Vascular Effects of Sildenafil in Hypertensive Cardiac Transplant Recipients

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Background: Sildenafil is commonly used in the treatment of erectile dysfunction in hypertensive male cardiac transplant recipients (CTR); however, little is known about the vascular effects of sildenafil in these patients.

Methods: Central and peripheral arterial blood pressure (BP), heart rate, and brachial artery reactivity were determined in 15 hypertensive male CTR before and after oral sildenafil (50 mg) administration.

Results: Sildenafil improved brachial and aortic systolic BP, pulse pressure, aortic augmentation index, left ventricular tension time index, travel time of the reflected aortic pressure wave, and brachial artery reactivity (P < .01 for each comparison). No patient became hypotensive with sildenafil despite continuation of usual antihypertensive medications.

Conclusions: Sildenafil (50 mg) is well tolerated in hypertensive CTR and improves BP, aortic augmentation index, and endothelial function. By decreasing the amplitude of the reflected pressure wave and delaying its return to the heart, sildenafil reduces left ventricular afterload and systolic stress. Am J Hypertens 2003;16:874–877 © 2003 American Journal of Hypertension, Ltd.

Key Words: Sildenafil, heart transplantation, hypertension, arterial compliance.
with a history of chronic post-transplant HTN were screened. All patients were taking one or more antihypertensive medications at the time of the study, and control of HTN was considered adequate based on measurements of brachial arterial cuff BP. The project was reviewed and approved by the local institutional review board, and all patients gave informed consent to participate in the study. Patients were in a fasting post-absorptive state at the time of the study, although they were instructed to continue to take their usual morning antihypertensive and anti-rejection medications, which should have been near their peak plasma concentrations at the time of the study.

Patients were placed supine in a quiet, temperature-controlled room and after a 15-min rest period, underwent duplicate measurements of heart rate, brachial cuff BP, and analysis of the radial arterial pulse wave. Radial arterial pulse wave analysis was performed in the dominant arm. Brachial arterial cuff BP was determined by an automated digital oscillometric sphygmomanometer (Omron, model HEM-739AC, Vernon Hills, IL). An aortic arterial pressure waveform was derived from the measured radial artery pulse waveform using applanation tonometry and a high fidelity ultrasound transducer (SPC-301, Millar Instruments, Houston, TX). A central aortic pressure wave was synthesized from the radial artery wave using the SphygmoCor device (AtCor Medical, Sydney, Australia) and a generalized transfer function, and various components of the wave were automatically calculated. Previous reports have confirmed the reproducibility and reliability of the SphygmoCor system for obtaining central aortic pressure waveforms.

Aortic augmentation index (AIa) was defined as the ratio of reflected wave amplitude and pulse pressure, or AIa = (Pp - Pa)/(Pp - Ps) where Ps = peak systolic pressure, Pp = end-diastolic pressure, and Pa = an inflection point marking the beginning upstroke of the reflected pressure wave. Because heart rate is known to affect AIa, and our patients had elevated resting heart rates due to cardiac denervation, AIa was determined at both the intrinsic heart rate and at a reference heart rate of 75 beats/min. Left ventricular ejection time (LVET) was measured from end-diastolic pressure to the trough of the dicrotic notch in the radial arterial pressure wave. Travel time, Δtp, of the forward traveling pressure wave from the heart to the major reflection site and back was measured as the time differential between Pa and Pp. Time duration of the reflected wave, Δt, was taken as the difference between LVET and Δtp. Left ventricular tension time index, a marker of myocardial oxygen demand, was estimated as the integral of aortic pressure and time during systole.

Brachial arterial FMD was determined in the contralateral arm after release of a 5-min transient brachial artery occlusion in the upper arm using high-resolution ultrasound (ATL/Phillips Medical Systems model 800, Bothell, WA). Arterial internal diameter was measured at end-diastole from the anterior to the posterior intimal images and FMD calculated as the percent increase in diameter from baseline to the diameter measured at 60 sec after release of the occlusion. Five minutes after baseline measurements were collected, patients were given 50 mg of oral sildenafil. Repeat measurements of brachial artery cuff BP, heart rate, and the radial artery pressure waveform were collected every 15 min for a total of 60 min after dose. A single repeat determination of brachial artery FMD was made at 45 min after dose. The brachial artery FMD results were compared with an age- and gender-matched historic control group of 13 randomly selected patients free of cardiovascular disease, studied in the same laboratory under similar conditions. Data are expressed as mean ± standard deviation. Changes from baseline values were tested using two-tailed standard Student t test for paired samples and a P value < .05 was considered statistically significant.

