PDE5A Inhibitor Treatment of Persistent Pulmonary Hypertension After Mechanical Circulatory Support

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Background—Pulmonary hypertension (PH) secondary to left heart failure portends a poor prognosis and is a relative contraindication to heart transplantation at many centers. We tested the hypothesis that when PH persists after adequate left ventricle unloading via recent left ventricular assist device (LVAD) therapy, phosphodiesterase type 5A inhibition would decrease PH in this population.

Methods and Results—We performed an open-label clinical trial using control patients not receiving therapy. Between 1999 and 2007, 138 consecutive patients undergoing cardiac transplantation evaluation with advanced left ventricular dysfunction, an elevated pulmonary capillary wedge pressure, and PH (defined by a pulmonary vascular resistance (PVR) >3 Woods Units), were treated with LVAD therapy. Fifty-eight of these patients reduced their pulmonary capillary wedge pressure to a value <15 mm Hg (11.8±2.0 mm Hg from baseline 23.2±6.2 mm Hg) 1 to 2 weeks after LVAD implantation, but despite this improvement, the PVR of these patients was only minimally affected (5.65±3.00 to 5.39±1.78 Wood Units). Twenty-six consecutive patients from this group with persistently elevated PVR were started on oral phosphodiesterase type 5A inhibition with sildenafil and titrated to an average of dose of 51.9 mg by mouth 3 times per day. The average PVR in the sildenafil-treated group fell from 5.87±1.93 to 2.96±0.92 Wood Units (P<0.001) and the mean pulmonary artery pressure fell from 36.5±8.6 to 24.3±3.6 mm Hg (P<0.0001) and was significantly lower when compared with the 32 LVAD recipients not receiving sildenafil at weeks 12 to 15 after the initial post-LVAD hemodynamic measurements (13 to 17 weeks post-LVAD implantation). In addition, hemodynamic measurements of right ventricular function in sildenafil-treated patients was also improved compared with patients not receiving sildenafil.

Conclusions—In patients with persistent PH after recent LVAD placement, phosphodiesterase type 5A inhibition in this open-label trial resulted in a significant decrease in PVR when compared with control patients. (Circ Heart Fail. 2008;1:213-219.)

Key Words: heart failure ■ PDE5A inhibition ■ sildenafil ■ hypertension, pulmonary ■ transplantation

Heart transplantation is a recognized treatment for end-stage heart disease. To ensure the best allocation of this scarce resource, significant risk factors for death after transplantation have been identified including an elevated pulmonary vascular resistance (PVR) ≥3 Wood Units.1 The International Society for Heart and Lung Transplantation database of 55 359 patients showed a linear relationship between PVR and transplant mortality.2 Therefore, pulmonary hypertension (PH), measured as increased PVR, has become not only a risk factor for mortality, but a relative contraindication to cardiac transplantation.

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PH from associated left-sided heart failure is thought to result from both a reactive increase in vascular smooth muscle tone as well as a relatively fixed structural remodeling.3 The former has been shown to be acutely reversible with vasodilators including nitroprusside,4,5 milrinone,6 dobutamine,7 prostaglandin E1,7,8 prostacyclin analogs,9,10 and inhaled nitric oxide (NO).11,12 The ability to respond to an acute vasodilator challenge has been shown to differentiate groups at high risk of perioperative mortality (those with persistently elevated, “fixed” PVR) from lower risk, transplantable groups.4,13,14 Two small studies have suggested that sildenafil may be useful as a method to test for acute vasodilatory reversibility in heart failure patients,15,16 Lewis et al17 recently demonstrated that a single dose of sildenafil reduced pulmonary artery pressure (PAP) and PVR in patients with PH secondary to New York Heart Association class III heart failure as well as improved peak V02 and exercise performance.

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Pulmonary vascular remodeling observed in patients with PH from left-sided heart failure leading to what has been sometimes termed “fixed” or persistent PH and may include medial hypertrophy with or without intimal fibrosis, but a noted absence of plexiform lesions (which are observed in primary PH). These structural changes and lack of acute reversibility may not represent an irreversible abnormality as 80% of patients who underwent a cardiac transplantation despite persistent PH normalized their PVR by 1 year. The precise time course for reversal is unknown, as a more recent study suggests that PVR can normalize as early as 30 days after transplantation. Although the pulmonary vascular remodeling may slowly revert once blood flow has normalized, cardiac transplantation in the setting of an elevated PVR increases the risk of acute right ventricular (RV) failure in the perioperative period.

