Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction
A Target for Therapy?
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Patients with heart failure with preserved ejection fraction (HFpEF) have an increased mortality and morbidity similar to patients with systolic heart failure and reduced ejection fraction. The incidence of HFpEF is increasing, and roughly 30% to 50% of all patients with heart failure have a normal ejection fraction. The underlying pathophysiology is increased left ventricular diastolic stiffness that leads to high filling pressures. Additionally, left ventricular hypertrophy, accumulation of cardiac collagen, endothelial dysfunction, a shift in titin isoform, and increased passive stiffness of cardiac myocytes all contribute to these changes. For reasons that are yet uncertain, a subset of patients with HFpEF will go on to develop pulmonary hypertension (PH). Patients with HFpEF and PH can be subdivided into those with a normal pulmonary vascular resistance (PVR) and those with an increased PVR and pulmonary arterial remodeling. In fact, patients with HFpEF account for a significant percentage of patients with PH and right-sided heart dysfunction.

Importantly, both PH and right ventricular dysfunction are associated with decreased survival compared with HFpEF patients without PH. Although the underlying pathophysiology is poor left ventricular diastolic compliance, treatment focused on improving stiffness has been lacking, and management of patients with HFpEF has focused on control of factors known to exert effects on left ventricular end-diastolic pressure. The main emphasis has been on aggressive treatment of systemic blood pressure and heart rate, limiting pressure and volume overload of the heart through control of circulating volume, and management of myocardial ischemia. Current treatment approaches have not specifically addressed the issue of PH. As any clinician caring for patients with HFpEF knows, current treatment strategies have been very disappointing.

It is well known that the nitric oxide (NO) system is centrally important in regulation of vascular tone in both the pulmonary and systemic vasculature. Experimental evidence also suggests that the NO system is important for diastolic function acutely by directly increasing cardiac compliance, in addition to exerting long-term antihypertrophic and antifibrotic effects. NO signaling is mediated via increased production of cyclic guanosine monophosphate (cGMP) and is attenuated when cGMP is catabolized by specific members of the phosphodiesterase (PDE) superfamily. The most widely studied cGMP esterase is PDE5A, which is important in the regulation of vascular tone in the corpus cavernosum and pulmonary vasculature. cGMP and receptors for PDE5 are not only present in pulmonary vascular cells but are also in cardiac myocytes and systemic vascular cells. Inhibition of PDE5 may affect cardiac myocyte relaxation via proslutropic activity. PDE5 inhibition may improve flow-mediated coronary vasodilation and vascular dysfunction as a result of its effects on arterial stiffness and endothelial function in both the pulmonary and systemic circulation. Because of its effects on both diastolic function and the pulmonary vasculature, inhibition of PDE5A may be uniquely suited for treatment of the diastolic dysfunction associated with PH.

Sildenafil, a potent inhibitor of PDE5A, is widely used to treat both erectile dysfunction and pulmonary arterial hypertension. PDE5A inhibition by sildenafil produces a significant vasodilation mediated by NO release and cGMP accumulation. Sildenafil produces beneficial effects due to potent vasodilation in ischemic heart disease and PH. Sildenafil increases myocardial performance in patients with systolic heart failure primarily because of the decreased afterload that results from reduction of the total systemic vascular resistance.

What is the experimental evidence that inhibition of PDE5A and stimulation of the NO system will have beneficial effects? In mice, sildenafil markedly reduced the development of cardiac hypertrophy in response to pressure overload and reversed preestablished cardiac enlargement and fibrosis, which allowed for improved cardiac function despite a sustained increase in afterload. In a second animal model that used salt-induced hypertension, pharmacological stimulation of the NO system attenuated diastolic dysfunction independent of arterial blood pressure. As is seen in the clinical disorder, both of these models of HFpEF are characterized by development of cardiac hypertrophy, fibrosis, and severe diastolic dysfunction. Development of hypertrophy and fibrosis was attenuated by pharmacological stimulation of the NO system, which was associated with improved diastolic function. Thus, in 2 experimental models of HFpEF, stimulation of the NO system resulted in favorable effects.
In this issue of Circulation, Guazzi et al. report that sildenafil treatment in patients with HFpEF complicated by PH and right ventricular dysfunction results in sustained improvement in cardiopulmonary hemodynamics and lung function. The authors evaluated 44 well-characterized patients with HFpEF. All subjects were undergoing stable conventional background therapy that included diuretics, afterload reducers, and β-blockers for at least 6 months. Although a relatively small number of subjects were studied, an important strength of this double-blind, randomized, placebo-controlled 1-year study was the degree to which all of the subjects were characterized on the basis of echocardiography and invasive hemodynamics. Improvements were noted in most hemodynamic parameters, including significant decreases in right atrial, right ventricular end-diastolic, pulmonary artery, and pulmonary capillary wedge pressures. There were coincident decreases in pulmonary arterial resistance (PVR) and elastance, consistent with improved vascular compliance. Subjects had evidence of improved left ventricular relaxation and quality-of-life measures. It is particularly interesting that the hemodynamic improvements spanned the cardiopulmonary vascular bed from the right atrium to the left. The fall in PVR was to a greater extent than the fall in pulmonary capillary wedge pressure, which suggests that there was a direct effect on PVR rather than the drop in PVR being secondary to the decrease in pulmonary capillary wedge pressure. It is unlikely that the decreases in PVR and pulmonary capillary wedge pressure were simply the result of diuresis, because all of the background therapy was stable for at least 6 months before entry into the study and was unchanged throughout the trial for all patients in the treatment group. Supportive of both remodeling and direct pro-lusitropic effects on cardiac function were the findings of decreased left ventricular mass, along with improved deceleration time and isovolumic relaxation time. Another important finding was the significant improvement in spirometry and the diffusing capacity for carbon monoxide. This was attributed to reduced lung fluid content and improved alveolar-capillary membrane conductance and correlated with the decrease in right atrial pressure and PVR. Not only were the observed improvements significant, but they were sustained over the course of the study, and despite a persistent elevation of the systemic blood pressure.

Together, these findings suggest that targeting the NO system will be beneficial for the treatment of HFpEF, and more specifically, PH in the setting of HFpEF. The high frequency of PH in HFpEF suggests that strategies aimed at reducing PVR may have an important role as disease-specific therapy in PH and HFpEF. It is not clear whether these findings can be generalized to patients with HFpEF who do not have evidence of PH or right ventricular dysfunction. On the basis of the present study by Guazzi et al., the use of PDE5 inhibitors in HFpEF appears to represent a significant advance in therapy for patients with HFpEF complicated by PH. It will be important to confirm these findings in a larger clinical trial such as the ongoing Phosphodiesterase-5 Inhibition to Improve Quality of Life AND Exercise Capacity in Diastolic Heart Failure (RELAX) trial.

Disclosures

None.

References


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