Effect of oral sildenafil citrate on intraoperative hemodynamics in patients with pulmonary hypertension undergoing valvular heart surgery

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Objective: Pulmonary hypertension remains a major problem during the perioperative period for surgical correction of long-standing valvular heart disease. Sildenafil citrate (INN sildenafil) is a selective phosphodiesterase type 5 inhibitor that is being increasingly recognized as a treatment modality for pulmonary hypertension. There is lack of evidence, however, regarding its pulmonary vasodilatory effect in anesthetized cardiac surgical patients. We therefore evaluated the effects of sildenafil on hemodynamics in patients with concomitant pulmonary hypertension undergoing valvular heart surgery in a controlled, prospective, randomized, double-blind trial.

Methods: Fifty-three patients scheduled for valvular heart surgery with mean pulmonary arterial pressure greater than 30 mm Hg were randomly treated with either 50 mg oral sildenafil (n = 26) or placebo (n = 27) 10 minutes before induction of anesthesia. Hemodynamic variables were measured 5 minutes after induction of anesthesia (baseline) and at 30 and 60 minutes after medication.

Results: Patient characteristics and baseline hemodynamics were similar between groups. Systolic and mean pulmonary arterial pressures and pulmonary vascular resistance were significantly lower in the sildenafil group at 30 minutes after medication, without any changes in mean systemic arterial pressure and systemic vascular resistance.

Conclusion: Sildenafil produced significant pulmonary vasodilatory effect relative to placebo in anesthetized cardiac surgical patients with pulmonary hypertension. With respect to the predominant selectivity of sildenafil to pulmonary vasculature shown in this study and other potentially beneficial effects such as myocardial protection, use of sildenafil in the intraoperative period in cardiac surgical patients with pulmonary hypertension should be considered.

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Pulmonary arterial hypertension (PAH) is characterized by progressive increase in pulmonary vascular resistance leading to right ventricular (RV) failure and death.¹ Pathologic processes behind the complex vascular changes associated with PAH include vasoconstrictor-vasodilator imbalance, thrombosis, misguided angiogenesis, and inflammation.^{2,3} Among the vasodilators, nitric oxide plays a critical role in pulmonary vasomotor regulation, which is mainly mediated by the guanylate cyclase–cyclic guanylate monophosphate (cGMP) pathway.⁴

Phosphodiesterase type 5 (PDE5) is an enzyme with predominant presence in the vascular smooth muscles, where it catabolizes cGMP. PDE5 inhibitors prevent cGMP degradation and thus potentiate the vasodilatory effect of the nitric oxide–cGMP pathway.⁵⁻⁷ Since the introduction of the selective PDE5 inhibitor sildenafil citrate (INN sildenafil), there has been growing evidence of its efficacy in treatment of both primary and secondary PAH.⁸⁻¹⁴ Its availability in oral, inhaled, and intravenous

Abbreviations and Acronyms

cGMP	= cyclic guanylate monophosphate
CPB	= cardiopulmonary bypass
PAH	= pulmonary arterial hypertension
PDE5	= phosphodiesterase type 5
PVRI	= pulmonary vascular resistance index
MPAP	= mean pulmonary arterial pressure
RV	= right ventricle
RVEDVI	= RV end-diastolic volume index
RVESVI	= RV end-systolic volume index
SPAP	= systolic pulmonary arterial pressure
SVRI	= systemic vascular resistance index

forms, its relative high degree of pulmonary selectivity, and its longer half-life than other pulmonary vasodilators are distinguishing features that make sildenafil a potentially useful drug for managing perioperative PAH.^{15,16}

PAH with subsequent RV failure remains a major problem during the perioperative period for surgical correction of congenital and long-standing valvular heart disease. There is still a lack of evidence, however, regarding the intraoperative pulmonary vasodilatory effects of sildenafil in anesthetized cardiac surgical patients. We therefore evaluated the effect of oral sildenafil on hemodynamics in patients with concomitant PAH undergoing valvular heart surgery in a controlled, prospective, randomized, double-blind trial.

