Original Article

Effect of sildenafil on arterial stiffness, as assessed by pulse wave velocity, in patients with erectile dysfunction

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Background: The problems of patients with erectile dysfunction have been recognized, leading to the emergence of sildenafil, which has led to successful treatment in many cases. The purpose of this study is to examine the effect of sildenafil on the pulse wave velocity of patients with erectile dysfunction.

Methods: Fifteen patients with erectile dysfunction were enrolled for this study. The brachial/ankle pulse wave velocity was determined before dosing and at 30, 60, 120, and 180 min after dosing with 25 or 50 mg of sildenafil citrate. Concurrently, the changes in blood pressure, heart rate, and brachial/ankle pulse wave velocity were measured. For the consideration of revised brachial/ankle pulse wave velocity by blood pressure, the systolic blood pressure-derived brachial/ankle pulse wave was also investigated, and we classified and examined those results with and without risk factors for arteriosclerosis.

Results: The systolic blood pressure decreased significantly at 60 min after dosing compared with the placebo control. The heart rate decreased at 120 min after dosing compared with the placebo control but that decrease was not significant. The brachial/ankle pulse wave velocity transiently decreased at 30 or 60 min after dosing compared with the placebo control, but the decrease was not significant; however, the systolic blood pressure-derived brachial/ankle pulse wave velocity decreased significantly. In those patients with risk factors for arteriosclerosis, the pulse wave velocity decreased significantly.

Conclusions: In patients with erectile dysfunction who were administered sildenafil, the pulse wave velocity, along with blood pressure, tended to decrease transiently after dosing. There is a possibility that sildenafil affects the improvement of erectile dysfunction via the decrease of pulse wave velocity, especially in patients with risk factors for arteriosclerosis.

Key words erectile dysfunction; pulse wave velocity, sildenafil.

Introduction

Lately, society has been changing in various ways and the number of patients with erectile dysfunction (ED) who have the courage to consult urologists has been increasing.1 Nerve-sparing techniques in radical prostatectomy or laparoscopic radical prostatectomy for patients with prostate cancer have been significantly improved and have enabled physicians to preserve erectile nerve function.2–4 Many patients have experienced an improvement of their erectile function postoperatively by administration of sildenafil citrate.5,6 The number of patients with ED who take sildenafil is gradually increasing.

Sildenafil is a selective inhibitor of phosphodiesterase. Its demand as a drug to treat ED in impotency therapy has increased. As for its pharmacological mechanism, sildenafil activates cyclic guanosine 3', 5'-monophosphate (cGMP) through the inhibition of phosphodiesterase type 5, relaxes vascular smooth muscles, and increases the inflow of arterial blood into the corpus cavernosum. This drug was originally developed as a vasodilator for patients with hypertension.7 During the clinical trial, it was found that this drug caused penile erection as another effect.

Sildenafil appears to have some influence on the cardiovascular system, but the details of its mechanism resulting in erection have not been sufficiently clarified. During systole, after blood is ejected into the systemic circulation, the intravascular pressure undergoes a small change. The wave motion through which the change of pressure is transmitted toward the periphery is known as the pulse wave.8

Pulse wave velocity (PWV) is the velocity of propagation of the arterial blood pressure wave along the vascular wall. It serves as an index to evaluate the stiffness of the vessels and the after-load of the heart, and as a marker related to motional capacity. The pulse wave is more rapidly transmitted when the inner diameter of the artery is thinner; when its wall is thicker, its distensibility is poorer. The higher the blood pressure, the higher the tension of the vascular wall, and the less the distensibility, resulting in a higher PWV.

Some authors reported that PWV can change according to blood pressure.9,10 Brachial/ankle PWV (BaPWV) has
no formula to correct it according to blood pressure that is different from aortic PWV, so we used the nomogram that shows the corrected baPWV by calculations from patients’ age and blood pressure for that comparison.\textsuperscript{11,12} It has been reported that PWV is, at least in part, a marker of the severity of arteriosclerosis-related vascular damage.\textsuperscript{13,14} Thus, we classified the patients according to the presence or absence of risk factors for arteriosclerosis and investigated each PWV change. In this study, we examined the effect of sildenafil on baPWV, blood pressure, and heart rate for patients with ED.

