Hemodynamic Effects of Sildenafil in Patients With Congestive Heart Failure and Pulmonary Hypertension*  

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Study objectives: In patients with pulmonary hypertension (PH) secondary to congestive heart failure, inhaled nitric oxide (NO) increases pulmonary vascular smooth-muscle intracellular cyclic guanosine monophosphate (cGMP) concentration, thereby decreasing pulmonary vascular resistance (PVR) and increasing cardiac index (CI). However, these beneficial effects of inhaled NO are limited in magnitude and duration, at least in part due to cGMP hydrolysis by the type 5 isoform of phosphodiesterase (PDE5). The goal of this study was to determine the acute pulmonary and systemic hemodynamic effects of the selective PDE5 inhibitor, sildenafil, administered alone or in combination with inhaled NO in patients with congestive heart failure and PH.

Design: Single center, case series, pharmacohemodynamic study.

Setting: Cardiac catheterization laboratory of a tertiary care academic teaching hospital.

Patients: We studied 11 patients with left ventricular systolic dysfunction due to coronary artery disease or idiopathic dilated cardiomyopathy who had PH.

Interventions: We administered oral sildenafil (50 mg), inhaled NO (80 ppm), and the combination of sildenafil and inhaled NO during right-heart and micromanometer left-heart catheterization.

Measurements and results: Sildenafil administered alone decreased mean pulmonary artery pressure by 12 ± 11%, PVR by 12 ± 15%, systemic vascular resistance (SVR) by 13 ± 6%, and pulmonary capillary wedge pressure by 12 ± 7%, and increased CI by 14 ± 5% (all p < 0.05) [± SEM]. The combination of inhaled NO and sildenafil decreased PVR by 50 ± 4%, decreased SVR by 24 ± 3%, and increased CI by 30 ± 4% (all p < 0.01). These effects were greater than those observed with either agent alone (p < 0.05). In addition, sildenafil prolonged the pulmonary vasodilator effect of inhaled NO. Administration of sildenafil alone or in combination with inhaled NO did not change systemic arterial pressure or indexes of myocardial systolic or diastolic function.

Conclusions: PDE5 inhibition with sildenafil improves cardiac output by balanced pulmonary and systemic vasodilation, and augments and prolongs the hemodynamic effects of inhaled NO in patients with chronic congestive heart failure and PH. (CHEST 2005; 127:1647–1653)

Key words: heart failure, congestive; hypertension, pulmonary; nitric oxide; type 5 phosphodiesterase; vasodilator agents

In patients with severe, chronic left ventricular (LV) systolic dysfunction, right ventricular (RV) performance is an important determinant of exercise capacity and survival.1 RV performance is closely linked to pulmonary vasomotor tone, and there has been recent interest in the use of pulmonary vasodilators to treat pulmonary hypertension (PH) in heart failure patients, thereby improving overall
cardiac performance. For example, endothelin antagonists decrease pulmonary vascular tone in heart failure patients, but their use has been limited by either systemic vasodilation and hypotension, as reported during administration of bosentan, or by a failure to increase cardiac output, possibly related to a negative inotropic effect, as reported during administration of sitaxsentan.

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator in patients with PH from a variety of causes. In patients with heart failure due to LV dysfunction, acute administration of inhaled NO reduces pulmonary vascular resistance (PVR) and increases cardiac index (CI) without altering systemic arterial pressure. This hemodynamic response has been used to assess pulmonary vascular reactivity in patients being evaluated for cardiac transplantation. In addition, breathing NO increases exercise capacity in patients with PH and chronic left heart failure.

Inhaled NO exerts its pulmonary vasodilator effect by diffusing into pulmonary vascular smooth-muscle cells and stimulating the production of cyclic guanosine monophosphate (cGMP) by soluble guanylate cyclase. cGMP acts as a second messenger stimulating cGMP-dependent protein kinase, thereby producing vasodilation. The metabolism of cGMP by the cGMP-specific type 5 isoform of phosphodiesterase (PDE5) in vascular smooth muscle cells is an important determinant of the extent and duration of vasodilation.

