Eisenmenger syndrome (ES) is characterized by elevated pulmonary vascular resistance and right-to-left shunting through a systemic-to-pulmonary circulation connection.1 A progressive increase in pulmonary vascular resistance (PVR) leads to right ventricular dysfunction, congestive cardiac failure, and death, usually in the fourth decade. Currently, no drug is routinely used to arrest the progressive increase in PVR and pulmonary artery (PA) pressure in ES patients. The pathological changes in the pulmonary vascular bed in ES patients are similar to those of patients of idiopathic PA hypertension (IPAH).2 Newer therapies like inhaled nitric oxide and phosphodiesterase-5 (PDE-5) inhibitors have shown a favorable hemodynamic response in patients of IPAH, leading to improvement in symptoms and exercise capacity.3–6 In contrast, little evidence is available with these drugs in ES because of a pulmonary vascular pathology similar to idiopathic pulmonary arterial hypertension.

Methods and Results—Sixteen symptomatic Eisenmenger syndrome patients (mean age, 25±8.9 years) were assessed hemodynamically at baseline and 90 minutes after a single dose of tadalafil (1 mg/kg body weight up to a maximum of 40 mg). The same dose was then continued daily for 12 weeks, and the patients were restudied. There was a significant decrease in mean pulmonary vascular resistance immediately (24.75±8.49 to 19.22±8.23 Woods units; P<0.005) and at 12 weeks (19.22±8.23 to 17.02±6.19 Woods units; P=0.03 versus 90 minutes). Thirteen of 16 patients (81.25%) showed a ≥20% decrease in pulmonary vascular resistance and were defined as responders. The mean systemic oxygen saturation improved significantly both immediately (84.34±5.47% to 87.39±4.34%; P<0.005) and at 12 weeks (87.39±4.34% to 89.16±3.8%; P<0.02 versus 90 minutes) without a significant change in systemic vascular resistance. None of the patients had a fall in systemic arterial pressure, worsening of systemic oxygen saturation, or any adverse reactions to the drug. The mean World Health Organization functional class improved from 2.31±0.47 to 1.25±0.44 (P<0.0001), and the 6-minute walk distance improved from 344.56±119.06 to 387.56±117.18 m (P<0.001).

Conclusions—Preliminary evaluation of tadalafil has shown efficacy and safety in selected patients with Eisenmenger syndrome, warranting further investigation in this subgroup of patients. (Circulation. 2006;114:1807-1810.)

Key Words: hypertension, pulmonary • Eisenmenger Complex • phosphodiesterase inhibitors • pulmonary heart disease • tadalafil

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Methods
Sixteen consecutive symptomatic ES patients were enrolled in the study after providing written informed consent. The study was approved by the institutional ethics committee. The diagnosis of ES was based on clinical findings, chest x-ray, ECG, and echocardiographic features. Cardiac catheterization, followed by oxygen study, was used in selected patients to diagnose reversible pulmonary hypertension; such patients were excluded. Severely ill patients (World Health Organization [WHO] class IV), patients with congestive cardiac failure or pulmonary capillary wedge pressure >15 mm Hg, those with abnormal baseline biochemical profile, patients with atrial fibrillation, and patients with hypersensitivity to PDE-5 inhibitors were excluded. Eleven patients were on stable doses of diuretics. Baseline investigations, ie complete hemogram, kidney function tests, liver function tests, and coagulation profile, were done in all patients.

After assessment of WHO functional class and a 6-minute walk test, the patients were taken for cardiac catheterization study. Under local anesthesia, vascular access was taken by inserting 5F and 7F sheaths in the femoral artery and vein, respectively. A Swan-Ganz catheter was advanced into the PA under fluoroscopic guidance. After the lines were placed, the patients

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ANOVA was used to assess changes over time; paired *t* tests were used to assess specific changes. A value of *P*≤0.05 was considered significant. Stata 9.0 statistical software (College Station, Tex) was used.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

**Results**

Sixteen consecutive ES patients were included. The baseline characteristics are shown in Table 1. Nine patients (57%) were male, with age ranging from 13 to 42 years (mean, 25±8.89 years) and weight ranging from 24 to 65 kg (mean, 41.93±8.83 kg). Three (18.75%) patients had atrial septal defect, 8 patients (50%) had ventricular septal defect, and 4 patients (25%) had patent ductus arteriosus. All 3 patients with atrial septal defect had large ostium secundum atrial septal defect (3.8, 4, and 4.3 cm, respectively) as assessed by echocardiography. One patient (6.25%) had both atrial and ventricular septal defects. Eleven patients (68.75%) were in WHO functional class II; the rest were in WHO class III (Table 1).