**Methods**

The subjects were 15 patients with ED. Their ages ranged from 40–84 years with a mean of 61 years. We excluded the patients with heart diseases. We measured the baPWV with a Form PWV/Ankle Brachial Index (ABI) (Colin Medical Instruments, Dallas, TX, USA) after the patients were administered 25 or 50 mg of sildenafil citrate. The Form PWV/ABI instrument measures pressure simultaneously at the arm and ankle and calculates the PWV. The measurement time is \(\approx 5\) min and the procedure is not invasive. All parameters were measured by the same investigator (N.Y.). We measured the baPWV just before administration and then at 30, 60, 120, and 180 min after administration of the drug. Simultaneously, we measured the blood pressure and heart rate at the same intervals.

Additionally, we compared the revised baPWV according to age and blood pressure with the measured baPWV as mentioned above. We classified those patients with risk factors (hypertension, smoking, body mass index (BMI) > 25, hypercholesteremia, hypertriglyceridemia, and hyperglycemia) for arteriosclerosis and those patients without those risk factors\textsuperscript{11} and examined each baPWV. We had 10 patients with ED (including six patients with hypertension) as a placebo control group.

Statistical analyses were performed using the Student’s \(t\)-test for blood pressure and heart rate and the Welch \(t\)-test for PWV, using StatView software (Abacus Concepts, Berkeley, CA, USA). We analyzed the change rate in the points of predosing and after-dosing of sildenafil and compared the group of patients with the dosing of sildenafil to the placebo control group. The statistical significance was set at \(P = 0.05\).

**Results**

Both systolic and diastolic blood pressures tended to decrease transiently between 30 and 90 min after dosing. The mean systolic blood pressure was significantly decreased at 60 min after dosing with sildenafil, as compared with the placebo control group (\(P = 0.0090\), systolic blood pressure, and \(P = 0.3165\), diastolic blood pressure) (Fig. 1).

The heart rate tended to decrease soon after dosing until 120 min afterwards. At 120 min after dosing with sildenafil, the heart rate tended to decrease compared with its baseline value slightly; however, the fall was not significant compared with the placebo control (\(P = 0.7704\)) (Fig. 2).

The baPWV was transiently lower 30–60 min after dosing with sildenafil and decreased more than that with the placebo control, but this decrease was not significant (\(P = 0.8328\)). However, the revised baPWV (shown as SBP-Dr baPWV [systolic blood pressure-derived baPWV]) according to age and blood pressure as mentioned above had decreased significantly at 60 min after dosing compared with the SBP-Dr baPWV of the placebo control group (\(P = 0.0188\)) (Fig. 3).

In our classification of patients with or without risk factors of arteriosclerosis as mentioned above, 11 patients had more than one risk factor for arteriosclerosis (group 1) and four patients did not have any of the risk factors above (group 2). In detail, of all 15 patients, seven patients had hypertension, six patients smoked, three patients had a BMI of > 25, one patient had hypercholesteremia, one patient had hypertriglyceridemia, and five patients had hyperglycemia. Therefore, we made the graphs of SBP-Dr baPWV for the patients in both groups 1 and 2 (Fig. 4). The SBP-Dr baPWVs decreased transiently after dosing with sildenafil compared to the placebo control group. The change rate was significant in those patients with risk factors for arteriosclerosis (\(P = 0.021\)) and not significant (\(P = 0.1374\)) in those patients without those risk factors.
Discussion

Sildenafil is now frequently prescribed for men with ED regardless of its etiology, which is often difficult to identify with certainty.15,16 Sildenafil is also a highly selective inhibitor of phosphodiesterase type 5, responsible for the degradation of the cGMP, and enhances the effects of either endogenous or exogenous nitric oxide (NO). The actions of nitroglycerin and other NO donors are mediated via the NO-cGMP pathway after their conversion or release; they diminish blood pressure in healthy humans. Exogenous nitrates requiring the NO-cGMP pathway can cause a modest decrease in systemic blood pressure. In addition, nitrates have been shown to improve arterial compliance and to markedly reduce the intensity of early wave reflection in the aorta without affecting systemic blood pressure. The relaxation of vascular smooth muscle in the corpus cavernosum, which is essential for penile erection, is mediated by NO and activates guanylate cyclase to produce cGMP.