Sildenafil is a selective PDE5 inhibitor that has been used extensively for the treatment of male erectile dysfunction. In an ovine model of PH, we have previously shown that oral sildenafil decreases pulmonary artery pressure without altering systemic arterial pressure. Reports have indicated that sildenafil is a pulmonary vasodilator in patients with primary PH or PH secondary to hypoxia or pulmonary fibrosis. In addition, in patients with primary PH, sildenafil can augment the pulmonary vasodilator response to inhaled NO and prevent the rebound pulmonary vasoconstriction that occurs following cessation of NO breathing. However, the acute hemodynamic effects of sildenafil in patients with PH associated with congestive heart failure have not been reported. In this study, we evaluated the acute hemodynamic effects of sildenafil administered alone and in combination with inhaled NO in patients with PH caused by LV dysfunction.

**Materials and Methods**

**Inclusion and Exclusion Criteria**

All patients under the care of the Massachusetts General Hospital Heart Failure Service who required hemodynamic assessment as part of a cardiac transplant evaluation were eligible for study. Inclusion criteria were a ≥ 12-month history of symptomatic heart failure; a LV ejection fraction < 40%, as identified by echocardiography within 1 month; and a mean pulmonary artery pressure of at least 25 mm Hg. Exclusion criteria included the presence of acutely decompensated heart failure (systemic arterial pressure < 85 mm Hg), or of provokable coronary ischemia, as assessed by radionuclide imaging. Patients with severe mitral or aortic valve disease were excluded from study. None of the patients were receiving sildenafil at the time of study. None of the patients had severe obstructive lung disease (FEV1 < 1.0 L/min), sleep apnea syndrome, or pulmonary embolism. The protocol was approved by the Massachusetts General Hospital Human Research Committee, and informed consent was obtained from all patients.

**Hemodynamic Measurements**

Twenty-four hours after discontinuation of all inotropic, vasodilator, and diuretic therapy, patients underwent right-sided cardiac and micromanometer LV catheterization (Millar Instruments; Houston, TX). Heart rate, mean systemic arterial pressure, right atrial pressure, mean pulmonary artery pressure, and pulmonary capillary wedge pressure (PCWP) were measured. LV end-systolic pressure was recorded as the LV pressure at the time of the dicrotic notch in the arterial pressure after correction for any time delay between arterial and LV pressure. Cardiac output was measured by the Fick oxygen technique. Oxygen consumption was measured with an MRM-2 VO2 monitor (Waters Associates; Rochester, MN) at baseline while breathing air. Systemic arterial and right atrial oxygen saturation was measured at each time point in the protocol. The PO2 of each arterial blood sample was measured in order to add the amount of oxygen dissolved in plasma to the arterial oxygen content used in the Fick calculation. Systemic vascular resistance (SVR), PVR, and CI were calculated using standard formulas. Indexes of LV systolic function (maximal rate of rise in LV pressure [+dP/dt max] and +dP/dt max normalized for developed pressure [+dP/dt max/DP]), and diastolic function (maximal rate of LV pressure decline [−dP/ dt max]; time constant of isovolumic relaxation, logarithmic
method [TL]; and time constant of isovolumic relaxation, derivative method [TD]) were determined. The Bonferroni test was used to compare changes in hemodynamic variables among the treatment periods of oxygen, oxygen and NO, oxygen and sildenafil, and oxygen in combination with NO and sildenafil. A repeated-measures analysis of variance followed by a Dunnett and sildenafil, and oxygen in combination with NO and sildenafil. A repeated-measures analysis of variance followed by the Newman-Keuls test, when appropriate, was used for multiple comparisons of sildenafil levels and for comparison of hemodynamic variables described previously. A control group of patients underwent the identical study protocol, with the exception that patients received serial administration of inhaled NO without concomitant administration of sildenafil.

