced by confounding variables, such as patient or provider-level differences. The study also had a relatively short follow-up duration, and although not probable, delayed adverse effects from the procedure itself may not yet be apparent. The mean time of the procedures in the study was 8.5 hours (range: 7 to 11.5 hours); however, the actual time required for the procedure was not indicated. Additionally, it is unclear if patients had to be on blood thinners during device placement, as it can influence the risk of thromboembolism due to the procedure. Furthermore, the mean gradient created by the Doraya catheter during the procedure was 4.6 ± 1.1 mm Hg, with a range of 0 to 10 mm Hg across all data points. One patient had a 0-mm Hg gradient; the reason for this is unknown and requires further evaluation regarding the underlying cause, such as failure of device to execute effectively. The study observed an immediate and significant decrease in venous pressure following Doraya deployment, accompanied by an immediate increase in renal arterial blood flow of 48% from baseline. However, this observation was limited to a single patient, hence, further research is necessary to draw any definitive conclusions regarding impairments in renal perfusion pressures as such observations may develop as a consequence of blunting of natriuretic and diuretic sensitivity in patients with AHF. Moreover, the study did not provide information on how diuretic administration was handled over the duration of the study, as this may have an impact on brain natriuretic peptide levels and diuretic response. The timing of diuretic administration could have affected the reliability of the urine output measurements. In future studies, the immediate period following device removal will be important to study. Do we see a rebound in renal venous and central venous pressures and what is the associated diuretic response? All of these factors must be considered in future trial development.

In summary, pilot studies of preload reducing therapies have shown the feasibility of such an approach for acute and maybe even chronic HF. The current study adds to the promise of a novel therapeutic strategy. Randomized clinical studies with relevant clinical endpoints are on the horizon.

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Dr Tedford has received consulting fees from Abbott, Medtronic, Aria CV Inc, Alleviant, Acceleron, Cytokinetics, Itamar, Edwards Lifesciences, Eidos Therapeutics, Lexicon Pharmaceuticals, Gradient, and United Therapeutics; has been the national co-principal investigator for the RIGHT-FLOW clinical trial (Edwards); has served on steering committees for Merck, Abbott, and Edwards; has served on a research advisory board for Abiomed; and has performed hemodynamic core lab work for Merck. Dr Fudim has received consulting fees from AxonTherapies and Cardioflow. Dr Khan has reported that he has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Marat Fudim, Division of Cardiology, Duke University Medical Center, 2301 Erwin Road, Durham, North Carolina 27710 USA. E-mail: marat.fudim@duke.edu.

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