Materials and Methods

After institutional review board approval and surrogate informed consent were obtained, 60 patients scheduled for valvular heart surgery with systolic RV pressure greater than 50 mm Hg, as measured by preoperative transthoracic echocardiography, were enrolled. Patients were randomly allocated to either sildenafil or placebo (control) group with a computerized randomization table. Patients with preexisting lung parenchymal disease, coronary artery occlusive disease, hepatic or renal disease, tricuspid regurgitation of at least 2, or New York Heart Association functional class of at least 3 were excluded. Patients taking nitrates were also excluded.

All cardiovascular medications except digoxin and diuretics were continued until the day of surgery. On the patient's arrival at the operating room, standard monitoring devices were applied, including a pulmonary arterial catheter (Swan-Ganz CCOmbo CCO/Svo2; Edwards Lifesciences, Irvine, Calif), which was inserted through the right internal jugular vein before induction of anesthesia. After pulmonary arterial catheter insertion, patients with mean pulmonary arterial pressures (MPAPs) greater than 30 mm Hg were eventually included in this study. Among the 60 patients, 53 patients met this criterion (control group $n = 27$, sildenafil group $n = 26$) and were treated with either oral sildenafil (50 mg) or placebo with 30 mL of sterile water before induction of anesthesia. Anesthesiology nurse who was not involved in this study prepared the drugs. Investigators and participants were

blinded to the assigned groups until their revelation after the study. Ten minutes after medication, anesthesia was induced with intravenous midazolam (2.0-3.0 mg) and sufentanil (1.5-3.0 $\mu\text{g/kg}$) and maintained with isoflurane (0.6-1%) and continuous infusion of sufentanil (0.5-1.5 $\mu\text{g}/[\text{kg} \cdot \text{min}]$). Neuromuscular blockade was achieved by administering rocuronium bromide (0.9 mg/kg) and maintained with continuous infusion of vecuronium bromide (1-2 $\mu\text{g}/[\text{kg} \cdot \text{min}]$). After the induction of anesthesia, the lungs were ventilated with a tidal volume of 10 mL/kg at a rate of 10 breaths/min in 60% oxygen with air, and positive end-expiratory pressure was not applied. After that, the accordance of Paco_2 with end-tidal carbon dioxide was confirmed before starting the study, and respiratory rate was adjusted to maintain Paco_2 between 33 and 38 mm Hg and pH around 7.4 throughout the study period. Central temperature, as measured by pulmonary arterial catheter, was maintained higher than 36°C with warm mattress, forced warm air blanket, and fluid warmer as necessary.

This study was planned to terminate if systolic arterial pressure was decreased more than 20% of postinduction value after medication, necessitating vasoactive drug administration. Hemodynamic variables were measured before induction of anesthesia (T0), 5 minutes after induction of anesthesia (baseline), and 30 and 60 minutes after medication (T30 and T60, respectively). Baseline hemodynamic values were measured at 18.0 ± 0.8 and 17.8 ± 0.8 minutes after medication in the control and sildenafil groups, respectively. Hemodynamic measurements included mean arterial pressure, systolic pulmonary arterial pressure (SPAP), MPAP, central venous pressure, cardiac index, RV ejection fraction, RV end-diastolic volume index (RVEDVI), and RV end-systolic volume index (RVESVI). Corresponding systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were calculated. Surgical incision was withheld until the last hemodynamic measurement was obtained. During the period of weaning from cardiopulmonary bypass (CPB), numbers of patients requiring norepinephrine 0.03-0.3 $\mu\text{g}/[\text{kg} \cdot \text{min}]$ or milrinone (0.3-0.7 $\mu\text{g}/[\text{kg} \cdot \text{min}]$) were recorded. Patients requiring at least 0.3 $\mu\text{g}/[\text{kg} \cdot \text{min}]$ norepinephrine were considered to require an excessive amount of vasopressors.

Statistical analyses were performed with SPSS 12.0 (SPSS Inc, Chicago, Ill). All data are expressed as mean $\pm$ SD or number of patients. Because there was no controlled study comparing the effect of oral single dose of sildenafil in cardiac surgical patients, sample-size calculation was based on a study by Trachte and colleagues¹⁷ with the following assumptions: clinical significance α at .05 with a independent t -test and power to expect a significant result at .9, the mean difference between groups at 10 mm Hg with SD at 9 mm Hg of the mean value of MPAP. This generated an estimate of 18 patients per group. Data were compared between the groups with χ^2 test, Fisher exact test, or independent t -test as appropriate. Changes between time points within the groups were compared with repeated measurements of analysis of variance with post hoc comparison by Dunnett test.