Statistical Analysis

The Wilk-Shapiro test was used to assess the normality of the distribution of the data. All data were found to be normally distributed except the PVR/SVR ratio. Normally distributed data were expressed as mean ± SEM and analyzed as follows. A paired t test was used to compare hemodynamic variables during breathing 100% oxygen with baseline variables breathing air. A repeated-measures analysis of variance followed by the Newman-Keuls test, when appropriate, was used for multiple comparisons of sildenafil levels and for comparison of hemodynamic variables among the treatment periods of oxygen, oxygen and NO, oxygen and sildenafil, and oxygen in combination with NO and sildenafil. A repeated-measures analysis of variance followed by a Dunnett test was used to compare changes in hemodynamic variables measured 5 min, 10 min, and 15 min after cessation of NO inhalation from those measured while breathing oxygen alone. The Bonferroni procedure for multiple comparisons was used to compare hemodynamic variables with and without sildenafil treatment measured at each time point after cessation of breathing NO.

As the ratio of PVR to SVR was not normally distributed in the study population, median values are given for this variable. The Friedman rank test, followed by the Wilcoxon signed-rank test with a Bonferroni modification, was used for comparison of this ratio among the treatment periods of oxygen, oxygen and NO, oxygen and sildenafil, and oxygen in combination with NO and sildenafil. All statistical testing was performed using software (RS/1 Version 5.2.3; BBN Domain; Cambridge, MA); p ≤ 0.05 was considered significant.

RESULTS

Study Protocol

We studied 11 heart failure patients (9 men and 2 women; mean age, 56 ± 3 years [± SEM] [Table 1]). Six patients had idiopathic dilated cardiomyopathy, and five patients had coronary artery disease. Seven patients were New York Heart Association (NYHA) functional class III, and four patients were NYHA functional class IV. At baseline, the PCWP was elevated, and the LV ejection fraction and CI were depressed. PH was present with a mean pulmonary artery pressure of 37 ± 2 mm Hg and PVR of 301 ± 44 dyne·s·cm⁻⁵.

Hemodynamic Effects of Oxygen, Inhaled NO, and Sildenafil

Breathing > 90% oxygen reduced PVR by 16 ± 9% (Fig 1, Table 2). Compared with breathing > 90% oxygen alone, NO inhalation reduced PVR by 38 ± 5% and SVR by 5 ± 3% (both p < 0.05) without altering mean pulmonary or systemic arterial pressures. The ratio of PVR to SVR decreased from 0.16 to 0.09 (p < 0.05), indicating that NO inhalation produced selective pulmonary vasodilatation. There was a trend to an increased CI during NO inhalation (7 ± 3%, p = 0.08). NO inhalation increased PCWP by 16 ± 7% and LV end-diastolic pressure by 14 ± 6% (both p < 0.05) without altering LV end-systolic pressure. All hemodynamic variables returned to baseline within 15 min after cessation of NO inhalation.

Table 1—Clinical Characteristics and Baseline Hemodynamic Variables

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Diagnosis</th>
<th>NYHA Class</th>
<th>LV Ejection Fraction</th>
<th>Mean PA, mm Hg</th>
<th>PCWP, mm Hg</th>
<th>PVR, dyne·s·cm⁻⁵</th>
<th>CI, L/min/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>64</td>
<td>CAD</td>
<td>4</td>
<td>0.15</td>
<td>43</td>
<td>25</td>
<td>424</td>
<td>1.9</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>52</td>
<td>DCM</td>
<td>4</td>
<td>0.38</td>
<td>28</td>
<td>19</td>
<td>136</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>67</td>
<td>DCM</td>
<td>3</td>
<td>0.20</td>
<td>35</td>
<td>18</td>
<td>412</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>57</td>
<td>CAD</td>
<td>4</td>
<td>0.29</td>
<td>35</td>
<td>26</td>
<td>171</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>59</td>
<td>CAD</td>
<td>3</td>
<td>0.16</td>
<td>37</td>
<td>29</td>
<td>173</td>
<td>1.6</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>64</td>
<td>DCM</td>
<td>4</td>
<td>0.35</td>
<td>42</td>
<td>22</td>
<td>356</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>66</td>
<td>DCM</td>
<td>3</td>
<td>0.15</td>
<td>39</td>
<td>16</td>
<td>409</td>
<td>2.4</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>58</td>
<td>CAD</td>
<td>3</td>
<td>0.22</td>
<td>35</td>
<td>18</td>
<td>239</td>
<td>2.8</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>37</td>
<td>DCM</td>
<td>3</td>
<td>0.17</td>
<td>36</td>
<td>30</td>
<td>185</td>
<td>1.4</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>51</td>
<td>CAD</td>
<td>3</td>
<td>0.15</td>
<td>53</td>
<td>20</td>
<td>587</td>
<td>2.6</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>41</td>
<td>DCM</td>
<td>3</td>
<td>0.15</td>
<td>25</td>
<td>16</td>
<td>218</td>
<td>1.5</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td>56 ± 3</td>
<td>3.4 ± 0.2</td>
<td>0.22 ± 0.03</td>
<td>37 ± 2</td>
<td>22 ± 12</td>
<td>301 ± 44</td>
<td>2.1 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>

