Sildenafil Reduces Exercise-induced Pulmonary Arterial Hypertension And Improves Exercise Capacity In Patients With Mitral Stenosis

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Sildenafil Reduces Exercise-induced Pulmonary Arterial Hypertension And Improves Exercise Capacity In Patients With Mitral Stenosis

Directed by Professor Namsik Chung

The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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This certifies that the Master's Thesis of Jaemin Shim is approved.

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ABSTRACT

Sildenafil Reduces Exercise-induced Pulmonary Arterial Hypertension And Improves Exercise Capacity In Patients With Mitral Stenosis

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Background: One of the most characteristic findings of cardiovascular response to exercise in mitral stenosis is the inappropriate increase in pulmonary artery pressure, which has been known to be a major limiting factor for exercise capacity. We sought to investigate whether sildenafil, selective phosphodiesterase-5 inhibitor can reduce exaggerated increase in pulmonary artery pressure and improve exercise tolerance in patients with mitral stenosis.

Methods: Twenty-four patients (19 females, 5 males; mean age 53 ± 10 years; 9 in normal sinus rhythm, 15 in atrial fibrillation) with moderate to severe mitral stenosis were studied. In all patients, supine bicycle exercise echocardiography was performed before and 60 minutes after 50 mg of sildenafil intake with simultaneous measurement of indices of cardiopulmonary exercise test.

Results: There were no significant changes in blood pressure, heart rate, arterial oxygen saturation, and transmitral mean pressure gradient before and after sildenafil. There was a significant reduction in pulmonary artery pressure at baseline from 39.0 ± 7.9 to 35.5 ± 6.2 mmHg (p< 0.001), at peak exercise
from 72.4 ± 15.3 to 62.0 ± 12.5 mmHg (p< 0.001), and at recovery after exercise from 41.4 ± 9.0 to 36.7 ± 6.9 mmHg (p< 0.001), respectively. Pulmonary vascular resistance defined as the ratio of TRV (tricuspid regurgitant velocity) to TVI_{RVOT} (right ventricular outflow tract time-velocity integral) was also significantly reduced (from 0.22 ± 0.09 to 0.19 ± 0.07, p=0.004), but cardiac output was not changed after administration of sildenafil (from 5.0 ± 2.8 to 5.3 ± 2.9 L/min, p=0.11). Furthermore, there was a significant increase in exercise duration (from 403 ± 115 to 442 ± 115 sec, p=0.016), VO₂ max (from 15.3 ± 6.5 to 18.3 ± 4.9 ml/kg/min, p=0.016), and AT/VO₂ max (from 17.5 ± 9.9 to 23.6 ± 12.6 %, p=0.014) after sildenafil administration.

**Conclusions:** Sildenafil improves exercise tolerance by modulating pulmonary artery pressure and pulmonary vascular resistance in patients with mitral stenosis.

Key words: sildenafil, mitral stenosis, pulmonary hypertension, exercise capacity
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I. INTRODUCTION

Pulmonary hypertension frequently complicates mitral stenosis and the presence of pulmonary hypertension is important because it affects exercise capacity and prognosis. Pulmonary arterial hypertension in patients with mitral stenosis is frequently out of proportion to the degree of pulmonary venous pressure, reflecting an increase in pulmonary vascular resistance. The increase in pulmonary arterial pressure has been ascribed to three factors. First, passive transmission of left atrial pressure across the pulmonary capillary bed, second, organic obliterative changes in the pulmonary vascular bed, which may be considered to be a complication of longstanding and severe mitral stenosis, and third, pulmonary arteriolar constriction, which presumably is triggered by left atrial and pulmonary venous hypertension that is called reactive pulmonary hypertension. Although symptoms of dyspnea and fatigue

