

Sildenafil in the Treatment of Postoperative Hypoxemia with High Resistance in Cyanotic Congenital Heart Disease

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Abstract: This study was designed to determine the effect of sildenafil treatment on postoperative hypoxemia with high resistance in cyanotic congenital heart disease. A total of 247 cases of cyanotic congenital heart disease were operated on from May 2006 to August 2014. Only 45 cases exhibited postoperative hypoxemia after symptomatic treatment. Sildenafil at doses of 0.30-5 mg/kg every 6 h was administered in 24 cases while the other 21 were administered a placebo (the control group). The partial pressure of oxygen in arterial blood (PaO₂), systolic blood pressure, pulmonary arterial pressure and positive inotropic drugs score were evaluated at four time points including before (T1), 1 h (T2) and 1 day (T3) after treatment and when the ventilator was disconnected (T4). Furthermore, we compared the mechanical ventilation time between the two groups. Finally, there was one death in the placebo group while the others were cured. Compared with the placebo group, in the sildenafil group, the PaO₂ rebounded faster and the pulmonary arterial pressure decreased significantly; furthermore, there were statistically significant differences from time point T2 between both groups ($p < 0.001$). The systolic blood pressure rose slowly and there were statistically significant differences between both groups from time point T3 ($p < 0.001$). The representations of the positive inotropic drug scores were obviously different between the two groups. The sildenafil group scores decreased soon and maintained this trend. The placebo group scores initially increased and then began to decline 1 day after treatment, but the final score was higher than that of the sildenafil group. Compared with the placebo group, in the sildenafil group, the respiratory and heart functions recovered rapidly and the patient's stay on the mechanical ventilation was shorter (67.52 ± 16.88 Vs. 44.25 ± 13.39 h, $p = 0.001$). Therefore, sildenafil reduced pulmonary vascular resistance and obviously corrected the postoperative hypoxemia in cyanotic congenital heart disease.

Keywords: Cyanotic Congenital Heart Disease, Hypoxemia, Sildenafil

Introduction

The hemodynamic characteristics of cyanotic congenital heart disease are pulmonary blood flow decreased (Sharkey and Sharma, 2012) while pathological examinations revealed small pulmonary artery hypoplasia in these patients due to a prolonged low blood flow (Chen *et al.*, 2014). Hypoxemia is a serious complication that can easily develop after a cardiac operation. The results of ultrasonographic diagnosis in patients with hypoxemia revealed that the right ventricular systolic function was good, but because the pulmonary artery resistance was high, the Pulmonary Arterial Pressure (PAP) and Central Venous Pressure (CVP) increased obviously. These patients show a poor curative response to using inotropes and diuretic and

would eventually die because of severe hypoxemia and low cardiac output.

Sildenafil acts by inhibiting cyclic Guanosine Monophosphate (cGMP)-specific Phosphodiesterase type 5 (PDE-5), an enzyme that promotes the degradation of cGMP, which causes smooth muscle relaxation (Niyazi *et al.*, 2006). Because PDE-5 is primarily distributed in the arterial wall of the smooth muscle of the lungs and penis, sildenafil acts selectively in both these areas without inducing vasodilation in other areas of the body. Since its availability in 1998, sildenafil has been the primary treatment option for erectile dysfunction (Khanavi *et al.*, 2012). In addition to erectile dysfunction, sildenafil was approved by the US Food and Drug Administration (FDA) for the treatment of Pulmonary Hypertension (PH) in June 2005 and it

selectively dilates pulmonary arteries and reduces pulmonary vascular resistance (Croom and Curran, 2008). Therefore, sildenafil has been widely used in clinical practice and has demonstrated improvement of exercise capacity, symptoms and hemodynamics in patients with PH (Barst *et al.*, 2014; Rubin *et al.*, 2011; Kovacicova *et al.*, 2007). However, there is currently very little clinical information on strategies to relieve high pulmonary vascular resistance after surgery for cyanotic congenital heart disease. Therefore, this study was designed to investigate the clinical effect of sildenafil treatment of postoperative hypoxemia with high resistance in cyanotic congenital heart disease.