*CAD = coronary artery disease; DCM = dilated cardiomyopathy; mean PA = mean pulmonary artery pressure.
Compared with breathing oxygen alone, administration of sildenafil decreased mean pulmonary artery pressure by 12 ± 7% and 16 ± 5%, respectively (all p < 0.05).

Combined administration of NO and sildenafil reduced mean pulmonary artery pressure to a similar extent as did administration of sildenafil alone. However, the combination of NO and sildenafil increased CI (by 30 ± 4%) and decreased SVR (by 24 ± 3%) and PVR (by 50 ± 4%) to a greater extent than did either agent alone. The combination of NO and sildenafil also decreased LV end-systolic pressure to a similar extent as did sildenafil alone. In contrast to administration of sildenafil alone that decreased LV end-diastolic pressure, administration of NO in combination with sildenafil did not affect LV filling pressure. The ratio of PVR to SVR decreased from 0.14 after sildenafil administration to 0.09 when NO was added, indicating that combining NO and sildenafil caused selective pulmonary vasodilatation (p < 0.05 vs either oxygen alone or with sildenafil). Combined administration of inhaled NO and sildenafil was well tolerated in that the patients did not report symptoms, and the mean systemic arterial pressure did not change.

**Effect of Sildenafil on Myocardial Function**

Although both sildenafil and the combination of inhaled NO and sildenafil increased the CI, they did not change isovolumic indexes of LV myocardial systolic function (+dP/dtmax, +dP/dtmax/DP) or diastolic function (−dP/dtmax, TL, or TD) [Table 3].
The major findings of the study were that sildenafil and inhaled NO, and their combination in 11 patients with PH produced pulmonary vasodilator effects of inhaled NO, sildenafil, and their combination in 11 patients with PH. The pulmonary vasodilator response produced by NO inhalation. PVR is shown following discontinuation of NO inhalation. The mean ± SEM value is indicated at each time point during NO inhalation in the absence of sildenafil administration (solid line) or during NO inhalation in combination with 50 mg oral sildenafil (broken line). O₂ = inhalation of >90% oxygen; NO = inhalation of 80 ppm NO gas in >90% oxygen. *p < 0.05 vs PVR during breathing oxygen alone; †p < 0.05 and ‡p < 0.01 for comparison of PVR breathing NO vs during combined NO and sildenafil administration.

**Table 2—Hemodynamic Effects of Oxygen, Inhaled NO, and Oral Sildenafil**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Air</th>
<th>O₂</th>
<th>O₂ Plus NO</th>
<th>O₂ Plus Sildenafil</th>
<th>O₂ Plus NO Plus Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systemic arterial pressure, mm Hg</td>
<td>82 ± 3</td>
<td>85 ± 2</td>
<td>85 ± 2</td>
<td>82 ± 3</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>81 ± 5</td>
<td>78 ± 5</td>
<td>81 ± 5</td>
<td>81 ± 6</td>
<td>80 ± 6</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>11 ± 2</td>
<td>12 ± 2</td>
<td>11 ± 2</td>
<td>11 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td>37 ± 2</td>
<td>37 ± 2</td>
<td>35 ± 1</td>
<td>33 ± 2†</td>
<td>32 ± 2†</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>22 ± 2</td>
<td>25 ± 2</td>
<td>28 ± 1†</td>
<td>22 ± 2</td>
<td>25 ± 2§</td>
</tr>
<tr>
<td>LV end-systolic pressure, mm Hg</td>
<td>103 ± 3</td>
<td>105 ± 3</td>
<td>104 ± 3</td>
<td>94 ± 2‡</td>
<td>94 ± 2‡</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mm Hg</td>
<td>23 ± 1</td>
<td>26 ± 1</td>
<td>29 ± 1†</td>
<td>22 ± 2</td>
<td>24 ± 2§</td>
</tr>
<tr>
<td>PVR, dynes/cm²</td>
<td>301 ± 44</td>
<td>230 ± 23†</td>
<td>138 ± 16‡</td>
<td>190 ± 23§</td>
<td>116 ± 17§</td>
</tr>
<tr>
<td>SVR, dynes/cm²</td>
<td>1,461 ± 121</td>
<td>1,418 ± 131</td>
<td>1,322 ± 107†</td>
<td>1,202 ± 109‡</td>
<td>1,056 ± 89‡</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.1 ± 0.1</td>
<td>2.3 ± 0.2†</td>
<td>2.4 ± 0.2‡</td>
<td>2.6 ± 0.2†</td>
<td>2.9 ± 0.2‡</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
†p < 0.05 vs air (comparison only shown for oxygen vs air).
‡p < 0.05 vs oxygen.
§p < 0.05 vs oxygen and NO.
¶p = 0.08 vs oxygen.