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are common in patients with mitral stenosis, mechanisms that limit exercise tolerance are poorly understood. One of the most characteristic findings of cardiovascular response to exercise in mitral stenosis is the inappropriate increase in pulmonary artery pressure which has been known to be a major limiting factor for exercise capacity.\textsuperscript{2-3} In general, a number of studies about molecular mechanisms of primary or secondary pulmonary arterial hypertension suggest that endothelial dysfunction plays a key role in this disease. Chronically impaired production of vasoactive mediators, such as nitric oxide and prostacyclin,\textsuperscript{4-5} along with prolonged overexpression of vasoconstrictors such as endothelin-1,\textsuperscript{6} not only affect vascular tone but also promote vascular remodeling. Sildenafil is a selective inhibitor of phosphodiesterase-5 that is highly expressed in penile and lung tissue, and leads to stabilization of cyclic guanosine monophosphate (cGMP). cGMP, a second messenger of nitric oxide (NO), promotes vasodilation in pulmonary vessels.\textsuperscript{7} Because of simplicity of administration and excellent safety profile, the oral sildenafil has come into the focus of investigation recently and a number of uncontrolled studies have reported the beneficial effect of sildenafil in the treatment of primary or secondary pulmonary hypertension.\textsuperscript{8-10} Although hemodynamic effects of inhaled nitric oxide in patients with mitral stenosis and pulmonary hypertension has been previously described,\textsuperscript{11} the effect of oral sildenafil in patients with mitral stenosis and pulmonary hypertension is unknown. We sought to investigate whether sildenafil, selective phosphodiesterase-5 inhibitor can reduce exaggerated increase in pulmonary artery pressure and improve exercise tolerance in patients with mitral stenosis.
II. MATERIALS AND METHODS

1. Study Subjects

Clinical, echocardiographic, and cardiopulmonary exercise data were obtained from 24 consecutive patients (5 males and 19 females, mean age 53 ± 10 years, range 29 to 65) with moderate to severe mitral stenosis. 9 patients were in normal sinus rhythm and 15 patients were in atrial fibrillation. Patients were included in the study if they were in New York Heart Association (NYHA) functional class I to III. Informed consent was obtained from all patients. Exclusion criteria included: (1) NYHA functional class IV, (2) left ventricular systolic dysfunction (LVEF<50%), (3) the presence of grade >1 of mitral regurgitation, (4) the presence of significant aortic regurgitation or stenosis, and (5) the clinical diagnosis of chronic obstructive pulmonary disease or other severe co-morbid conditions. All patients continued to take their medications such as diuretics, digitalis, warfarin according to physician’s decision, but no one was being treated with vasodilators.

2. Echocardiographic study

Two-dimensional and Doppler echocardiography were performed in all patients before exercise. Echocardiography was performed with a Vivid 3 equipment (GE medical company, USA). LA dimension and left ventricular end-diastolic and end-systolic dimensions were measured. Mitral valve areas were measured from 2-dimensional images and the pressure half-time method from the continuous mitral flow velocity profile. Mean mitral gradient was also measured by continuous-wave Doppler echocardiography. Pulmonary artery pressure were obtained from tricuspid and pulmonary regurgitation jet velocity tracings. Pulmonary vascular resistance (PVR) was determined noninvasively by Doppler echocardiography as the ratio of TRV (tricuspid regurgitant velocity) to TVI_{RVOT} (right ventricular outflow tract time-velocity
integral) which have been previously described by Abbas et al.\textsuperscript{13} Cardiac output was measured from velocity time integral of aortic flow, left ventricular outflow tract diameter measured at the aortic annulus, and heart rate. A mean of three to five values for patients in normal sinus rhythm and five to ten values for those in atrial fibrillation was taken respectively.

3. Cardiopulmonary exercise test (CPET)

Subjects performed a symptom limited, progressively increasing (25 W increase every 3 minutes) work rate cardiopulmonary exercise test (CPET) on a cycle ergometer (Medical Positioning, Inc., Kansas City, Missouri) in supine position. Ventilatory gas exchange for oxygen uptake (VO\textsubscript{2}), carbon dioxide output (VCO\textsubscript{2}), and minute ventilation (VE) was measured on a breath-by-breath basis with a gas analyzer (Medical Graphics, St.Paul, MN). VO\textsubscript{2} max was defined as the VO\textsubscript{2} measured during the last 30 seconds of peak exercise. Heart rate, 12-lead electrocardiogram, cuff blood pressure, and oxygen saturation by pulse oxymetry were monitored and recorded.

