Oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in children

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Abstract

Objective: Sildenafil is a strong pulmonary vasodilator that increases the intracellular cyclic guanosine monophosphate concentration through inhibition of phosphodiesterase-5. We assessed the benefit of oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in paediatric patients. Methods: Sildenafil was administered at a starting dose of 0.5 mg kg⁻¹ following admission to the intensive care unit. With careful monitoring of haemodynamics, the dose was increased stepwise by 0.5 mg kg⁻¹ every 4–6 h up to a maximum of 2 mg kg⁻¹. After successful weaning from a ventilator and from other vasodilators, sildenafil was gradually discontinued over the next 5–7 days. Results: A retrospective review of medical records showed an age distribution of <1 month (n = 26), ≥1 – <6 months (n = 36), ≥6 – <12 months (n = 19), 1–3 years (n = 8), 4–9 years (n = 9) and >10 years (n = 2) at the time of surgery. The surgeries were performed for ventricular septal defect closure (n = 17), arterial switch (n = 30), truncus arteriosus repair (n = 10), complete atrioventricular septal defect repair (n = 12), total anomalous venous drainage repair (n = 9), and other open-heart surgery (n = 22). The aforementioned concomitant inhaled nitrous oxide treatment was performed in 66 patients. Pulmonary arterial pressure decreased in 28, was unchanged in five and elevated in one patient out of the total of 34 cases for which data from continuous pressure monitoring were available. Bosentan was added in three cases with persistent symptoms due to pulmonary hypertension despite sildenafil treatment. After sildenafil administration, modest oxygen desaturation occurred in seven cases, but no ‘rebound’ pulmonary hypertension occurred. There were no significant adverse events during sildenafil treatment. Conclusions: Our results suggest that oral sildenafil is a safe and effective alternate for persistent pulmonary hypertension following congenital heart surgery in children.

Keywords: Cardiac surgery; Congenital cardiac anomaly; Pulmonary hypertension; Sildenafil

1. Background

Severe pulmonary excess flow or marginal growth of the pulmonary artery often causes impairment of the pulmonary circulation early after congenital cardiac surgery. The resultant elevated vascular resistance may lead to pulmonary hypertension (PH), which is a major cause of postoperative morbidity [1,2]. Endothelial dysfunction during and following cardiopulmonary bypass [3,4] may have deleterious effects on the pulmonary circulation, which may explain the limited efficacy for this type of PH of endothelium-dependent intravenous vasodilator therapy with nitroglycerine or prostaglandins. Therefore, endothelium-independent pulmonary vasodilators may be indicated to treat persistent PH early after congenital surgery. At present, two such vasodilators are available: inhaled nitric oxide and sildenafil.

Inhaled nitric oxide (iNO) involves direct nitric oxide delivery to medial smooth muscle of the pulmonary artery, which enhances local cyclic guanosine monophosphate (cGMP) production independent of endothelial cells. In infants and children with severe PH early after congenital heart surgery, iNO reduces pulmonary artery (PA) pressure without altering systemic haemodynamic parameters [5,6]. iNO has been used as the first-line therapy for severe PH in the intensive care unit (ICU) after congenital cardiac surgery, even though ‘rebound’ PH may occur after discontinuation of iNO, with elevation of PA pressure, hypoxia and haemodynamic instability in some cases [7,8].

Sildenafil citrate (Revatio® and Viagra®; Pfizer Japan, Tokyo, Japan) has been used to treat various types of PH [9–14]. Sildenafil produces a strong pulmonary vasodilative response by increasing the intracellular cGMP concentration.
through inhibition of phosphodiesterase-5 (PDE5), an enzyme that degrades cGMP [11,12,15]. The limited number of studies of sildenafil for postoperative PH following paediatric heart surgery appears to suggest that sildenafil ameliorates this condition in paediatric patients [9,12,16—18]. Therefore, this open-label and one-arm cohort study aimed to assess the effects of sildenafil in the treatment of persistent severe PH early after congenital cardiac surgery in a relatively large heterogeneous sample of paediatric patients.