**DISCUSSION**

In this study, we evaluated the systemic and pulmonary vasodilator effects of inhaled NO, sildenafil, and their combination in 11 patients with PH secondary to severe chronic left heart failure. The major findings of the study were that sildenafil administered alone increased CI by producing balanced systemic and pulmonary vasodilatation, and that inhaled NO administered in combination with sildenafil produced additional pulmonary vasodilatation and further increased CI. Importantly, the combination of inhaled NO and sildenafil did not increase LV end-diastolic pressure or decrease mean systemic arterial pressure. In addition, sildenafil administration prolonged the duration of the pulmonary vasodilator response produced by inhaled NO.

**Hemodynamic Effects of Sildenafil and NO**

In patients with severe left heart failure, PH can limit exercise capacity and increase the morbidity and mortality associated with cardiac surgery, including cardiac transplantation. The pulmonary vasodilator effect of agents currently used in the treatment of heart failure is limited by systemic vasodilation, depression of myocardial contractility, or both, with subsequent systemic hypotension. This can be particularly deleterious in patients with compromised LV function and limited contractile reserve. In contrast, we found that sildenafil produces pulmonary and systemic vasodilatation, decreases LV filling pressure, and increases CI without causing systemic hypotension. Consistent with these hemodynamic effects, sildenafil has been reported to increase exercise capacity in patients with left heart failure.

Similar to previous studies from our laboratory and others, inhaled NO decreased PVR accompanied by a slight rise in LV filling pressure. The increases in PCWP and LV end-diastolic pressure observed in heart failure patients breathing NO have been attributed to reduced RV afterload causing increased filling of a noncompliant LV, and are a potential limitation to its use in treating patients with
severe left heart failure. In contrast, sildenafil decreased both RV and LV afterload (as indicated by decreases in pulmonary artery pressure, PVR, LV end-systolic pressure, and SVR) and increased CI, while decreasing LV end-diastolic pressure and PCWP. The decrease in LV preload by sildenafil was due to either the initiation of diastolic filling at a lower end-systolic volume or an increase in pulmonary venous capacitance. The addition of inhaled NO to oral sildenafil further increased CI in these heart failure patients. This is likely due to a greater effect of this combination on reducing RV afterload than either agent alone, with the additional beneficial effect of NO on CI related to further augmentation of LV preload. Our findings suggest a potential beneficial application of PDE5 inhibitors, alone or in combination with administration of inhaled NO for the treatment of patients with CHF and PH.

A limitation of our assessment of changes in CI was the use of a single measurement of oxygen consumption at the beginning of the study to calculate subsequent CI determinations. Our laboratory has previously observed no difference between oxygen consumption measurements at the beginning and end of a clinical study of similar length.20 The possibility of a direct effect of NO or sildenafil administration on oxygen consumption has not been previously investigated, and if present could affect the accuracy of CI determinations in this study.

