Phosphodiesterase Type 5 Inhibition
A Support of the Left Ventricular Assist Device Bridge to Transplant
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The development of right heart failure has been a clinical concern of physicians caring for patients after cardiac transplantation since the inception of the field. Although the problem of "fixed" pulmonary vasoconstriction that does not respond to the reduction of left ventricular filling pressure seems to have diminished since the early days of transplantation, there are still some patients in whom this remains a problem. Data from the International Society of Heart Transplantation Registry suggests that right ventricular (RV) dysfunction accounted for 50% of all cardiac complications and 19% of all early deaths among heart transplantation patients, with persistent pulmonary vasoconstriction a major contributing factor to early RV dysfunction. The cause of the increase in vasoconstriction is unknown, although it may be a result of humoral factors, including cytokines, promoting changes in vascular smooth muscle gene expression. The hallmark of this problem is a lack of sensitivity to endogenous and exogenous vasodilators, be they nitric oxide (NO) released from pulmonary vascular endothelium or exogenous agents acting through NO, endothelin, or prostaglandin signaling pathways. Heart failure patients with fixed pulmonary hypertension can be disqualified from consideration for transplant surgery, given their worse prognosis for early survival. One alternative for these patients is to attempt to reverse the vasoconstriction with a combination of pharmacological agents and reduction of one of the presumed stimuli to vasoconstriction, an elevated pulmonary venous pressure. Variable success in reducing "fixed" pulmonary vasoconstriction has been reported with the use of inotropes such as milrinone and dobutamine in combination with vasodilators such as nesiritide.

Given the success of agents such as inhaled NO and the NO donor compounds nitroprusside and nitroglycerin in vasodilating the pulmonary circulation in heart failure patients, it is reasonable to consider other agents that can augment NO-cGMP signaling. Inhibitors of phosphodiesterase type 5 (PDE5), the enzyme that hydrolyzes cGMP in many tissues, including pulmonary vascular smooth muscle, are available, and their chronic administration is well tolerated by heart failure patients. Recently, De Santo et al. observed that PDE5 inhibitor therapy with sildenafil rapidly improved cardiac performance and permitted a decrease in mechanical and inotropic support in transplant recipients with RV dysfunction and persistent pulmonary hypertension.

In a study published in this issue of Circulation: Heart Failure, Tedford et al. reviewed the effects of sildenafil administered to patients with persistent pulmonary hypertension after left ventricular assist device (LVAD) implantation. Both the treatment patients and the control patients had fairly severe pulmonary vasoconstriction, with transpulmonary gradients of 25 and 21 mm Hg, respectively, after reduction of the LV filling pressure to 12 mm Hg by the LVAD. After 2 to 4 weeks of oral PDE5 inhibitor therapy with sildenafil, mean pulmonary artery pressure decreased by approximately one third, with an increase in cardiac output contributing to a decrease of pulmonary vascular resistance by approximately one half. There were only trends to a reduction in pulmonary vasoconstriction in the untreated historical control patients, even though their repeat hemodynamic assessment occurred after a longer duration of LVAD support. The majority of the patients treated with sildenafil had a sufficient reduction in pulmonary resistance to make them eligible for transplantation, and 10 of 26 patients studied have been transplanted. It is significant that only 1 of 10 had RV dysfunction after transplant; the remainder had an uncomplicated postoperative course. The persistence of this effect on the pulmonary circulation raises the possibility of more than just an acute vasomotor effect; it suggests that there may be a role for these agents in reversing pulmonary vascular remodeling occurring in chronic heart failure, much of which has been observed during in vitro studies.

The authors also report that sildenafil improved indices of RV myocardial systolic and diastolic function, specifically dP/dtmax/IP and τ in the LVAD patients. The accuracy of these measurements using fluid-filled catheters with limited frequency response characteristics is uncertain, and measurements in the control population are not reported. Thus, we are not certain how significant this effect is, nor whether it is related to the PDE5 inhibitor or to changes in RV myocardial function that are a function of ongoing LVAD support, such as increased neurohormonal activation or the effects on interventricular dependence of significant LV unloading. Nonetheless, given the work of Nagendran et al. that suggests direct myocardial inotropic effects of PDE5 inhibition occur as a consequence of an increase in myocardial cAMP, the observations of Tedford et al. are worthy of consideration. Further clinical studies are needed to determine whether

**Disclosures**

None.

**References**


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