4. Protocol

After baseline measurement of two dimensional and Doppler echocardiographic data, all patients performed graded supine bicycle exercise with simultaneous measurement of echo Doppler parameters and indices of cardiopulmonary exercise test. After a 30-minute rest, 50 mg of sildenafil was administered orally. Then sixty minutes later (to coincide with the expected peak plasma concentration after oral dosing\textsuperscript{14}), the second supine bicycle exercise echocardiography was repeated as the same method in first exercise.

5. Statistical analysis

All data are expressed as mean ± SD. The non-parametric Wilcoxon signed-rank test was used to compare baseline and sixty minutes after sildenafil administration (Doppler echocardiographic hemodynamic data, exercise
indices). Statistical analyses were performed by means of the SPSS software package (version 11.5, SPSS Inc., Chicago, Illoinois) and a p value <0.05 was considered statistically significant.
III. RESULTS

1. Patients characteristics

The baseline characteristics of patients are given in Table 1. All had preserved left ventricular function, eight patients were in New York Heart Association (NYHA) functional class I, 15 in class II, and 1 in class III. Electrocardiography showed sinus rhythm in 9 patients and atrial fibrillation in 15 patients. Mean mitral valve area was $1.31 \pm 0.24 \text{cm}^2$ (range 0.68 to 1.73). Mean mitral gradient by Doppler echocardiography was $5.18 \pm 1.97 \text{mmHg}$ (range 2.65 to 9.4). Left atrial volume index was $69.2 \pm 27.3 \text{ml/m}^2$ (range 25.9 to 129).

Table 1. Baseline Characteristics of Study Subjects (n=24)

<table>
<thead>
<tr>
<th>Patient Data</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 \pm 10</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>5 : 19</td>
</tr>
<tr>
<td>NYHA class (I/II/III)</td>
<td>8/15/1</td>
</tr>
<tr>
<td>NSR : A.fib</td>
<td>9 : 15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62.2 \pm 7.4</td>
</tr>
<tr>
<td>LA VI (ml/m$^2$)</td>
<td>69.2 \pm 27.3</td>
</tr>
<tr>
<td>MVA (cm$^2$)</td>
<td>1.31 \pm 0.24</td>
</tr>
<tr>
<td>MG (mmHg)</td>
<td>5.18 \pm 1.97</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>34.1 \pm 10.7</td>
</tr>
<tr>
<td>SBP / DBP (mmHg)</td>
<td>121.6 \pm 19.6 / 74.8 \pm 8.7</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68.5 \pm 12.1</td>
</tr>
</tbody>
</table>

NYHA: New York heart association; NSR: normal sinus rhythm; A.fib: atrial fibrillation; LVEF: left ventricular ejection fraction; LAVI: left atrial volume index; MVA: mitral valve area; MG: mean mitral pressure gradient; PAP: pulmonary artery pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.
2. Changes of hemodynamics after oral sildenafil

There were no statistically significant changes in systolic, diastolic blood pressure, and heart rate after sildenafil administration (Fig. 1-2). Transmitral mean pressure gradient and arterial oxygen saturation was also not changed significantly after sildenafil (Fig. 3-4). Sildenafil caused pulmonary artery pressure to decline at baseline from 39.0 ± 7.9 to 35.5 ± 6.2 mmHg (p< 0.001), at peak exercise from 72.4 ± 15.3 to 62.0 ± 12.5 mmHg (p< 0.001), and at recovery after exercise from 41.4 ± 9.0 to 36.7 ± 6.9 mmHg (p< 0.001) (Fig. 5). The magnitude of reduction tends to be greater at peak exercise (13.2 ± 12.6 %) than baseline (8.2 ± 9.3 %) (p=0.15). Sildenafil also resulted in significant PVR decrease from 0.22 ± 0.09 to 0.19 ± 0.07 (p=0.004) defined as described above (Fig. 6). Cardiac output was changed from 4.0 ± 2.8 to 4.3 ± 2.9 L/min, which was not statistically significant (p=0.11).