Materials and Methods

Materials

A total of 247 cases of cyanotic congenital heart disease were operated on by the same senior cardiac surgeon from May 2006 to August 2014 in the Department of Cardiac Surgery of the First Affiliated Hospital of Nanyang Medical College. These included 153, 85 and 9 cases of Tetralogy of Fallot (TOF), severe Pulmonary Stenosis (PS) and Double Outlet Right Ventricle (DORV), respectively. Hypoxemia occurred 1-3 days after the operations in 45 cases. The clinical manifestations of hypoxemia were a partial pressure of oxygen in arterial blood (PaO_2) < 80 mm Hg, peripheral capillary oxygen saturation (SpO_2) < 90%, $\text{CVP} > 20$ mmHg and associated cardiac dysfunction including low blood pressure, liver enlargement and edema. The patients were enrolled in the study after approval was received from the Institutional Ethics Committee after obtaining written consent. Twenty-four patients were administered sildenafil as the treatment group while the other 21 received a placebo as the control group.

Surgical Methods

Radical corrections in patients with TOF or PS were performed under hypothermia and general anesthesia with cardiopulmonary bypass. In all the patients, a median sternotomy was performed. A Cardiopulmonary Bypass (CPB) was initiated after the standard aorta-bicaval cannulation. A membrane oxygenator was used for all the patients during the CPB. Myocardial protection was achieved by using a blood cardioplegia solution with a cardioplegia delivery system. Modified ultra filtration was used to filter the excess water and part of the inflammatory mediators during the CPB (Hu *et al.*, 2014). The same surgical team performed all of the operations. The longitudinal incision was made from the right ventricular outflow tract to the pulmonary artery. The abnormal hypertrophic muscle bundle was appropriately removed and then an autologous or bovine pericardial patch was used to relieve the stenosis of the pulmonary artery. The standard of widening was in accordance with the criteria of Naito *et al.* (1980);

specifically, a body surface area of 0.4 m^2 requires the width of the right ventricular outflow tract to be 10 mm. The right ventricular outflow tract was increased by 1 mm with every 0.1 m^2 increase in the body surface area.

Management and Monitoring

All patients maintained the inserted arterial and central venous catheter. The mechanical ventilation system was a PRVC model without PEEP, which was operated with a tidal volume of 8-10 mL/kg with the respiratory rate adjusted according to the age and weight, aimed at maintaining a PaCO_2 of 30-35 mmHg. Appropriate inotropes and diuretic agents were added to maintain the patient's hemodynamics. When hypoxemia developed, we took appropriate measures including increasing the fraction of inspired oxygen (FiO_2) from 50 to 60% using additional inotropic drugs such as adrenaline and milrinone, adding colloids and enhancing the diuretic therapy. In the sildenafil group, the patients with parental consent were administered sildenafil at the standard dose of 0.3-0.5 mg/kg every 6 h. The control group was administered a similar volume of normal saline. The PaO_2 , SBP, PAP and Positive Inotropic Drugs Score (PIDS) were measured at four time points, before (T1), 1 h (T2) and 1 day after treatment (T3), as well as when the patient was taken off the ventilator (T4). Finally, we compared the ventilation time of the two groups. The PAP was measured by using the tricuspid regurgitation velocity method. The PIDS was calculated based on the type and dosage of inotropes and using the following formula designed to account for the relative potencies of the various inotropes (Gaies *et al.*, 2010):

$$\text{PIDS} = \text{Dopamine } \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \times 1 + \text{dobutamine } \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \times 1 + \text{milrinone } \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \times 10 + \text{epinephrine } \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \times 100 + \text{nor epinephrine } \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1} \times 100. \text{ A PIDS value } > 20 \text{ indicates cardiac insufficiency}$$

Statistical Analysis

All statistical comparisons were performed using the Statistical Analysis Software (SAS) OriginPro version 8.0. The quantitative data were expressed as mean \pm Standard Deviation (SD). A one-way Analysis of Variance (ANOVA) was used for the statistical analysis of the interior-group quantitative data. The inter-group quantitative and the qualitative data were analyzed by using a two-group t-test and Chi-square test, respectively. A p-value < 0.05 was considered statistically significant.