Several strategies, described in case reports, have attempted to reverse the persistent component of PH to obtain a transplantable PVR value in patients not responsive to acute vasodilatory challenge including long-term prostacyclin administration, cardiac resynchronization therapy, long-term inotropic therapy so-called “vasodilator conditioning” with milrinone or dobutamine, and nesiritide. In addition, small studies report a decrease PVR in persistent PH to a transplantable level after implantation of a left ventricular assist device (LVAD). Importantly, this reversal occurred over 6 weeks to 1 year.

In an attempt to augment this process, oral phosphodiesterase type 5A (PDE5A) inhibitor, sildenafil, appeared as a good candidate. In dogs, long-term oral PDE5A inhibitors significantly inhibited the development of PH secondary to heart failure. Furthermore, Jabbour et al recently published a case series of 6 patients with cardiomyopathy, an elevated pulmonary capillary wedge pressure (PCWP; average 26.3 mm Hg), and an elevated PVR who were treated with sildenafil to allow for transplantation. In most of these patients, a decrease in PVR and transpulmonary gradient was observed and transplantation was performed. Several case reports exist in which long-term oral sildenafil therapy decreased PVR in a patient with an elevated PCWP to a transplantable level.

Given its pharmacological properties and success in patients with other clinical profiles, we performed an open-label clinical trial of sildenafil in LVAD recipients and compared them with historical controls. We hypothesized that PDE5A inhibition will decrease PVR when PH persists despite adequate left ventricle unloading.

Methods and Results

Patients

A research protocol designed to determine the effects of sildenafil on PAP and PVR was approved by the Johns Hopkins University Institutional Review Board for the open-label use of human subjects. Twenty-six consecutive patients with advanced left ventricular dysfunction, treatment with LVAD implantation, and persistent PH (defined by a PVR > 3 Wood Units 7 to 14 days after LVAD implantation) despite normalization of their PCWP to a value < 15 mm Hg were consented for and received treatment with sildenafil in an attempt to reduce PVR before cardiac transplantation. Patients with the combined use of LVADs and RVADs were not used. Patients receiving chronic inotrope therapy were excluded from this study. No patients received placebo. Patients in the sildenafil treatment group did not have their angiotensin converting enzyme inhibitor/angiotensin receptor blocker, hydralazine, or β-blocker therapy increased after initiation of sildenafil treatment.

For comparison with the sildenafil-treated patients, we reviewed and included all 138 consecutive patients who received LVAD implantation from 1999 to 2007 at our institution. From this group, a total of 58 patients had persistently elevated PVR at the time of subsequent right heart catheterization performed 7 to 14 days post-LVAD implantation of which 26 received sildenafil and 32 did not receive sildenafil. No patients refused sildenafil therapy.

Statistical Analysis

All patients underwent routine right heart catheterization 7 to 14 days (average time, 9.7 days) after the implantation of their LVAD to determine the presence or absence of PVR > 3 Woods Units and repeated serially at 1- to 3-month intervals after the institution of sildenafil treatment. Patients received no medications by mouth on the morning of subsequent right heart catheterizations. Right heart catheterization was performed as described previously. Cardiac output was determined by thermodilution. Right heart catheterization pressure waveforms data were additionally analyzed for augmentation index (PA dP/PP), contractility index (dP/dt max/IP), and isovolumic relaxation time constant (τ) to determine parameters of pulmonary arterial stiffness, RV systolic function, and RV diastolic function, respectively. This analysis was performed using custom software (WinPVAN, version 3.5.8). Transthoracic echocardiograms were conducted on all patients after right heart catheterization to measure tricuspid annular plane systolic excursion (an echocardiographic surrogate of RV systolic function).

Sildenafil Treatment

Patients meeting the above inclusion criteria were started on sildenafil at a dose of 25 mg by mouth 3 times per day with a target dose of 75 mg 3 times a day. The dose was advanced every 2 to 4 days based on tolerability (symptomatic hypotension, gastric reflux, headache, facial flushing) to a final average dose of 51.9 ± 4.4 mg. All patients tolerated some dose of the medication, and the final dose was achieved in 5 to 7 days. After this initial dose titration, there was no further alteration.