![Figure 1. Responses of systolic blood pressure (SBP) and diastolic blood pressure (DBP) to exercise before and after sildenafil administration. Base: at baseline; Peak: at peak exercise; Rec: at recovery 10 minutes after exercise; NS: non significant](image)
Figure 2. Response of heart rate (HR) to exercise before and after sildenafil administration. Base: at baseline; Peak: at peak exercise; Rec: at recovery 10 minutes after exercise; NS: non significant

Figure 3. Response of mean mitral pressure gradient (MG) to exercise before and after sildenafil administration. Base: at baseline; Peak: at peak exercise; Rec: at recovery 10 minutes after exercise; NS: non significant
Figure 4. Response of arterial oxygen saturation (%) to exercise before and after sildenafil administration. Base: at baseline; Peak: at peak exercise; Rec: at recovery 10 minutes after exercise; NS: non significant

Figure 5. Response of pulmonary artery pressure (PAP) to exercise before and after sildenafil administration. Base: at baseline; Peak: at peak exercise; Rec: at recovery 10 minutes after exercise.
Figure 6. Change of pulmonary vascular resistance after sildenafil administration at peak exercise. PVR\textsubscript{echo} = \text{TRV}/\text{TVI\textsubscript{RVOT}} (TRV: tricuspid regurgitant velocity; TVI\textsubscript{RVOT}: right ventricular outflow tract time-velocity integral).
3. Change of exercise capacity after oral sildenafil

There was a significant increase in exercise duration from 403 ± 115 to 442 ± 115 seconds after sildenafil administration (p=0.016) (Fig. 7). Sildenafil also caused VO₂ max to increase from 15.3 ± 6.5 to 18.3 ± 4.9 ml/kg/min (p=0.016) (Fig. 8), and AT/VO₂ max to decrease from 17.5 ± 9.9 to 23.6 ± 12.6 % (p=0.014), which was statistically significant.

Figure 7. Change of exercise duration after sildenafil administration. Each line represents an individual’s exercise duration value before and after sildenafil.
Figure 8. Change of maximal oxygen consumption (VO₂ max, ml/kg/min) after sildenafil administration. Each line represents an individual’s VO₂ max values after sildenafil.

4. Adverse effects

No significant hemodynamic or other clinical adverse effects were noted with the sildenafil administration during this study.
IV. DISCUSSION

In this observational study, we evaluated the acute hemodynamic effects of oral sildenafil during supine bicycle exercise. In patients with mitral stenosis (MS), exercise can cause an inappropriate increase in pulmonary artery systolic pressure beyond the changes in left atrial pressure. These changes in the pulmonary vascular bed may also exert a protective effect, because the elevated precapillary resistance makes the development of symptoms of pulmonary congestion less likely by tending to prevent blood from surging into the pulmonary capillary bed and damming up behind the stenotic mitral valve, but this protection occurs at the expense of an increased afterload for the right ventricle which limit the exercise capacity and ultimately lead to right ventricular failure.

The exact mechanism of inappropriate increase in pulmonary artery pressure during exercise is not entirely understood. One possible mechanism is reversible vasoconstriction and increased pulmonary vascular resistance (PVR) due to development of pulmonary edema and alveolar hypoxia with exercise. If elevated pulmonary vascular resistance (PVR) was due to an endothelium dependent regulation of pulmonary vascular tone, then sildenafil should be able to decrease PVR acutely. However, if the increased PVR was predominantly due to fixed anatomic remodeling of the pulmonary vasculature, then administration of sildenafil would not reduce PVR. In present study, the immediate decline of PVR was noted after 1 hour of oral sildenafil administration. This suggests that a reversible, endothelium-dependent regulatory abnormality of vascular tone is an important mechanism of elevated PVR in mitral stenosis.