Results

There was one death in the placebo group due to severe low cardiac output syndrome during the study period while the others were all cured. The demographic characteristics were similar for both groups (Table 1).

Other parameters like the CPB time, PaO₂, SBP and PAP were similar for both groups before the study, but the PIDS values of the sildenafil group were higher than those of the placebo group were ($p = 0.029$) (Table 2). This is because we used sildenafil when treatment with the positive inotropic drugs showed a poor curative effect, which worsened the patient's condition.

The PaO₂ between the two groups showed statistically significant differences at T2, T3 and T4 ($p < 0.001$, Table 3). A repeated measure ANOVA determined that the PaO₂ of the sildenafil group differed significantly between time points ($p < 0.001$) but that of the placebo group did not differ significantly between T1 and T2 ($P = 0.240$). This indicated that the PaO₂ of the sildenafil group rebounded faster than that of the placebo group did (Fig. 1).

The PAP was significantly different between the two groups at T2 and T3 ($p < 0.001$, Table 4), but was not at

T1 and T4 ($p < 0.001$). A repeated measure ANOVA determined that the PAP of the sildenafil group differed significantly between time points ($p < 0.001$), but that of the placebo group showed not a significant difference between T1 and T2 ($p = 0.488$). This indicated that both treatments effectively the PAP eventually, but that of the sildenafil group dropped faster than that of the placebo group did (Fig. 2).

The SBP was significantly different between the two groups at T3 and T4 ($p < 0.006$) but not at T1 and T2 ($p > 0.05$, Table 5). A repeated measure ANOVA determined that both groups equally showed a significant difference between T3 and T4 ($p < 0.001$) but not between T1 and T2 ($p > 0.05$). This indicated that the SBP of the two groups recovered slowly and the effect was evident 1 day later while the sildenafil group recovered more quickly than the placebo group did (Fig. 3).

Table 1. Preoperative characteristics of study patients

Parameter	Sildenafil group (n = 24)	Placebo group (n = 21)	P-value
Sex (M/F)	14/10.00000	13/8.000000	0.800
Age (year)	3.3±1.5000	3.5±1.9000	0.736
Weight (kg)	14.38±4.210	16.12±6.590	0.347
McGoon (mm/mm)	1.21±0.170	1.18±0.300	0.521
Nakata (mm ² /m ²)	133.71±10.05	131.37±13.47	0.764

Table 2. Intra-operative and post-operative data of study patients

Data	Sildenafil group (n = 24)	Placebo group (n = 21)	P-value
CPB time (min)	69.33±13.17	62.63±17.29	0.438
PaO ₂ (mm Hg)	77.67±4.51	78.14±3.76	0.704
SBP (mm Hg)	88.42±4.05	87.09±3.49	0.167
PAP (mm Hg)	64.00±6.33	62.67±6.42	0.488
PIDS	33.37±2.99	31.33±3.07	0.029*

Cardiopulmonary Bypass, (CPB); Systolic Blood Pressure, (SBP); Pulmonary Arterial Pressure, (PAP); Positive Inotropic Drug Score, (PIDS); * $p = 0.029$ and $p < 0.05$ between both groups

Table 3. Comparison of partial pressure of oxygen in arterial blood (PaO₂) of both study groups at each time point

Variables	Group	T1	T2	T3	T4
PaO ₂ (mm Hg)	Sildenafil (n = 24)	77.67±4.51	93.79±5.99	108.50±10.57	143.75±14.00
	Placebo (n = 21)	78.14±3.76*	81.14±6.03*	90.67±9.480	125.52±11.36
P value		0.7040000	0.0000000	0.0000000	0.0000000

* $p = 0.240$, $p > 0.05$, no statistically significant difference. T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

Table 4. Comparison of Pulmonary Arterial Pressure (PAP) of both study groups at each time point