Results

Twenty-six consecutive patients with advanced left ventricular dysfunction, treatment with LVAD implantation, and persistent PH (defined by a PVR > 3 Wood Units 7 to 14 days after LVAD implantation) despite normalization of PCWP to a value < 15 mm Hg were treated with sildenafil to lower PVR before cardiac transplantation. Thirty-two consecutive LVAD control subjects were identified as outlined above. Table 1 outlines the characteristics of these 2 groups including pre- and post-LVAD medication use. Baseline pre- and post-LVAD hemodynamic values are shown in Table 2 in both groups before open-label treatment with sildenafil. Both
Table 1. Baseline Patient Characteristics Before Intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sildenafil Group (n = 26)</th>
<th>LVAD Control Group (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.4±9.0</td>
<td>48.1±10.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>18/8</td>
<td>22/10</td>
<td></td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.80±0.18</td>
<td>1.93±0.21</td>
<td>0.65</td>
</tr>
<tr>
<td>Etiology of cardiomyopathy, %</td>
<td>58</td>
<td>53</td>
<td>0.70</td>
</tr>
<tr>
<td>% ischemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>15.2±2.2</td>
<td>16.17±3.6</td>
<td>0.83</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>6.43±1.07</td>
<td>6.86±1.17</td>
<td>0.79</td>
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<tr>
<td>NYHA</td>
<td>3.9±0.2</td>
<td>3.8±0.4</td>
<td>0.84</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>96.4±15.2</td>
<td>96.9±12.6</td>
<td>0.87</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.1±1.6</td>
<td>11.3±1.2</td>
<td>0.92</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>132.0±2.2</td>
<td>133.2±1.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.8±0.9</td>
<td>1.7±1.1</td>
<td>0.95</td>
</tr>
<tr>
<td>Known pulmonary disease (COPD/asthma), %</td>
<td>12</td>
<td>14</td>
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</tr>
<tr>
<td>Pre-LVAD medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker use, %</td>
<td>85</td>
<td>74</td>
<td>0.31</td>
</tr>
<tr>
<td>ACEI/ARB, %</td>
<td>84</td>
<td>78</td>
<td>0.56</td>
</tr>
<tr>
<td>ISDN/hydralazine, %</td>
<td>15</td>
<td>8</td>
<td>0.40</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>35</td>
<td>41</td>
<td>0.64</td>
</tr>
<tr>
<td>&gt;1 diuretic, %</td>
<td>57</td>
<td>65</td>
<td>0.53</td>
</tr>
<tr>
<td>Post-LVAD medications, 2–4 wk after implantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker use, %</td>
<td>54</td>
<td>50</td>
<td>0.76</td>
</tr>
<tr>
<td>ACEI/ARB, %</td>
<td>50</td>
<td>53</td>
<td>0.82</td>
</tr>
<tr>
<td>ISDN/hydralazine, %</td>
<td>31</td>
<td>28</td>
<td>0.80</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>19</td>
<td>22</td>
<td>0.78</td>
</tr>
<tr>
<td>&gt;1 diuretic, %</td>
<td>81</td>
<td>87</td>
<td>0.53</td>
</tr>
</tbody>
</table>

LVAD indicates left ventricular assist device; NYHA, New York Heart Association; BP, blood pressure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ISDN, isosorbide dinitrate.

groups were similar with regard to pre- and post-LVAD hemodynamics. Figure 1 shows summary data including the influence of LVAD therapy on cardiac output, mean pulmonary arterial pressure, PCWP, and calculated PVR of the entire combined cohort. Despite normalization of PCWP and a significant increase in cardiac output, this cohort of patients had a change in PVR after intervention with LVAD (5.65±3.00 to 5.39±1.78 Wood Units) that was not statistically significant (P=0.56; Figure 1). The transpulmonary gradient increased significantly from 13.7±6.9 to 22.8±7.9 mm Hg (P<0.001).

In the 26 patients receiving sildenafil, there was a significant lowering of mean PAP from 36.5±8.6 to 24.2±3.6 mm Hg (P<0.0001; Figure 2) and PVR from 5.87±1.93 to 2.96±0.92 Wood Units (mm Hg L⁻¹·min⁻¹; P<0.001; Figure 2) after 2 to 4 weeks of therapy. This improvement in PVR was maintained through 12 to 15 weeks after sildenafil initiation (Figure 3). In contrast, in LVAD control patients with similar baseline clinical (Table 1) and hemodynamic parameters, there was not a statistically significant reduction in PVR during the same time period (13 to 17 weeks post-LVAD implantation; P=0.074), although there was a trend toward significance.