In this study, the vasodilatory response of sildenafil was restricted to the pulmonary circulation as systolic, diastolic blood pressure, and heart rate showed no significant change. We also observed no statistically significant increase of cardiac output, which probably would explain the maintenance of
systemic blood pressure. Inconsistent results about effects of sildenafil on
cardiac output in primary or secondary pulmonary hypertension have been
reported in previous studies.\textsuperscript{16-19} The effect of selective vasodilation may be
due to the different distribution of phosphodiesterase-5 (PDE-5) in different
vascular beds, PDE-5 is expressed abundantly in the lung vasculature.\textsuperscript{20} High
levels of PDE-5 expression in pulmonary arteries provides a good explanation
for the pulmonary selective vasodilative property of sildenafil as observed in
this study.

Pulmonary hypertension and elevated PVR have been reported as
independent risk factors for decreased survival in patients with mitral
stenosis.\textsuperscript{21} Several investigators have examined the acute effects of
percutaneous balloon valvuloplasty on PVR in patients with MS and
pulmonary hypertension. In most series,\textsuperscript{22-23} no significant change in PVR was
observed immediately after valvuloplasty despite a significant decrease in
pulmonary artery systolic pressure and left atrial mean pressure. In pulmonary
hypertension secondary to mitral stenosis, increased PVR may be due to a
combination of passive hydrostatic pressure, anatomic remodeling of the
pulmonary vasculature leading to decreased compliance, and or altered
endothelial-dependent vasculature tone (excess vasoconstriction or deficient
vasodilation). After valvuloplasty, the element of increased resistance due to
passive hydrostatic pressure is relieved, and this is a minor component of
elevated PVR. The component of PVR due to chronic, pressure-induced
anatomic remodeling of the pulmonary vasculature should be essentially fixed
immediately after valvuloplasty. Because PVR is not changed immediately
after valvuloplasty, anatomic remodeling has been suggested as the dominant
factor in the regulation of PVR in patients with severe MS. However, when
selective vasodilator nitric oxide (NO) was administered,\textsuperscript{11} PVR was acutely
reversible, suggesting that physiologic regulation of vascular endothelial
dependent tone plays a critical role in the pathophysiology of elevated PVR in
patients with MS. Provocative testing with inhaled NO in patients with severe
MS and pulmonary hypertension to determine the reversibility of PVR may prove useful for risk stratification before cardiac surgery or valvuloplasty. It may also help to identify patients who may benefit from postoperative management with NO or other pulmonary vasodilators. We propose sildenafil can be used more easily and safely as a substitute for NO according to the results of this study.

The improvement in exercise duration and VO$_2$max in the present study is likely due to improvement in pulmonary hemodynamics and reduction in right ventricular afterload. However, because we could not observe a significant increase of cardiac output, the improvement of exercise capacity could not be entirely explained. One possible explanation could be improved arterial oxygenation due to increased lung diffusing capacity after sildenafil administration. In congestive heart failure, elevation of hydrostatic pressure, enhancement of sodium transport across the capillary endothelium, and reduction in active fluid reabsorption by alveolar epithelium may concur to facilitate alveolar interstitial fluid accumulation and to limit gas exchange.$^{24}$ Improvement of lung diffusing capacity after oral sildenafil administration in congestive heart failure has been described in previous study.$^{25}$ in which sildenafil improved lung diffusing capacity for carbon monoxide (DL$_{CO}$) significantly, although hydralazine and nitrates failed to improve DL$_{CO}$ in other study despite a substantial pulmonary vasodilating activity.$^{26}$ Activation of the release of substances such as endothelium-derived NO has been offered as an explanation of this effects, because NO modulates the pulmonary vascular permeability and can reduce the tissue component of resistance to the oxygen transfer from the alveolus to hemoglobin. Although we can not validate this mechanism because we evaluated only arterial oxygen saturation (%) by pulse oxymetry, not partial pressure of oxygen by arterial blood gas analysis, improvement of exercise capacity after sildenafil administration in this study could be explained by greater nitric oxide availability, which results in not only the diminished pulmonary vascular tone but also facilitation of gas
diffusion. Additionally, because previous study showed that sildenafil could increase exercising muscle perfusion and improve oxygen diffusion from the capillaries to mitochondria in peripheral tissues\textsuperscript{22, 27}, this can be another possible explanation for mechanism of improved exercise tolerance after sildenafil administration.