Variables	Group	T1	T2	T3	T4
PAP (mm Hg)	Sildenafil (n = 24)	64.00±6.33	50.42±4.84	42.46±4.11	37.13±3.92
	Placebo (n = 21)	62.67±6.42*	60.52±6.35*	55.86±5.94	39.42±5.08
P-value		0.4880000	0.0000000	0.0000000	0.0930000

* $p = 0.248$, $p > 0.05$, no statistically significant difference. T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

Table 5. Comparison of Systolic Blood Pressure (SBP) between both study groups at each time point

Variables	Group	T1	T2	T3	T4
SBP (mm Hg)	Sildenafil I (n = 24)	88.42±4.05*	89.12±4.34*	97.17±3.21	102.70±6.70
	Placebo (n = 21)	87.09±3.49 [#]	88.09±4.25 [#]	91.52±3.16	98.00±3.561
P-value		0.1670000	0.4290000	0.0000000	0.0060000

* $p = 0.608$, $p > 0.05$, [#] $p = 0.179$ and $p > 0.05$, no statistically significant difference. T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

Table 6. Comparison of Positive Inotropic Drug Score (PIDS) between both study groups at each time point

Variables	Group	T1	T2	T3	T4
PIDS	Sildenafil (n = 24)	33.37±2.99	30.54±2.57	23.63±2.43	17.46±2.04
	Placebo (n = 21)	31.33±3.07*	33.00±2.68*	32.90±3.10*	23.86±3.51
P-value		0.0290000	0.0030000	0.0000000	0.0000000

*p = 0.086, 0.105, 0.921; p>0.05, no significant difference in T1, T2 and T3 of placebo group. T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

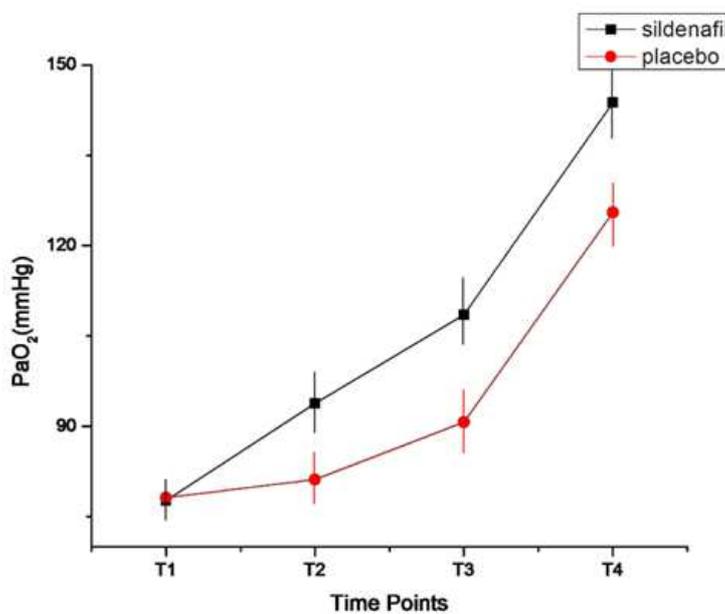


Fig. 1. Rebound trend of partial pressure of oxygen in arterial blood (PaO₂) in both study groups at each time point T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