2. Patients and methods

2.1. Operative procedures

All operations were performed under general anaesthesia with modified neuroleptanaesthesia (NLA; intravenous fentanyl and midazolam). During cardiopulmonary bypass (CPB), the flow rate was maintained at 150 ml min⁻¹ kg⁻¹ with mild to moderate hypothermia. Deep hypothermic arrest was not used. When necessary, the heart was arrested using intermittent cold-blood cardioplegia. Modified ultrafiltration was used after discontinuation of CPB. A pressure-monitoring catheter was directly inserted into the main PA via the free wall of the right ventricular (RV) outflow, depending on the surgeon’s preference. Following admission to the ICU, all patients were routinely sedated using a combination of midazolam, morphine and dexmedetomidine, and an optimal sedation level was maintained. Patients who required delayed chest closure were paralysed with a combination of fentanyl, midazolam and vecuronium. After delayed chest closure, the patients were sedated with the routine sedatives listed above. All patients were ventilated with partial pressure of arterial oxygen (PaO₂) maintained at 100—120 mmHg and partial pressure of arterial carbon dioxide (PaCO₂) at 35—45 mmHg. Hyperventilation with an excess high inspiratory concentration of oxygen was not used as a first-line treatment for postoperative PH. Intravenous dopamine (3—10 µg kg⁻¹ min⁻¹) and milrinone (0.25—0.75 µg kg⁻¹ min⁻¹) were used for haemodynamic management. Adrenaline (0.05—1 µg kg⁻¹ min⁻¹) was added when necessary. In patients without a PA pressure-monitoring catheter who showed PH-related symptoms (haemodynamic instability, hypoxaemia, elevated central venous pressure, etc.), PH was confirmed as elevated systolic RV pressure by estimation from the shape of the interventricular septum or using standard equations from the peak instantaneous echocardiographic Doppler-derived pressure difference between simultaneous measurements of the systolic RV pressure and the central venous pressure when measurable tricuspid regurgitation existed.

2.2. Indication for sildenafil treatment

Following an equilibrium period after ICU admission, patients meeting one of the following five criteria for PH were considered to be eligible for sildenafil treatment as follows from (A) to (E). (A) Severe PH occurred with PA pressure constantly being more than half of the systemic pressure or frequently equal to or more than the systemic pressure with oxygen desaturation and/or haemodynamic instability despite use of iNO or other intravenous vasodilators. (B) PH was well managed by iNO. To prevent rebound PH at the time of extubation and iNO discontinuation, iNO was replaced with sildenafil prior to weaning from the ventilator, with prophylactic use of sildenafil for rebound PH. (C) Sildenafil was administered as a first-line therapy instead of iNO when severe PH occurred. (D) When ‘rebound’ severe PH occurred after withdrawal of iNO or new onset of PH after weaning from a ventilator but the patient’s respiration was well maintained, re-intubation was avoided for commencement of iNO. (E) In the case of right-heart bypass surgery (bidirectional cavopulmonary shunt and Fontan-type operation), the transpulmonary pressure gradient was elevated >10 mmHg with haemodynamic instability and desaturation although this condition did not meet the definition of pure pulmonary arterial hypertension due to excess pulmonary blood flow. The transpulmonary pressure gradient was calculated using the mean central venous pressure, which is equivalent to the mean PA pressure minus the mean left atrial pressure, and is a good clinical indicator of the pulmonary circulation in right heart bypass surgery. A gradient of >10 mmHg with haemodynamic instability indicates deterioration of the pulmonary circulation.

2.3. Protocol

Following informed consent from parents or guardians, sildenafil was administered via a nasogastric tube or orally at a starting dose of 0.5 mg kg⁻¹ (Fig. 1). The dose of sildenafil was increased stepwise by 0.5 mg kg⁻¹ every 4—6 h up to a maximum dose of 2 mg kg⁻¹ with careful haemodynamic monitoring. After successful weaning from a ventilator, sildenafil was gradually reduced and discontinued over the next 5—7 days. This protocol was approved by the Human Ethics Committee for clinical trials at the Osaka Medical College Hospital, Osaka, Japan.

2.4. Outcome measures

The efficacy of sildenafil therapy on postoperative PH was evaluated based on the decrease in PA pressure, prevention of severe PH crisis (elevation of PA pressure equal to or more than blood pressure with haemodynamic instability), prevention of rebound PH after withdrawal of iNO and uneventful weaning from iNO and other intravenous vasodilators. Evaluation of the safety of sildenafil was based on changes in oxygenation and systemic haemodynamic parameters and other adverse events.

Fig. 1. Protocol for oral sildenafil administration for persistent postoperative pulmonary hypertension in paediatric patients. Each dose was given via a nasogastric tube or orally after obtaining consent from parents or guardians.
2.5. Statistics

Pressure data are expressed as mean ± standard deviation. Time-series comparison of systolic PA pressure, transpulmonary pressure gradient and mean blood pressure were performed using the paired t-test. Values of <0.05 were considered statistically significant.