There are some limitations of this study. Because this was a open-label, non-randomized study, there was no control placebo group and only small number of patients studied. Another limitation of the study was that hemodynamic evaluation was performed by non-invasive methods. Finally, because the study evaluated acute effects of sildenafil, long-term safety and clinical significance can not be concluded from this study.
V. CONCLUSION

Sildenafil may improve exercise tolerance by modulating pulmonary arterial pressure and pulmonary vascular resistance without reducing systolic and diastolic arterial pressure in patients with moderate to severe mitral stenosis. Because of the efficacy, simplicity, and potential cost savings of the oral PDE-5 inhibitor, larger trials to determine long term effect and clinical significance is warranted.
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ABSTRACT (IN KOREAN)

Sildenafil은 승모판 협착증 환자에서 운동시 유발되는 폐동맥 고혈압을 감소시키고 운동능력을 향상시킨다.

지도교수 정남식
연세대학교 대학원 의학과

연구배경: 승모판 협착증 환자에서 가장 특징적인 혈역학적인 변화 중 하나는 운동시에 폐동맥압력이 과도하게 상승하는 것이며 이러한 현상이 승모판 협착증 환자들의 운동능력을 결정하는 가장 중요한 인자로 알려져 있다. 본 연구에서는 phosphodiesterase-5의 선별적 저해제인 sildenafil (Viagra®)이 승모판 협착증 환자에서 운동시에 과도하게 상승하는 폐동맥 고혈압을 감소시키고 운동능력의 향상을 가져오지는지를 조사하였다.

재료 및 방법: 중등도에서 중증의 승모판 협착증을 가진 총 24명 (남자 5명, 여자 19명; 평균연령 53±10 세; 정상 동율동 9명, 심방세동 15명)의 환자를 대상으로 연구를 시행하였다. 모든 환자들은 누운 상태에서 자전거를 통한 운동부하 심초음파 검사를 시행하였고 동시에 심폐운동 검사를 시행하였다. 이후 sildenafil 50 mg을 경구 복용하고 60분 후에 같은 방식으로 검사를 반복하여 sildenafil 복용 전과 후의 결과를 비교하였다.

결과: 환자의 혈압, 맥박수, 산소 포화도, 그리고 평균 승모판 압력차는 sildenafil 복용 전과 후에 통계적으로 유의한 차이를 보이지 않았다. 최대 운동시의 폐동맥압은 sildenafil 복용 전 72.4 ± 15.3 mmHg에서 복용 후 62.0 ± 12.5 mmHg로 통계적으로 유의하게 감소하
었고 (p < 0.001), 삼첨판 역류 속도 (tricuspid regurgitant velocity, TRV)와 우심실 유출로에서의 시간-속도 적분값 (right ventricular outflow tract time-velocity integral, TVI_{RVOT})의 비 (TRV/TVI_{RVOT})로 정의한 폐혈관 저항도 0.22 ± 0.09에서 0.19 ± 0.07로 통계적으로 유의하게 감소하였다 (p=0.004). 심박출량은 4.0 ± 2.8에서 4.3 ± 2.9 L/min로 통계적으로 유의한 차이를 보이지 않았다 (p=0.11). 또한 심폐운동검사 결과에서는 총 운동시간이 sildenafil 복용 전 403 ± 115초에서 복용 후 442 ± 115초로 통계적으로 유의하게 증가하였으며 (p=0.016), 최대 산소소비량 (VO_{2} max)도 15.3 ± 6.5에서 18.3 ± 4.9 ml/kg/min로 통계적으로 유의한 상승을 보였다 (p=0.016).

결론: Sildenafil은 폐동맥 고혈압을 낮추고 폐혈관 저항을 감소시킴으로써 승모판 협착증 환자의 운동능력을 향상시킨다.

핵심되는 말: sildenafil, 승모판 협착증, 폐동맥고혈압, 운동능력