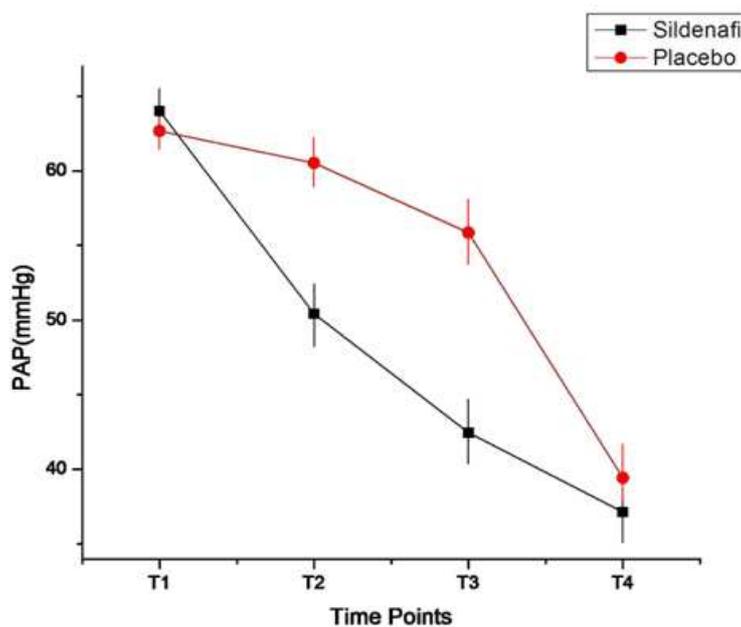


Fig. 2. Rebound trend of Pulmonary Arterial Pressure (PAP) in both study groups at each time point T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

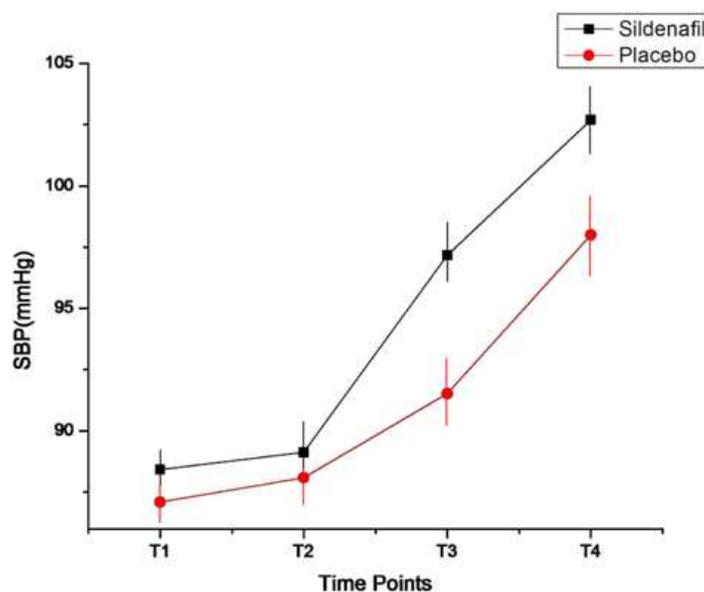


Fig. 3. Rebound trend of Systolic Blood Pressure (SBP) in both study groups at each time point T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

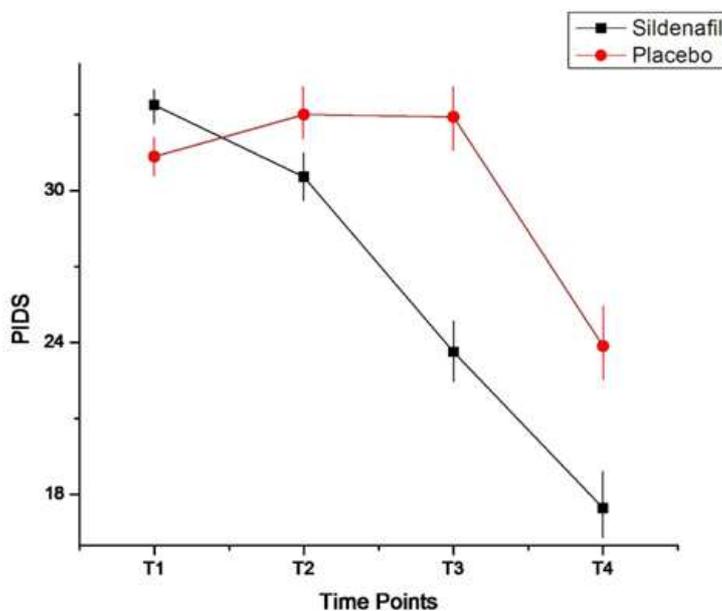


Fig. 4. Rebound trend of Positive Inotropic Drug Score (PIDS) in both study groups at each time point T1, before treatment; T2, 1 h after treatment; T3, 1 day after treatment; T4, after patient was taken off ventilator