2.6. Characteristics of the patients

Sildenafil was administered to 100 patients with postoperative PH between October 2003 and March 2008. A total of 818 paediatric open-heart surgeries were performed during the study period. Operative and in-hospital mortality comprised 17 cases during this period. There was no operative death in the sildenafil-treated cases. The age distribution of the sildenafil-treated patients is shown in Fig. 2: 62% were in early infancy (under 6 months) and 81% were younger than 1 year of age. The surgeries performed are listed in Table 1. An arterial switch operation was the most common procedure in which sildenafil was used after surgery (30 out of 51), followed by ventricular septal defect closure (17 out of 99), atrioventricular defect repair (12 out of 18), truncus arteriosus repair (10 out of 15) and total anomalous pulmonary drainage repair (9 out of 21). The numbers in the parenthesis indicate numbers of cases treated with sildenafil divided by the numbers of cases operated up on in the study period. The high incidence of Down’s syndrome patients treated with sildenafil was noted as being 16 out of 17 cases of ventricular septal defect closure and 11 cases out of 12 cases of atrioventricular defect repair. There were no residual lesions such as left-to-right shunt and pulmonary venous obstruction found in intra-operative transoesophageal echocardiography. Intravenous vasodilators, such as prostaglandin E1 or nitroglycerine, were used initially in 10 patients and iNO was given prior to sildenafil in 66 cases. Among the 66 cases, sildenafil was administered in 61 cases for indication (A), four cases for indication (B), 28 cases for indication (C) and two cases for indication (D) as previously described in the section on indications. Sildenafil was also administered in five cases following right heart bypass surgery for indication (E) as bidirectional cavopulmonary shunt (4 out of 11) and Fontan-type operation (1 out of 9; the definition of the numbers in the parenthesis is as described above).

3. Results

3.1. Effects of sildenafil on pulmonary circulation

Changes in the systolic PA pressure from before sildenafil treatment until 6 h after reaching the maximum dose of sildenafil are shown in Fig. 3a in 34 cases for which data from

![Number of patients](image)

*Fig. 2. Age distribution of the patients (n = 100).*

<table>
<thead>
<tr>
<th>Operation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial switch</td>
<td>30</td>
</tr>
<tr>
<td>VSD closure</td>
<td>17</td>
</tr>
<tr>
<td>AVSD repair</td>
<td>12</td>
</tr>
<tr>
<td>Truncus arteriosus repair</td>
<td>10</td>
</tr>
<tr>
<td>TAPVD repair</td>
<td>9</td>
</tr>
<tr>
<td>Other biventricular repair</td>
<td>17</td>
</tr>
<tr>
<td>Bidirectional cavopulmonary shunt</td>
<td>4</td>
</tr>
<tr>
<td>Fontan completion</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

VSD, ventricular septal defect; AVSD, atrioventricular defect; TAPVD, total anomalous venous drainage.

![mmHg](image)

*Fig. 3. Changes in systolic pulmonary arterial pressure before and after sildenafil treatment. (a) Individual data of the 34 cases in whom continuous pulmonary arterial (PA) pressure monitoring was available throughout the ICU stay. White open circle: data before sildenafil (SIL) administration; black closed circle: data at 6 h after reaching the maximum dose of sildenafil administration. (b) Overall change in systolic pulmonary arterial pressure before and after sildenafil treatment.*
Continuous PA pressure monitoring were available with a good wave-trace throughout the ICU stay. Overall, the systolic PA pressure was significantly decreased following sildenafil treatment from 51.8 ± 12.7 to 36.1 ± 11.8 mmHg (p < 0.05; Fig. 3b). Although PA pressure decreased in 28 of the 34 cases (82.4%), the change in PA pressure was modest or almost zero in five cases, but severe PH with haemodynamic instability disappeared after sildenafil treatment in all five of these cases. PA pressure was elevated despite iNO and sildenafil administration in one patient with severe respiratory distress who required further treatment with an endothelin-1 receptor blocker, as discussed below. Although it was difficult to collect summarised RV pressure data estimated by echocardiography because of its subjective nature compared to direct PA measurement, PH-related symptoms regressed after sildenafil administration in other patients without continuous PA-pressure tracing.

Changes in the transpulmonary pressure gradient prior to and following sildenafil administration in the five cases of right heart bypass surgery (bidirectional cavopulmonary shunt and Fontan-type operation) are shown in Fig. 4a. This gradient was significantly reduced after sildenafil administration from 14.8 ± 4.0 mmHg to 7.2 ± 2.2 mmHg (p < 0.05; Fig. 4b).

We encountered three cases that had sustained PH-related symptoms despite receiving sildenafil treatment. The demographic data for these patients are presented in Table 2. Following bosentan, a dual endothelin-receptor blocker, was added at a dose of 1.5 mg kg⁻¹ per day, the symptoms were relieved and sildenafil was discontinued without difficulty. No patient experienced rebound PH after withdrawal of iNO and other intravenous vasodilators during sildenafil administration. Sildenafil treatment was successfully completed in all cases and no rebound PH was found by echocardiography after discontinuation of sildenafil.