As for the mechanism of erection, penile arteries are relatively small, with the average cavernosal artery being 0.5 mm in diameter, and helicine arteries, which run between the cavernosal artery and the sinusoids, are much smaller. These smaller arteries need to dilate up to 80% to provide the blood flow necessary to produce enough venous compression to sustain an erection.17 In addition, the penile vascular bed depends on NO for the vasodilation of arteries in order to produce a rapid blood inflow, as well as for the vasodilation of trabecular smooth muscle for lacunar spaces in order to prevent venous outflow. The relaxation of lacunae and their filling with arterial blood under high pressure cause the lacunae to swell and press the penile drainage veins against the resistant tunica albuginea, thereby trapping the blood in the penis. In many other vascular beds, the role of NO on the venous side of the circulation is minimal. This high degree of dependence on NO for both normal and rapid arterial inflow and to prevent venous outflow might account for the increased susceptibility of this vascular bed to deficiencies in the NO-cGMP vasodilator system. Sildenafil is considered to exert its effect on patients with ED via this mechanism.

In our results, the systolic blood pressure tended to decrease transiently after dosing with sildenafil and those decreases were statistically significant at 60 min compared with the placebo control group. These results were consistent with those reports in the relevant literature.8 Those blood pressures tended to return to baseline values by 180 min after dosing with sildenafil. These results suggest that in patients with ED, sildenafil affects the blood pressure temporarily. The mean heart rate gradually decreased after the administration of sildenafil, reaching the lowest value at 120 min after dosing. However, this change was not statistically significant compared with the placebo control group. Interestingly, these changes in the mean heart rate were not reported in other studies.8,18

The baPWV gradually decreased after dosing with sildenafil. In particular, it tended to decrease at 30–60 min after dosing, but the decrease was not statistically significant compared with that of the placebo control group. Some authors have reported the effects of blood pressure on baPWV; of those, Yamashina et al. reported the nomogram in which the relationship of baPWV with blood pressure is shown, concluding that this nomogram application makes it unnecessary to revise the baPWV according to blood pressure.11,12 Therefore, we can evaluate this study correctly by the use of the SBP-Dr baPWV and the investigation of the combined results of the measured baPWV and SBP-Dr baPWV. Our data suggest that sildenafil might affect the PWV and penile erection transiently and significantly. However, the PWV tended to recover to values close to the baseline at 120–180 min after dosing. This examination might provide a standard for the clinical administration of sildenafil.

We studied the baPWV in relation to the presence and absence of the risk factors for arteriosclerosis. From those
investigations, we reveal that the effect of sildenafil might be greater in those patients with the risk factors of arteriosclerosis than in those patients without them.

The decrease in PWV after dosing with sildenafil indicates that the drug has the potential to reduce the stiffness of the vessels, that the vessels become elastic, and that their distensibility increases. This would result in an increase of arterial blood inflow into the corpus cavernosum, which would in turn contribute to maintaining a penile erection. Another study showed that arterial wave reflection was reduced after dosing with sildenafil, suggesting that the distensibility of the arterial wall was increased by sildenafil.\(^8,19,20\) These effects and the vasodilator action of the drug are considered to contribute to penile erection. In addition, the reduction in PWV might contribute to the improvement of coronary artery flow, the reduction of cardiac output resistance, or even to the improvement of the motional capacity during sexual intercourse, suggesting the possibility of various synergistic effects of sildenafil.

**Conclusions**

In patients with ED who were administered sildenafil, the BaPWV and blood pressure tended to decrease transiently after dosing. Sildenafil might have the ability to improve ED via the decrease of PWV, especially for patients with risk factors for arteriosclerosis.

**References**