The representations of the PIDS showed an obvious difference between the two groups. The sildenafil group showed a decrease soon after treatment and maintained this trend. The value of the placebo group initially increased and then began to decline from T1, but the final value was higher than that of the sildenafil group. There were statistically

significant differences between the two groups at each time point ($p < 0.001$, Table 6). A repeated measure ANOVA determined that the PIDS of the sildenafil group differed significantly between time points ($p < 0.001$), but that of the placebo group did not at T1, T2 and T3 ($p > 0.05$). This indicated that sildenafil group needed fewer positive inotropic drugs to

maintain their hemodynamic stability than the placebo group did (Fig. 4). The patients in the sildenafil group spent less time on the mechanical ventilation and extubated earlier than those in the placebo group did (44.25 ± 13.39 vs. 67.52 ± 16.88 h, $p = 0.001$).

Discussion

Cyanotic congenital heart disease accounts for 25% of all congenital heart diseases, which commonly includes TOF, severe pulmonary stenosis or atresia, transposition of The Great Arteries (TGA), tricuspid atresia and DORV with pulmonary stenosis (Patra *et al.*, 2014; Baig *et al.*, 2014). Patients with these conditions could develop cyanosis immediately after birth, which further affects the growth and development of the children because of hypoxia. Furthermore, critical patients could die because of the severe hypoxemia and heart failure (Kaulitz *et al.*, 2001).

Surgery is the main treatment for cyanotic congenital heart disease while pulmonary artery hypoplasia is a major indicator of the required surgical procedure method and prognosis prediction (Agnoletti *et al.*, 2004). Presently, most surgeons still use the McGoon ratio and Nakata index to evaluate the development of pulmonary vasculature. A McGoon ratio ≥ 1.2 and Nakata index $\geq 150 \text{ mm}^2/\text{m}^2$ suggest that the development of pulmonary small vessels is acceptable and a radical procedure is generally recognized as safe (Liu *et al.*, 2006). However, a McGoon ratio < 1.0 and Nakata index $< 120 \text{ mm}^2/\text{m}^2$ indicates that there is an existing severe pulmonary hypoplasia. Patients with this condition require staged procedures. In our study, the preoperative McGoon ratio and Nakata index were between two standard-radical and staged procedures. Therefore, it was difficult to accurately determine the development of pulmonary arteries, which could lead to the occurrence of hypoxemia and cardiac insufficiency after the operation.

The factors influencing the McGoon ratio and Nakata index during measurement and calculation are the operators' experience and technical background as well as possible interference from the acoustic window or lung gas. When echocardiography is performed to observe the degree of pulmonary artery development, certain errors may occur in the calculated result. Furthermore, differences in the body surface areas and associated diseases of patients also affect the data. The body-pulmonary collateral vessels may also complicate the source of the blood supply to the pulmonary vascular bed and cause an uneven development of the entire pulmonary vasculature. Therefore, it is possible that the distal pulmonary vascular developmental issues could be more serious than initially anticipated (Agnoletti *et al.*, 2004). The selection of inappropriate surgical methods and opportunities by surgeons based on such unanticipated complications is associated with an

increased risk of postoperative hypoxemia and heart failure. However, there is currently no better strategy for ensuring the accuracy of the preoperative evaluation of the development of the distal pulmonary vasculature than the McGoon ratio and Nakata index.

In general, we thought that the postoperative hypoxemia developed because of the decreased right ventricular systolic function following the incision of the right ventricular outflow tract, which likely damaged the integrity. Therefore, the pulmonary blood flow decreased and the ventilation/perfusion ratio was unbalanced. When hypoxemia occurred, we instituted appropriate measures to increase FiO_2 , which were the administration of additional drugs such as adrenaline and milrinone, the addition of colloids such as albumin and the enhancement of diuresis. Because vasodilator drugs such as nitroglycerin and sodium nitroprusside have poor selectivity, they can reduce the pulmonary vascular resistance while reducing the systemic resistance and may cause the blood pressure to drop. Therefore, this conventional treatment worked slowly and the effect was inadequate. This could lead to the extension of the mechanical ventilation time, which could cause complications such as pulmonary infection, the need for a tracheotomy, low cardiac output syndrome and death (Poonam *et al.*, 2013). There was one death in the placebo group, which occurred because of severe low cardiac output syndrome during the study period.