Results

All 53 patients could be successfully studied without any requirement for vasopressor or inotropic agents during the period of hemodynamic measurements. Also, all patients could be successfully weaned from CPB without adverse

TABLE 1. Patient characteristics

Characteristic	Control (n = 27)	Sildenafil (n = 26)	P value
Age (y, mean $\pm$ SD)	53 $\pm$ 12	57 $\pm$ 13	.3
Sex (male/female)	11:16	10:16	.87
Body surface area (m ²)	1.6 $\pm$ 0.2	1.6 $\pm$ 0.2	.42
Disease (No.)			
MS	11	12	
MR	10	11	
MSR	4	2	
ASR	9	7	
Procedure (No.)			
MVR	19	19	
AVR	3	1	
DVR	5	6	
Electrocardiography (NSR/A-fib)	16:11	13:12	.6

MS, Mitral stenosis; MR, mitral regurgitation; MSR, mitral stenosis and regurgitation; ASR, aortic stenosis and regurgitation; MVR, mitral valve replacement; AVR, aortic valve replacement; DVR, double valve replacement; NSR, normal sinus rhythm; A-fib, atrial fibrillation.

events or requirement of excessive amounts of vaso-pressors.

Patient characteristics and hemodynamic variables measured at T0 were similar between the groups (Tables 1, 2, and 3). There were no significant differences in baseline hemodynamic variables between the groups. SPAP, MPAP, PVRI, mean arterial pressure, and SVRI after anesthesia

(baseline values) were significantly decreased in both groups relative to values at T0 (preinduction values; Table 2). Also, heart rate in the sildenafil group and pulmonary capillary wedge pressure in the control group after anesthesia were significantly decreased relative to values at T0 (Table 3).

At T30, SPAP, MPAP, and PVRI were significantly lower in the sildenafil group than in the control group (Table 2). And also, SPAP and MPAP at T30 were significantly decreased relative to baseline values only in the sildenafil group (Table 2).

At T60, hemodynamic variables were similar between the groups. SPAP, MPAP, and PVRI were lower in the sildenafil group, but without statistical significance ($P = .07$, $P = .087$, $P = .09$, respectively; Table 2). PVRI, RVEDVI, RVESVI, and SVRI at T60, however, were significantly increased relative to baseline values only in the control group (Tables 2 and 3). Cardiac index was significantly decreased in both groups, and central venous pressure in the sildenafil group was significantly increased relative to baseline (Table 3).

During the period of weaning from CPB, the numbers of patients requiring norepinephrine ($n = 9$ in both groups) and milrinone ($n = 9$ in control group, $n = 4$ in sildenafil group) were similar between the groups.

Discussion

In this controlled, prospective, randomized, double-blind study, a single dose of oral sildenafil immediately before

TABLE 2. Changes in pulmonary and systemic arterial pressures and vascular resistances

Group	T0	Baseline	T30	T60	P value	
					Baseline	Control
SPAP (mm Hg)						
Control	65 $\pm$ 21	47 $\pm$ 13*	48 $\pm$ 13	52 $\pm$ 18		
Sildenafil	58 $\pm$ 11	45 $\pm$ 11*	40 $\pm$ 8†‡	45 $\pm$ 11	.02	.02
MPAP (mm Hg)						
Control	45 $\pm$ 13	33 $\pm$ 9*	33 $\pm$ 8	37 $\pm$ 12		
Sildenafil	40 $\pm$ 8	32 $\pm$ 6*	29 $\pm$ 6†‡	32 $\pm$ 7	.03	.04
PVRI (dynes $\cdot$ sec $\cdot$ cm ⁻⁵ $\cdot$ m ²)						
Control	396 $\pm$ 193	263 $\pm$ 130*	290 $\pm$ 139	345 $\pm$ 163†	.02	
Sildenafil	355 $\pm$ 138	234 $\pm$ 123*	217 $\pm$ 114‡	273 $\pm$ 142		.04
MAP (mm Hg)						
Control	96 $\pm$ 15	78 $\pm$ 12*	75 $\pm$ 11	77 $\pm$ 13		
Sildenafil	94 $\pm$ 16	78 $\pm$ 12*	74 $\pm$ 12	74 $\pm$ 12		
SVRI (dynes $\cdot$ sec $\cdot$ cm ⁻⁵ $\cdot$ m ²)						
Control	2291 $\pm$ 624	1872 $\pm$ 565*	1821 $\pm$ 482	2106 $\pm$ 706†	.021	
Sildenafil	2271 $\pm$ 839	1809 $\pm$ 493*	1831 $\pm$ 613	2001 $\pm$ 783		