Results

Fifteen adult male CTR participated in the study, with an average age of 55 ± 10 years. Patients were an average of 38 months after transplantation (range, 4 to 127 months) and were all taking one or more antihypertensive medications. The average number of antihypertensive drugs taken was 2.4 ± 0.9 (range, 1 to 5 medications/patient). Thirteen of the 15 patients had hyperlipidemia necessitating drug therapy and 4 patients were diabetic. Patients were each taking a minimum of two antirejection medications.

Resting heart rate was 92 ± 11 beats/min and did not change after sildenafil administration. Significant reductions were noted, however, in both peripheral and central arterial BP that were obvious at 15 min, reached a maximum at 30 to 45 min, and continued throughout the study period of 60 min. Significant reductions were noted in brachial systolic, mean, diastolic, and pulse pressure with sildenafil (P < .01 for each comparison) (Table 1). The absolute reduction in brachial artery BP with sildenafil ranged from 3 to 19 mm Hg for systolic pressure (average 10 mm Hg) and from 1 to 7 mm Hg for diastolic pressure (average 4 mm Hg). Despite the continuation of usual antihypertensive medications, no patient became hypotensive with sildenafil or had any observed adverse reaction.

Central aortic pressure was also substantially reduced with sildenafil use and was reduced to a greater extent than brachial BP (Table 1). Average aortic systolic pressure was reduced by 13 mm Hg as compared to a 10 mm Hg reduction in average brachial artery systolic pressure. Likewise, aortic pulse pressure was reduced by 6 mm Hg as compared to a 3 mm Hg reduction in brachial pulse pressure.

Central aortic AIa, a measure of wave reflection intensity, also declined significantly with sildenafil use (Table 1). When AIa was referenced to a heart rate of 75 beats/min, the reduction was even more pronounced. Sildenafil increased the travel time (Δtp) of the reflected aortic pressure wave to and from the periphery, thereby delaying return of the reflected wave to the heart. This increase in
Table 1. Maximum changes in hemodynamic variables after sildenafil

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Mean ± SD)</th>
<th>Maximum Effect (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>92 ± 11</td>
<td>90 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial systolic pressure (mm Hg)</td>
<td>134 ± 10</td>
<td>124 ± 9.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Brachial diastolic pressure (mm Hg)</td>
<td>87 ± 9.4</td>
<td>80 ± 8.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Brachial pulse pressure (mm Hg)</td>
<td>47 ± 13</td>
<td>44 ± 10</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Brachial mean pressure (mm Hg)</td>
<td>103 ± 8.1</td>
<td>94 ± 7.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>120 ± 10</td>
<td>107 ± 8.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Aortic pulse pressure (mm Hg)</td>
<td>33 ± 11</td>
<td>27 ± 8.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Amplitude of forward wave (mm Hg)</td>
<td>29 ± 7.3</td>
<td>26 ± 5.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Amplitude of reflected wave (mm Hg)</td>
<td>3.3 ± 5.3</td>
<td>0.7 ± 3.7</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Alc (%) corrected to heart rate of 75 beats/min (%)</td>
<td>10.0 ± 13</td>
<td>2.5 ± 12</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Travel time of reflected wave, (\Delta t_r) (msec)</td>
<td>139 ± 8.1</td>
<td>148 ± 9.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LV ejection duration (msec)</td>
<td>278 ± 27</td>
<td>288 ± 22</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Duration of reflected wave, (\Delta t_r) (msec)</td>
<td>139 ± 28</td>
<td>140 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic TTI (mm Hg/sec/min)</td>
<td>2822 ± 241</td>
<td>2550 ± 225</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Brachial artery FMD (%)</td>
<td>5.4 ± 0.9</td>
<td>6.8 ± 1.2</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

\(\text{Al}_c\) = central aortic augmentation index; \(LV\) = left ventricular; \(TTI\) = tension time index; \(FMD\) = flow mediated dilation.