**Hemodynamic Profile**

The hemodynamic effects of tadalafil are shown in Table 2. The baseline mean PA pressure was elevated (81.75±14.21 mm Hg), along with the PVR (24.75±8.49 Woods units [WU]). After tadalafil administration, there was a significant decrease in PVR immediately from 24.75±8.49 to 19.22±8.23 WU (*P*<0.005). Of 16 patients, 13 (81.25%) showed a ≥20% decrease in PVR; these patients were defined as responders. There was no significant change in the SVR (23.69±7.04 to 24.63±7.94; *P*=0.73) compared with baseline. There was a significant decrease in the PVR-to-SVR ratio immediately (1.09±0.34 to 0.79±0.26; *P*<0.005), showing preferential pulmonary vasodilatory effect of tadalafil. Furthermore, there was a significant decrease in the estimated right-to-left shunt (1.71±0.92 to 1.27±0.50 L/min; *P*<0.03), resulting in an improvement in the effective pulmonary blood flow (2.46±0.69 to 2.57±0.83 L/min; *P*=0.06) and significant improvement in systemic oxygen saturation (84.34±5.47% to 87.39±4.34%; *P*<0.005) (Table 2).

At 12 weeks, there was a further significant reduction in PVR compared with that obtained at 90 minutes (19.22±8.23 to 17.02±6.19 WU; *P*=0.03), along with a significant improvement in systemic arterial oxygen saturation (87.39±4.34% to 89.16±3.8%; *P*=0.02). There was no significant change in SVR (24.63±7.94 to 23.76±8.01 WU; *P*=0.73). The preferential pulmonary vasodilator effect of the drug was maintained at 12 weeks as assessed by the PVR-to-SVR ratio (1.09±0.34 to 0.71±0.26; *P*<0.005).

**Table 1. Baseline Characteristics of the Study Sample**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Sample (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>25±8.89</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9 (57)</td>
</tr>
<tr>
<td>Body surface area</td>
<td>1.36±0.14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>41.93±8.83</td>
</tr>
<tr>
<td>WHO class</td>
<td>2.31±0.47</td>
</tr>
<tr>
<td>6-Minute walk distance, m</td>
<td>344.56±119.06</td>
</tr>
<tr>
<td>Cardiac defect, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Atrial septal defect*</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>4 (25)</td>
</tr>
</tbody>
</table>

All values are mean±SD when appropriate.

*One patient with a large atrial septal defect also had a ventricular septal defect.

**Table 2. Hemodynamic Results After Tadalafil**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At 90 min After Tadalafil</th>
<th>At 12-Week Follow-Up</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR, WU</td>
<td>24.75±8.49</td>
<td>19.22±8.23†</td>
<td>17.02±6.19‡</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SVR, WU</td>
<td>23.69±7.04</td>
<td>24.63±7.94</td>
<td>23.76±8.01</td>
<td>0.73</td>
</tr>
<tr>
<td>PVR-to-SVR ratio</td>
<td>1.09±0.34</td>
<td>0.79±0.26†</td>
<td>0.71±0.26‡</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean PA pressure, mm Hg</td>
<td>81.75±14.21</td>
<td>76.43±14.43†</td>
<td>75.5±15.09†</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>SPo2, %</td>
<td>84.34±5.47</td>
<td>87.39±4.34‡</td>
<td>89.16±3.81‡</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Effective pulmonary blood flow, L/min</td>
<td>2.46±0.69</td>
<td>2.57±0.83</td>
<td>2.82±0.88†</td>
<td>0.08</td>
</tr>
<tr>
<td>Right-to-left shunt, L/min</td>
<td>1.71±0.92</td>
<td>1.27±0.50</td>
<td>1.16±0.62</td>
<td>0.018</td>
</tr>
</tbody>
</table>

n=16.