Values are mean $\pm$ SD. T0, Before induction of anesthesia; Baseline, 5 minutes after induction of anesthesia; T30, 30 minutes after 50 mg oral sildenafil or placebo; T60, 60 minutes after 50 mg oral sildenafil or placebo; SPAP, systolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; PVRI, pulmonary vascular resistance index; MAP, mean systemic arterial pressure; SVRI, systemic vascular resistance index. * $P < .05$ versus T0. † $P < .05$ versus baseline. ‡ $P < .05$ versus control group.

TABLE 3. Changes in hemodynamic variables

Group	T0	Baseline	T30	T60	P vs baseline
HR (beats/min)					
Control	85 ± 14	75 ± 20	73 ± 16	70 ± 13	
Sildenafil	87 ± 21	77 ± 21*	74 ± 17	73 ± 14	
CVP (mm Hg)					
Control	8 ± 3	10 ± 3	10 ± 3	11 ± 3	
Sildenafil	8 ± 4	9 ± 3	9 ± 3	11 ± 4†	.002
PCWP (mm Hg)					
Control	30 ± 10	24 ± 8*	23 ± 7	26 ± 9	
Sildenafil	26 ± 7	23 ± 6	22 ± 5	23 ± 5	
CI (L/[min · m ²])					
Control	3.2 ± 0.9	3.2 ± 1.2	3.0 ± 0.8	2.7 ± 0.7†	.01
Sildenafil	3.3 ± 0.9	3.2 ± 0.8	3.0 ± 0.7	2.7 ± 0.7†	.003
RVEF (%)					
Control	23 ± 9	25 ± 10	24 ± 10	24 ± 9	
Sildenafil	27 ± 9	26 ± 10	26 ± 9	27 ± 9	
RVESVI (mL/m ²)					
Control	129 ± 40	134 ± 65	146 ± 73	141 ± 52†	.031
Sildenafil	122 ± 45	143 ± 77	134 ± 69	125 ± 46	
RVEDVI (mL/m ²)					
Control	179 ± 47	167 ± 50	179 ± 58	193 ± 61†	.048
Sildenafil	170 ± 48	189 ± 72	193 ± 80	186 ± 65	

Values are mean ± SD. T0, before induction of anesthesia; T0, Before induction of anesthesia; Baseline, 5 minutes after induction of anesthesia; T30, 30 minutes after 50 mg oral sildenafil or placebo; T60, 60 minutes after 50 mg oral sildenafil or placebo; HR, heart rate; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume index; RVEDVI, right ventricular end diastolic volume index. **P* < .05 versus T0. †*P* < .05 versus baseline.

induction of anesthesia produced significant pulmonary vasodilation without eliciting systemic effects 30 minutes after medication. At 60 minutes after medication, sildenafil prevented the increase in PVRI that occurred in the control group, although significant differences in MPAP and PVRI between the groups could not be observed.

PAH frequently complicates perioperative management of cardiac surgical patients with valvular heart disease and has adverse effects on prognosis. The most important clinical significance of PAH lies in the subsequent RV failure. Because CPB exacerbates PAH and the RV is particularly susceptible to ischemic injury during CPB,¹⁸ perioperative management strategies to deal with PAH and RV dysfunction are necessary. In the area of managing PAH, preserving coronary perfusion of the RV while decreasing pulmonary arterial pressure is the desirable goal¹⁹; research in recent years has therefore been directed toward selective pulmonary vasodilators.