Hall *et al.* (2000; 2002) discovered that due to severe pulmonary stenosis or atresia, long-term low blood flow and hypoxia could cause small pulmonary artery in the medium to develop disuse atrophy, which decreased the number of units of small pulmonary arteries in the area. We thought that failure to surgically repair the pulmonary stenosis or atresia could lead to the increased pulmonary blood flow not matching the development of the pulmonary vascular bed. Furthermore, the resulting blood flow overload would lead to increased pulmonary vascular resistance and ventilation/perfusion ratio imbalance. Moreover, the incision performed on the right ventricular outflow tract and the resulting integrity damage likely decreased the right ventricular systolic function. These factors could lead to hypoxemia and cardiac dysfunction. In addition, we found that when the preoperative McGoon ratio and Nakata index were in accord with the standard of the radical procedure, the patients recovered smoothly after the operation. Moreover, this observation proved that the adequate development of the pulmonary artery and lower pulmonary vascular resistance would ensure that hypoxemia seldom occurs.

PDE-5 is the main PDE in pulmonary vascular, which hydrolyzes intracellular cGMP. Sildenafil is a highly selective PDE-5 inhibitor that prevents the hydrolysis of cGMP, thereby increasing its intracellular concentration and the associated pulmonary artery dilation, which reduces the pulmonary vascular

resistance (Simoneau *et al.*, 2002). Yang *et al.* (2014) found that sildenafil increases the smooth muscle gap junction protein, which reshapes the pulmonary artery.

Our study found that patients administered conventional treatment required more positive inotropic drugs to increase the right ventricular preload and pulmonary blood flow to maintain hemodynamic stability than those on sildenafil did. Furthermore, the respiratory and heart functions recovered slowly while sildenafil enhanced the rapid recovery of these functions by reducing the pulmonary vascular resistance and right ventricular after load. Therefore, fewer positive inotropic drugs were required to maintain the hemodynamic stability. The patients in the sildenafil group spent less time on mechanical ventilation and exhibited a reduced occurrence of pulmonary complications.

Comments

This study describes an innovative use of Sildenafil, but further evaluation of the potential side effects is required. The major side effects of sildenafil include headache, flushing, dyspepsia and abnormal vision. Data from previous studies has shown that some patients presented with serious hypotension when they combined sildenafil with nitrates. However, there is an ongoing argument on whether the use of sildenafil alone has effects on the systolic blood pressure. Leuchte *et al.* (2014) successively investigated 10 patients with primary PH administered oral sildenafil to evaluate their acute hemodynamic response during right-heart catheterization. The study considered that 50-100 mg sildenafil could reduce the pulmonary artery pressure without reducing the systemic pressure (Leuchte *et al.*, 2004). Ghofrani *et al.* (2003) observed patients taking oral sildenafil for a prolonged time and found that their pulmonary arterial pressure decreased and simultaneously, the systemic average arterial pressure dropped from the original 92.8 to 80.6 mmHg. In our study, patients did not exhibit a significant decrease in systolic blood pressure or serious adverse drug effects. This confirmed the safety of sildenafil for the treatment of PH.

Conclusion

Sildenafil effectively reduced the pulmonary artery resistance and had no significant effects on the peripheral arteries. Therefore, in patients with cyanotic congenital heart disease who develop postoperative hypoxemia with high resistance and do not benefit from the effect of conventional treatment, sildenafil can be considered as a treatment option. Furthermore, its use in these patients can reduce pulmonary artery resistance, improve the oxygenation of the lungs and relieve the symptoms of heart failure.

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Author's Contributions

Zhou Jiawang: Designed the research plan, participated in all experiments and contributed to the writing of the manuscript.

Lv Yong: Participated in all experiments and contributed to the writing of the manuscript.

Hu Zhendong: Organized the study and participated in all experiments.

Qiu Zongli: Coordinated the data-analysis.

Peng Ran and Xue Yibai: Coordinated the data-analysis and contributed to the writing of the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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