\(\Delta t_r\) resulted in a reduction in the amplitude of the reflected pressure wave \((P_r - P_i)\) and in \(\text{AI}_c\). The amplitude of the forward traveling pressure wave \((P_i - P_d)\) was also substantially reduced with sildenafil. Combined reduction in both forward and reflected aortic pressure waves resulted in a substantial reduction in tension time index, a marker of left ventricular systolic stress and myocardial oxygen demand. The LVET increased after sildenafil administration with the maximal effect occurring somewhat later than the maximal reduction in arterial pressure. Because both LVET and pressure wave travel time increased, the systolic duration of the reflected wave, \(\Delta t_r\), did not change.

Baseline brachial artery FMD was 5.4% ± 0.9%, indicating impaired endothelial function in our group of CTR as compared to an age- and gender-matched control group of 13 patients without cardiovascular disease (control group FMD, 7.1% ± 2.5%; \(P < .001\)). A significant improvement in brachial artery FMD was noted 45 min after sildenafil administration, with a post-drug FMD value similar to that of the control population (Table 1).

### Discussion

This pilot investigation demonstrates that low-dose oral sildenafil is well tolerated in adult male CTR under active treatment for systemic HTN. No patient became hypotensive with the use of sildenafil despite continuation of background antihypertensive medication. The average maximum reductions in brachial systolic and diastolic pressure with sildenafil were similar to values previously reported in patients with cardiovascular disease, but less than that observed in a group of hypertensive men with erectile dysfunction taking antihypertensive medication. This may be due to the fact that baseline brachial BP and augmented pressure were higher in those previous studies than was noted in our patients before administration of sildenafil. Previous studies have shown that, although CTR with chronic post-transplant HTN are on antihypertensive medication, they still have a substantially high \(\text{AI}_c\), indicating early return of reflected waves to the central aorta, which augments pressure during systole. These changes in wave reflection properties result in an increase in left ventricular afterload, myocardial mass, and myocardial oxygen demand. Although all patients in our study were taking antihypertensive medication, the baseline \(\text{AI}_c\) was abnormally high, indicating elevated wave reflection amplitude. Therefore, although these patients were believed to have “controlled” post-transplant HTN based on brachial cuff BP measurement, they still had a significantly abnormal \(\text{AI}_c\) as determined by arterial pulse wave analysis. Sildenafil appears to substantially improve this marker of arterial wave reflection intensity when added to baseline antihypertensive therapy, and likewise improves endothelial function. Pulse pressure was also significantly reduced both centrally and in the periphery with sildenafil. Pulse pressure is now recognized to be an important marker of cardiovascular risk, and would ideally be lowered in populations like CTR, who have a high baseline risk for adverse cardiovascular events.

Although several studies have investigated the effects of sildenafil on standard hemodynamics, only one study has investigated the effects of sildenafil on wave reflections. In that study in men with erectile dysfunction taking antihypertensive medication, oral sildenafil (50 mg) caused a delay (increased \(\Delta t_r\)) in the return of the reflected wave to the central aorta and thus reduced its amplitude \((P_i - P_r)\), indicating a decreased arterial pulse wave velocity. Because vasoactive drugs have little direct effect on large elastic arteries, the wave reflection action of sildenafil is likely confined to the muscular arteries. Like sildenafil, angiotensin-converting enzyme inhibitors,
angiotensin II receptor blockers, and nitrates decrease reflected wave amplitude and reduce aortic systolic and pulse pressure more than brachial cuff systolic and pulse pressure. Therefore, sildenafil appears to exhibit hemodynamic effects comparable to these commonly used vasodilators, especially nitroglycerin. The favorable effects of sildenafil on several measures of vascular function indicate that this novel compound may warrant further investigation for use as a chronic vasodilator in CTR with chronic post-transplant HTN.

In conclusion, the results of this study indicate that sildenafil reduces central aortic augmentation index and BP and improves endothelial function in hypertensive CTR. This action on wave reflection properties implies that sildenafil reduces arterial pulse wave velocity and causes the reflected wave to be delayed in returning to the heart. This delay in arrival of the reflected wave reduces its amplitude, decreases systolic and pulse pressure, and reduces LV afterload and myocardial oxygen demand. The wave reflection property indices in this study were obtained using pulse wave analysis and a generalized transfer function that may be subject to varying degree of inaccuracy according to some investigators but not others. The report by Hope et al suggested that generalized transfer functions may not be universally applicable across all waveform parameters of potential interest, and gender-specific transfer functions may be more appropriate. The accuracy of the generalized transfer function in our study may be improved, however, as all the patients in the study were men.

References