*Probability value for repeated-measures ANOVA.
†*P*<0.05 (paired *t* test) vs baseline values.
‡*P*<0.05 (paired *t* test) vs 90-minute values.
The abundance of PDE-5 in lung vascular smooth muscle, which provides a strong molecular basis for PDE-5 inhibitor in the treatment of pulmonary hypertension. PDE-5 inhibitors cause relaxation of pulmonary vascular smooth muscles by activating large-conductance, calcium-activated potassium channels. In IPAH patients, the PDE-5 inhibitors have been shown to reduce mean PA pressure and the pulmonary-to-systemic vascular resistance ratio, resulting in improved ventilation-perfusion mismatch, arterial oxygenation, and functional capacity. However, ES patients have traditionally been excluded from trials of PDE-5 inhibitors in PA hypertension that included a small number of patients with ES have reported a similar beneficial effect in these patients. The effects of the drug on the hemodynamics, systemic arterial oxygen saturation, and exercise capacity in individual patients with ES are not available, however. Hence, PDE-5 inhibitors are still not used to manage patients with ES on the pretext that even a small decrease in the SVR would increase the right-to-left shunt and thus worsen the systemic hypoxia. In the present study, there was a significant increase in effective pulmonary blood flow and mean systemic arterial oxygen saturation after tadalafil administration that resulted from preferential pulmonary vasodilation. None of the patients, including nonresponders, showed any worsening of systemic oxygen saturation. This can be explained by the preferential distribution of the PDE-5 enzyme, which is located primarily in lungs and penis.

Sildenafil is a short-acting PDE-5 inhibitor that has been studied extensively in patients with IPAH. However, its short half-life (4 hours) mandates frequent daily administration. Tadalafil has a half-life of ≈18 hours and requires once-daily administration. Hence, using tadalafil may improve patient compliance and reduce treatment cost. The pharmacotherapeutic studies of tadalafil have shown that the maximum vasodilatory effect with tadalafil occurs at 90 minutes in humans. Therefore, in our study, we measured the postdrug hemodynamic effect at 90 minutes.

Discussion

The primary finding of this study is that a single daily dose of tadalafil is a potent and preferential pulmonary vasodilator that produces a significant decrease in PVR in selected ES patients. Apart from a significant decrease in PVR immediately, all the responders showed a further decrease in PVR over the 12-week period, resulting in a significant decrease in the right-to-left shunt and further improvement in the systemic arterial oxygen saturation than that obtained immediately (Figure). Furthermore, the nonresponders did not show any increase in PVR or worsening of systemic oxygen saturation at 12 weeks compared with baseline. There are no studies available to date on the hemodynamic effects of PDE-5 inhibitors in patients with ES.

In vitro studies of human PA have shown that there is abundance of PDE-5 in lung vascular smooth muscle, which provides a strong molecular basis for PDE-5 inhibitor in the treatment of pulmonary hypertension. PDE-5 inhibitors cause relaxation of pulmonary vascular smooth muscles by activating large-conductance, calcium-activated potassium channels. In IPAH patients, the PDE-5 inhibitors have been shown to reduce mean PA pressure and the pulmonary-to-systemic vascular resistance ratio, resulting in improved ventilation-perfusion mismatch, arterial oxygenation, and functional capacity. However, ES patients have traditionally been excluded from trials of PDE-5 inhibitors in patients with IPAH. Studies of PDE-5 inhibitors in PA hypertension that included a small number of patients with ES have reported a similar beneficial effect in these patients. The effects of the drug on the hemodynamics, systemic arterial oxygen saturation, and exercise capacity in individual patients with ES are not available, however. Hence, PDE-5 inhibitors are still not used to manage patients with ES on the pretext that even a small decrease in the SVR would increase the right-to-left shunt and thus worsen the systemic hypoxia. In the present study, there was a significant increase in effective pulmonary blood flow and mean systemic arterial oxygen saturation after tadalafil administration that resulted from preferential pulmonary vasodilation.

None of the patients, including nonresponders, showed any worsening of systemic oxygen saturation. This can be explained by the preferential distribution of the PDE-5 enzyme, which is located primarily in lungs and penis. Sildenafil is a short-acting PDE-5 inhibitor that has been studied extensively in patients with IPAH. However, its short half-life (4 hours) mandates frequent daily administration. Tadalafil has a half-life of ≈18 hours and requires once-daily administration. Hence, using tadalafil may improve patient compliance and reduce treatment cost. The pharmacotherapeutic studies of tadalafil have shown that the maximum vasodilatory effect with tadalafil occurs at 90 minutes in humans. Therefore, in our study, we measured the postdrug hemodynamic effect at 90 minutes.