In addition to improvements in PVR and transpulmonary gradient, patients treated with sildenafil showed marked improvement in RV systolic and diastolic function, as measured by RV contractility index (dP/dtₘₐₓ/IP; 8.69±1.78 to 13.1±3.3; P<0.0001) and τ (91.9±17.7 to 63.6±17.8 ms; P<0.0001), respectively (Figure 4). Pulmonary artery augmentation index was also decreased after sildenafil treatment from 0.195±0.04 to 0.126±0.02; P<0.0001) and tricuspid annular plane systolic excursion increased from 1.73±0.21 to 2.00±0.2 cm (P<0.001), suggesting a reduced large artery pulmonary vascular stiffness. The increase in RV dP/dtₘₐₓ/IP in patients that received sildenafil at 2 to 4 weeks was sustained through 12 to 15 weeks.

Treatment with sildenafil did not elevate the PCWP or diminish cardiac output (Figure 2). Furthermore, sildenafil was well tolerated, and there was no increased incidence of arrhythmias (atrial fibrillation, ventricular tachycardia, and ventricular fibrillation) based on bimonthly interrogation of internal cardioverter defibrillators as well as Holter monitoring (data not shown). Four patients experienced facial flushing that occurred immediately after the first 2 doses. Two patients reported gastric reflux that began after the first administered dose and continued until day 3 of treatment with spontaneous resolution. None of these reported events resulted in the alteration of dose or discontinuation of drug therapy until after transplantation. After cardiac transplantation, patients were maintained on sildenafil until their first right heart catheterization, at which time patients’ dosing was tapered over the following week.

Of the 26 sildenafil-treated patients, 24 reduced their PVR to below 3 Wood Units, and 19 were deemed transplant candidates.
eligible with the remainder being classified for destination LVAD therapy. Of this group 10 patients have been transplanted to date without surgical complication. One patient treated with sildenafil had postoperative RV dysfunction defined as either requirement of inhaled NO for >48 hours or intravenous inotrope therapy for >72 hours posttransplant for RV dysfunction. Of the LVAD control patients, 18 were transplanted without surgical complication. Five of the 18 patients had RV dysfunction postoperatively (P = 0.27).

Discussion

End-stage heart failure is associated with significant mortality. Cardiac transplantation is the treatment of choice. PH as defined by an elevated PVR has consistently been identified as a risk for peritransplant mortality and is a relative contraindication to transplantation at most centers. Among potential cardiac transplant candidates with severe left ventricular systolic dysfunction and subsequent PH, there exists a subset of patients in which traditional vasodilators or LVAD therapy does not acutely lower PVR to a level < 3 Wood Units. In our cohort of patients with persistent PH who failed to improve early after LVAD implantation, addition of PDE5A inhibition with sildenafil along with continued LVAD support substantially and rapidly lowered mean PAP and PVR to levels < 3 Wood Units. Measurements of RV function also showed significant improvement after sildenafil treatment. There were no adverse reactions to the therapy.

Our cohort supports and extends the findings by Alaeddini et al,16 who showed that sildenafil acutely lowered PVR in ICU patients with left-sided cardiac failure, all of which were already on some type of inotrope or vasodilator therapy and had an elevated PCWP. With regard to its potential to allow for transplantation, it supports and extends to the case report by Gomez-Moreno et al,31 in which a dilated cardiomyopathy patient with a persistently elevate PVR (from Becker muscular dystrophy) failed dobutamine infusion and was treated with 4 months of sildenafil and later successfully transplanted after lowering PVR to a level considered acceptable for transplantation. Jabbour et al30 used sildenafil to lower PVR in potential cardiac transplant patients, although these patients had elevated PCWP and also demonstrated a response to nitrates or prostacyclins. Thus, the degree of persistent PH in these patients could not be quantified.
Our study suggests that sildenafil may lead to significant hemodynamic improvement in patients with PH from left heart failure unresponsive to LVAD therapy (despite normalization of the PCWP). After initiation of sildenafil, there was a marked reduction in PVR, allowing for potential transplantation at our center. Although previous studies have indicated the PVR will improve with LVAD therapy alone, the time period for improvement is relatively lengthy (6 weeks to 1 year).\textsuperscript{27,28} In our control LVAD patients, PVR began to trend lower by 12 to 15 weeks (13 to 17 weeks post-LVAD implantation) as seen in Figure 4; however, these patients still had an average PVR $>4$, a value not yet ideal for transplantation. The decrease in PVR was not statistically significant at this time point. Although previous findings suggest PVR values would continue to decline after persistent unloading of the left ventricle and return of normal pulmonary flow, the time frame to achieve this normalization may be prolonged. In our sildenafil cohort, PVR dropped to a transplantable level by 2 to 4 weeks, and this drop was maintained and sustainable with continued therapy over the next several months. It is possible that PVR was lowered even before this time period since Alaeddini et al witnessed a drop in as little as 4 hours. The ability to lower PVR in such a short time frame allows for the potential of earlier transplantation as well as improved hemodynamics in destination LVAD patients. In fact, Klodell et al\textsuperscript{13} recently reported using sildenafil to wean inotropic support and inhaled NO from 10 newly implanted LVAD patients.

