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JOURNAL WATCH

Nitric Oxide Signaling in Heart Failure With Preserved Ejection Fraction

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SUMMARY

There has been considerable focus on the potential role of nitric oxide (NO) and phosphodiesterase (PDE)-5 inhibition in treating heart failure with preserved ejection fraction (HFpEF). However, the results from studies have been conflicting. In a preclinical study, pre-treatment of diabetic rats with a PDE-5 inhibitor, vardenafil, resulted in a significant decrease in left ventricle stiffness. However, the results from clinical trials have been neutral. In this perspective piece, the authors discuss whether or not it is time to move on from targeting NO and PDE5 for the treatment of HFpEF. (J Am Coll Cardiol Basic Trans Science 2017;2:341–3) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The lack of therapeutic options in heart failure with preserved ejection fraction (HFpEF) is well documented. In part, because of the high incidence of pulmonary hypertension (PH) in HFpEF, there has been consistent interest in repurposing pulmonary arterial hypertension (PAH)-specific therapies for HFpEF with considerable focus on nitric oxide (NO) and phosphodiesterase (PDE)-5 inhibition. NO is recognized as a potent vasodilator, and its activity is mediated through stimulation of soluble guanylate cyclase (sGC), which results in formation of the second messenger cyclic guanosine monophosphate (cGMP) and increased activity of protein kinase G (PKG). cGMP is degraded by PDE-5. PDE-5 inhibitors (PDE-5i) have been successfully used in for the treatment of PAH due to their significant vasodilatory effects. More recently, different strategies to stimulate the NO pathway for pulmonary vasodilatory purposes have been successfully explored, resulting in the approval of the sGC stimulator riociguat for treatment of PAH as well as chronic thromboembolic pulmonary hypertension. This class of drugs directly stimulates sGC independently of the presence of NO, thereby providing a second avenue through which to increase formation of cGMP and dilate the pulmonary vasculature.

The NO pathway has also been shown to be involved in the pathophysiology of heart failure, which has made PDE-5i an attractive therapeutic option for the treatment of HFpEF. There is evidence of decreased NO bioavailability in cardiomyocytes in HFpEF, which results in reduced PKG activity in these cells and contributes to the development of cardiac hypertrophy. A study published in 2011 from Guazzi et al. (1) showed promise as sildenafil resulted in improved hemodynamics in 44 patients with PH secondary to HFpEF. However, in the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction) trial, which involved 216 patients

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with HFpEF, there was no difference in clinical status and 6-min walking distance between patients treated with sildenafil and with placebo in the primary or secondary outcomes (2). Although the RELAX trial was negative, some enthusiasm remained for PDE-5i, because investigators continued to see whether there was a class of patients who might respond to these agents.

It is in this context that a recently published paper by Mátyás et al. (3) takes on increased relevance. The authors studied the use of a different PDE-5i, vardenafil, in an animal model of HFpEF, the Zucker diabetic fatty rats. Mátyás et al. (3) found that the pre-treatment of diabetic rats with vardenafil resulted in a significant decrease in cardiac remodeling and increased levels of plasma cGMP levels when compared with vehicle-treated animals. There was a significant decrease in left ventricle stiffness and improved relaxation time at the sarcomeric level, which indicated prevention of HFpEF in the group treated with vardenafil. The diabetic mice that developed HFpEF showed decreased levels of cGMP and decreased PKG activity despite the increased expression of PKG itself, demonstrating dysfunction of the NO-sGC-cGMP-PKG axis.

There are different possibilities to explain the inconsistency in the data that has so far been published on the use of PDE-5i in HFpEF. One possibility is that the effect observed is not intrinsically a class effect, but rather specific to each drug. Interestingly, the levels of circulating cGMP were not increased after treatment with sildenafil in patients enrolled in the RELAX trial, whereas an increase in those levels was seen in the mice treated with vardenafil in the study by Mátyás et al. (3). The specific patient population also might help explain the discrepancies. In a condition with such diverse phenotypes as HFpEF, it is not hard to imagine that different groups with diverse pathophysiological mechanisms of disease would have varied responses to the use of a therapeutic agent.

Of course, it is also possible that the contrasting results of these different clinical and preclinical studies may reflect the fact that PDE-5is are not beneficial in HFpEF. Although theoretically very attractive, they simply might not have the desired effect in vivo, and it might be time to move on to therapeutically targeting the NO-sGC-cGMP-PKG axis in a different manner. Although the use of isosorbide mononitrate in HFpEF patients was associated with a significant decrease in function activity, there are ongoing studies using inorganic nitrites (NO_2^-) in HFpEF. In contrast to nitrates (NO_3^-), endothelial dysfunction or tolerance does not develop with nitrites.

sGC stimulation may represent another approach for therapeutically targeting the NO pathway in HFpEF. However, the results of studying sGC stimulation in HFpEF have also been conflicting. In the DILATE-1 (Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Diastolic Heart Failure) trial, a single dose of riociguat (2 mg) improved cardiac output, and right ventricle size, although there was no significant change in pulmonary pressure or pulmonary vascular resistance (4). In the SOCRATES-PRESERVED (Soluble Guanylate Cyclase Stimulator in Heart Failure Patients With Preserved EF) trial, a recently published phase 2b study of the sGC stimulator vericiguat in patients hospitalized with HFpEF, there was no difference in the primary endpoint of change in N-terminal pro-B-type natriuretic peptide levels or left atrial volume at 12 weeks compared with placebo (5). There was an improvement in quality of life, but what the significance of this in the setting of this overall negative study is unclear.

The enthusiasm and interest for studying the NO pathway in HFpEF persists, despite repeated disappointments and inconsistent results. Challenges persist in translating the preclinical work by Mátyás et al. (3) into a clinical study. The timing of the treatment with PDE-5i might also play a significant role in the efficacy of these agents. In the study by Mátyás et al., the mice were treated with vardenafil before development of HFpEF, suggesting a potential preventive role of these agents. However, studying PDE-5i as a preventative therapy in patients with risk factors for developing HFpEF would be challenging.

The preclinical study by Mátyás et al. (3) represents another insightful study, but with the challenges experienced thus far of translating preclinical work on NO in HFpEF into robust, reproducible clinical outcomes, it is important to ask ourselves at what point we should move on from this therapeutic target and focus on other, more promising therapies for HFpEF.

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