The final messenger for vascular smooth muscle relaxation, c-GMP, is metabolized by PDE5.⁶ Among the various phosphodiesterases, PDE5 is the predominant type in the normal pulmonary vasculature that may be upregulated after CPB.²⁰ The inhibition of PDE5 is therefore a logical step to increase the bioavailability of cGMP and support endogenous vasodilation in patients with PAH. Sildenafil is a potent and selective inhibitor of cGMP-specific PDE5.⁴ Its

potent and relatively selective pulmonary vasodilatory effects have been demonstrated in animal models,¹⁶ in children,⁸ and in adults with PAH.^{9-13,21-23} In addition, its beneficial effects with regard to myocardial preconditioning and remodeling further advocate its potential use in cardiac surgical patients.²⁴⁻²⁶ There has been little experience with the use of oral sildenafil in adult cardiac surgical patients with PAH, mostly limited to the postoperative period. To the best of our knowledge, this study is the first controlled, prospective, randomized, double-blind study to confirm sildenafil's pulmonary vasodilatory effect in the intraoperative period.

Pulmonary hemodynamics are markedly variable and affected by numerous factors during the perioperative period, especially during the period of weaning from CPB and immediately thereafter.¹⁹ To minimize factors affecting PVRI, hemodynamic values including the baseline values were measured under same conditions: (1) general anesthesia with same agents, (2) strict control of mechanical ventilation to maintain normocarbia and normal pH value, (3) and withholding of surgical stimulation until after the last measurement at 60 minutes after medication. In addition, to ensure constant drug delivery to the stomach without adding too much water, the drugs were given before induction of anesthesia. Thus baseline values were obtained about 18 minutes after medication in both groups. Although pulmo-

nary vasodilatory effects of oral sildenafil have been reported after 12 to 15 minutes, mean time to peak concentration is 0.8 to 0.9 h with most of the studies reporting time to maximal pulmonary vasodilatory effect of 30 to 60 minutes.^{12,15,27} In accordance with this value, the baseline hemodynamic values were similar between the groups in this study.

As with previous reports, we could observe significant decreases in pulmonary arterial pressure and PVRI without any changes in mean arterial pressure and SVRI, which supports sildenafil's predominantly selective activity on pulmonary vasculature.⁹ Sildenafil also had clinically insignificant effects on cardiac index, heart rate, and other hemodynamic variables measured in this study. We could not observe any statistically significant subsequent improvement in RV ejection fraction or reduction in RVEDVI and RVESVI in the sildenafil group, even at T30 when maximal pulmonary vasodilation had occurred. The findings that RVESVI and RVEDVI were significantly increased in the control group at T60 relative to baseline values and that RVESVI showed a trend toward decrease in the sildenafil group, however, indicate that there may have been potential improvement in RV performance.

Sildenafil has an elimination half-life of 3.7 hours,²⁴ and a pulmonary vasodilatory effect lasting for at least 3 hours without affecting systemic arterial pressure has been reported.⁵ In this study, significant intergroup differences in pulmonary arterial pressure could not be observed after 60 minutes of medication. The finding that PVRI and RVEDVI and RVESVI were significantly increased relative to baseline values only in the control group, however, indicates that there may have been some beneficial effect of sildenafil at this time point. Possible explanations are that adverse effects of continued mechanical ventilation on PVRI attenuated the vasodilatory effect of sildenafil. Reduced absorption of sildenafil as a result of general anesthesia also may have affected the results. Even though 50 mg oral sildenafil has been proved to be sufficient to produce significant pulmonary vasodilation,^{12,28} studies with oral sildenafil in anesthetized animals have reported reduced plasma concentration rather than delayed absorption,^{29,30} which could not be verified in this study and is a limitation of this study. Further investigations regarding pharmacokinetics of oral sildenafil in anesthetized patients are therefore necessary to clarify optimal dosing and dosing interval.

In conclusion, oral sildenafil produced significant pulmonary vasodilatory effects relative to placebo in anesthetized cardiac surgical patients with PAH. Because of the predominant selective activity of sildenafil on the pulmonary vasculature shown in this study and such other potentially beneficial effects as myocardial protection, use of sildenafil in the intraoperative period in cardiac surgical patients with PAH should be considered.

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