In addition to its effect on PVR and PAP, sildenafil treatment combined with LVAD improved several measurements of RV function including RV dP/dt$\text{max}$/IP and $\tau$ (Figure 4). Nagendran et al\textsuperscript{34} recently showed that PDE5A is upregulated in hypertrophied human RV and acute inhibition with sildenafil can improve contractility evidenced by an increase in RV dP/dt$\text{max}$. Sildenafil has previously been shown to influence $\tau$ in animal models of heart failure.\textsuperscript{35} These findings

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**Figure 3.** Influence of sildenafil treatment on PVR and dP/dt$\text{max}$/IP compared with consecutive LVAD control patients at pre-LVAD, post-LVAD, and 2 to 4, 6 to 9, and 12 to 15 weeks posttreatment with sildenafil or with no treatment. Data are presented as mean $\pm$ SD. Post-LVAD measurement is time of first right heart catheterization and also when patients were initiated on sildenafil. $n$ indicates number of patients. $^*P<0.05$ vs control patients at 12- to 15-week right heart catheterization. Comparisons for the week 12 to 15 time point were made with unpaired Student $t$ test.

**Figure 4.** Effect of sildenafil on RV dP/dt$\text{max}$/IP, isovolumic relaxation time constant ($\tau$), augmentation index (RV dP/PP), and tricuspid annular plane systolic excursion (TAPSE). $n$ indicates number of patients. $^*P<0.05$ vs pre-sildenafil. Comparisons made with paired $t$ test.
may suggest that sildenafil can improve RV function through mechanisms other than simply lowering PVR and PAP. The relative contribution to hemodynamic improvement is yet to be elucidated. Sildenafil-treated patients witnessed an improvement in tricuspid annular plane systolic excursion, which has previously been shown to be of significant prognostic value.26 A decrease in pulmonary arterial stiffness measured by augmentation index was also observed.

PDE5A, the enzyme responsible for catabolism of cGMP in the lung, has previously been shown to be upregulated in animal models of hypoxia induced PH as well as in humans with pulmonary arterial hypertension.37,38 Because of the success in lowering PVR with sildenafil (a potent PDE5A inhibitor) in our cohort, it is likely that PDE5A plays an important role in this human disease process, specifically one component of persistent PH in left-sided heart failure. This could be the result of upregulation of PDE5A. Patients with persistent PH are unresponsive to inhaled NO in terms of vasodepressor response.11,12 cGMP is the second messenger of the NO vasodilatory cascade. If PDE5A is upregulated to the point where it can immediately catabolize any cGMP produced from the inhaled NO, this may explain the lack of vasodilatory response. If this is true in persistent PH in heart failure, then inhibition of the catabolism of cGMP may allow for pulmonary vasodilatation and subsequent lowering of PVR.

This study has its limitations that must be considered. It is an open-label trial, which uses controls that were not treated with sildenafil before those that received the PDE5A inhibitor. With this in mind, other changes in selection or therapies in addition to the sildenafil may have occurred during the more recent time period. Moreover, the actual timing of the initial PVR drop cannot be determined as the first measure of PVR after initiation of sildenafil therapy did not occur until 2 to 4 weeks. It is possible that other vasodilator therapies such as nesiritide or chronic nitrates may reduce mean PAP and PVR in LVAD patients with persistently elevated PVR. Six patients in our cohort were receiving nitrate/hydralazine combination for afterload reduction in the setting of angiotensin converting enzyme inhibitor/angiotensin receptor blocker intolerance. This group was on nitrate therapy before LVAD implantation as well as afterward. No patients received nesiritide.

Certainly further study is needed to define the role of chronic PDE5A inhibition in the setting of left ventricular dysfunction associated with persistent PH including randomized controlled trials with morbidity and mortality outcomes. Several important questions are yet to be answered, including the timing at which to initiate sildenafil therapy. If PDE5A is upregulated in this disease process, earlier treatment with PDE5A inhibitors might prevent the development of PH as seen in animal models.29 It is not yet known whether PDE5A inhibition should be started before LVAD therapy.

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**Disclosures**

Dr Champion is a speaker for Pfizer related to pulmonary arterial hypertension (WHO category 1).

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