**Lack of Effect of Sildenafil or NO on LV Myocardial Function**

It is possible that sildenafil, administered alone or in combination with inhaled NO, may have had direct myocardial effects in addition to its effects on ventricular afterload. Senzaki et al21 reported that PDE5 is expressed in normal canine myocardium and that the PDE5 inhibitor EMD82639 modestly diminishes myocardial contractility and blunts the inotropic and lusitropic response to β-adrenergic stimulation. However, in their canine model of pacing-induced left heart failure, LV PDE5 expression and activity were decreased, and PDE5 inhibition had a minimal effect on myocardial contractility and did not alter the myocardial response to β-adrenergic stimulation. In our study, PDE5 inhibition with sildenafil did not alter isovolumic indexes of LV myocardial contractility and relaxation. In addition, previous studies in our laboratory of the effect of sildenafil on RV rate of pressure increase, RV rate of pressure increase normalized for developed pressure, TL, and TD in patients with primary PH did not reveal an effect on RV myocardial function.12 The lack of effect of PDE5 inhibition on myocardial function in heart failure patients is consistent with either a lack of PDE5 expression in human myocardium, as has been reported in one study,22 or down-regulation of PDE5 expression or activity in the failing human heart similar to that reported in the canine model.12 Although sildenafil did not directly alter basal myocardial contractility in our study, it will be important to determine in future studies whether PDE5 inhibition, by augmenting myocardial NO-cGMP signaling, might alter the positive inotropic response to β-adrenergic stimulation in heart failure patients.

**Effect of Sildenafil on the Pulmonary Vasodilator Effects of Inhaled NO**

We observed that both the magnitude and duration of pulmonary vasodilatation were increased after the addition of oral sildenafil to NO inhalation as compared with breathing NO alone. To exclude the possibility that this observation was due to variations in pulmonary vascular tone unrelated to administration of NO or sildenafil, we observed the hemodynamic effect of serial administration of NO in three additional patients who underwent the identical study protocol, with the exception that sildenafil was not administered. In these three patients, the hemodynamic variables measured prior to the second administration of NO did not differ from those obtained prior to the initial administration of NO. Furthermore, the hemodynamic effects of NO during the two administration periods were similar (data not shown). Thus, our findings support and extend previous observations that oral sildenafil can augment and prolong the pulmonary vasodilator effects of inhaled NO in patients with primary PH.12,13 The

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**Table 3—Effects of Inhaled NO, Oral Sildenafil, and Their Combination on Indices of Myocardial Function**

<table>
<thead>
<tr>
<th>Variables</th>
<th>O₂</th>
<th>O₂ Plus NO</th>
<th>O₂ Plus Sildenafil</th>
<th>O₂ Plus NO Plus Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>+dP/dtmax, mm Hg/s</td>
<td>776 ± 106</td>
<td>754 ± 104</td>
<td>775 ± 92</td>
<td>739 ± 100</td>
</tr>
<tr>
<td>+dP/dtmax/DT, s</td>
<td>24 ± 4</td>
<td>23 ± 3</td>
<td>27 ± 5</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>−dP/dtmax, mm Hg/s</td>
<td>786 ± 104</td>
<td>753 ± 94</td>
<td>770 ± 78</td>
<td>735 ± 86</td>
</tr>
<tr>
<td>TL, s</td>
<td>107 ± 8</td>
<td>99 ± 6</td>
<td>94 ± 4</td>
<td>98 ± 7</td>
</tr>
<tr>
<td>TD, s</td>
<td>113 ± 2</td>
<td>104 ± 5</td>
<td>108 ± 2</td>
<td>109 ± 6</td>
</tr>
</tbody>
</table>

*Indices of LV diastolic and systolic function were not measured in patients 3 and 9 because of technical limitations.*
likely mechanism by which this occurred was via inhibition by sildenafil of PDE5-mediated cGMP hydrolysis.

Conclusions

The data presented in this report indicate that oral sildenafil can be safely administered to patients with chronic, severe congestive heart failure and PH, in whom it reduces RV and LV afterload, resulting in increased CI. In addition, sildenafil increases the magnitude and duration of pulmonary vasodilatation induced by NO inhalation. If proven safe and effective for longer periods of administration, oral sildenafil alone or in combination with intermittent NO inhalation may be useful in the treatment of chronic PH complicating congestive heart failure.

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REFERENCES