In our study, the maximum dose of tadalafil that was tolerated was 40 mg. Initially, in 2 nonresponders, a repeat hemodynamic study was done after 1 week with 60 mg of tadalafil (the maximum dose used until now in studies of IPAH). Both patients remained nonresponders. Furthermore, on initiating therapy with 60 mg tadalafil, both patients complained of severe gastroesophageal reflux; the dose was decreased to 40 mg, which was well tolerated.

Although the present study is a small, single-center study, our results are in agreement with the results of studies of PDE-5 inhibitors in patients with IPAH. This can be explained by the fact that the pathology in the pulmonary vascular bed in patients with ES is similar to that in patients with IPAH. Although the exact mechanism involved in the hemodynamic improvement in patients of IPAH who have predominantly fixed pulmonary vascular obstructive lesions is not known, it has been suggested that reverse remodeling of pulmonary vascular changes as a result of the antiproliferative effects of PDE-5 inhibitors may be responsible.

Early observations of the effects of bosentan on systemic oxygen saturations and echocardiographic parameters in ES are encouraging and are similar to those observed in IPAH. In a recently
reported placebo-controlled trial, bosentan has been shown to improve exercise capacity and hemodynamics without compromising the peripheral oxygen saturation.17 Observing the favorable hemodynamic effect of tadalafil on the pulmonary vascular bed and on the systemic arterial oxygen saturation, we can infer that the drug may produce improvements in symptoms and exercise capacity in this subgroup of patients with PA hypertension, as has already been documented in patients with IPAH. Further studies are needed, however, to establish the role of PDE-5 inhibitors in ES.

**Study Limitations**

This was a nonrandomized study without a control group. Although all patients, including the nonresponders, showed improvement in functional class and exercise capacity (which might be due to the placebo effect), a double-blind, placebo-controlled trial should be undertaken to assess the effect of the drug on exercise capacity and functional status. Furthermore, the use of assumed oxygen consumption to calculate PVR and SVR may have altered the absolute values, but the changes in PVR and SVR immediately and in the short term after tadalafil administration showed preferential pulmonary vasodilator effect of tadalafil. The same finding was reiterated by the PVR-to-SVR ratio, which is independent of oxygen consumption. Hence, this limitation is unlikely to change the study results significantly.

**Conclusions**

The present study is the first to assess the hemodynamic effects of PDE-5 inhibitors in a group of ES patients. Preliminary evaluation of tadalafil has shown efficacy and safety in selected ES patients, warranting further investigation in this subgroup of patients.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Eisenmenger syndrome (ES) is characterized by a progressive increase in pulmonary vascular resistance and right-to-left shunting through a systemic-to-pulmonary circulation connection. Currently, no drug is routinely used to alter the pulmonary vascular resistance in ES patients. The pathological changes in the pulmonary vascular bed are similar in idiopathic pulmonary arterial hypertension and ES. Phosphodiesterase-5 (PDE-5) inhibitors have been shown to produce a significant decrease in pulmonary vascular resistance in patients of idiopathic pulmonary arterial hypertension, translating into improvement in functional class and exercise capacity. However, PDE-5 inhibitors have not been used in ES patients on the pretext that the vasodilators may worsen systemic hypoxia by decreasing systemic vascular resistance. PDE-5 inhibitors like sildenafil and tadalafil are preferential pulmonary vasodilators; hence, the risk of systemic desaturation resulting from a decrease in systemic vascular resistance is low. The present observational study is the first study to report the effects of tadalafil, a PDE-5 inhibitor, on short-term hemodynamics, tolerability, and efficacy over a 12-week period in ES patients. Sixteen symptomatic patients of ES were assessed hemodynamically at baseline and 90 minutes after a single dose of tadalafil. The same dose was then continued daily for 12 weeks, and the patients were restudied. There was a significant decrease in mean pulmonary vascular resistance, along with an improvement in systemic oxygen saturation, both immediately and at 12 weeks. Treatment with tadalafil was well tolerated, with an improvement in functional class and 6-minute walk distance. None of the patients had a fall in systemic arterial pressure, worsening of oxygen saturation, or any adverse reactions to the drug. Our preliminary data warrant further investigation with tadalafil in patients of Eisenmenger syndrome.
Phosphodiesterase-5 Inhibitor in Eisenmenger Syndrome: A Preliminary Observational Study

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