3.2. Effects of sildenafil on systemic haemodynamic parameters and oxygenation

Overall, mean blood pressure increased significantly from 59.6 ± 11.1 mmHg before sildenafil administration to 64.2 ± 12.2 mmHg 6 h after reaching the maximum dose of sildenafil (p < 0.05). There were 10 cases in which blood pressure significantly decreased from 65.7 ± 10.9 mmHg to 57.9 ± 9.0 mmHg (p < 0.05), but the change was modest: a mean change of −7.2 ± 5.8%. Heart rate was unchanged throughout the period of sildenafil therapy.

3.3. Effects of sildenafil on oxygenation

Mild oxygen desaturation was clinically noticed during sildenafil treatment in seven cases (there were no standardised parameters such as alveolar-arterial partial oxygen difference to express oxygenation). All patients who showed decreased oxygen saturation had either lobar atelectasis or pneumonia. Oxygen saturation improved in all patients after improvement of the lung lobar lesions, even during sildenafil treatment.

3.4. Adverse events during and after sildenafil treatment

The only adverse event was facial flush, which occurred temporarily in five cases.

Fig. 4. Changes in the postoperative transpulmonary pressure gradient (TPG). TPG normalized after administration of oral sildenafil in all right heart bypass surgeries. (a) Individual data of the five cases. (b) Overall change in TPG before and after sildenafil treatment TPG (mmHg) was calculated as mean PAP — mean CAP, where the mean PAP (pulmonary arterial pressure) is equivalent to the pressure of the superior vena cava and the mean CAP (common atrial pressure) is equivalent to the pressure of the inferior vena cava. BCPS: bidirectional cavopulmonary shunt. TCPC: total cavopulmonary connection.

Table 2
Demographic data for patients treated with bosentan, an endothelin-1 dual receptor blocker, for sustained PH-related symptoms despite treatment with oral sildenafil.

<table>
<thead>
<tr>
<th>Age</th>
<th>Operation</th>
<th>Down syndrome</th>
<th>Pre-op PVR (Wood unit m²)</th>
<th>Severe PH</th>
<th>iNO</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months</td>
<td>VSD closure</td>
<td>Yes</td>
<td>8.4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4 months</td>
<td>AVSD repair</td>
<td>Yes</td>
<td>3.8</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>15 days</td>
<td>Truncus arteriosus repair</td>
<td>No</td>
<td>N/A</td>
<td>Yes*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VSD, ventricular septal defect; AVSD, atrioventricular defect; OP, operation; PVR, pulmonary vascular resistance; PH, pulmonary hypertension; iNO, Inhaled nitric oxide.

* Severe respiratory distress (+).
4. Discussion

There are three major findings in this study. First, oral sildenafil reduced PA pressure and prevented severe PH, leading to haemodynamic instability and oxygen desaturation that accompanied an abrupt increase in PA or central venous pressure. Second, oral sildenafil had no adverse influence on systemic haemodynamic parameters such as blood pressure and heart rate. Although oxygen saturation decreased in seven cases after the maximum dose of sildenafil (2 mg kg$^{-1}$) was given, the change was modest and normalised after lung lobes (atelectasis or pneumonia) improved. There was no major adverse event during and after sildenafil treatment. Third, PH-related symptoms persisted in three out of 100 cases despite sildenafil treatment.

We explored the literature to find the appropriate dosage of oral sildenafil for treatment of PH in children. However, there are currently no suggested regimens of sildenafil supported by pharmacokinetic data in critically ill children. Therefore, the timing and dose of oral sildenafil used in the study were based on previous reports [13,14] and pharmacokinetic data in healthy adults provided by Pfizer Japan. These data show that enteral sildenafil is very well absorbed and that the maximum plasma concentration is reached within 1 h of administration. The subsequent elimination half-life is between 3 and 4 h. Our dose range for oral sildenafil for postoperative PH was similar to a previously suggested dose [18] and is, therefore, at least partly clinically reproducible.

The current study provides evidence of the efficacy of sildenafil for lowering elevated PA pressure and preventing crisis in the postoperative course of congenital cardiac surgery. This adds to the findings in two previous randomised control trials [9,16]. Our sample size was relatively large and the operative procedures and age of the patients were more heterogeneous compared to those in the earlier trials [9,16]. However, beneficial effects of sildenafil were seen in a large percentage of our patients over a range of ages (neonate to school age) and after various types of surgery. The mechanism of impaired pulmonary circulation after right heart bypass surgery may differ from that following biventricular repair for left—right shunt defects. However, oral sildenafil reduced the transpulmonary pressure gradient in this and a previous report [19] which suggests that sildenafil is a strong and comprehensive pulmonary vasodilator irrespective of the nature of the impairment of the pulmonary circulation. Oral sildenafil appears to be as effective as iNO for normalising the pulmonary circulation after congenital cardiac surgery using CPB and may be an alternative to iNO-mediated enhancement of tissue and serum cGMP.

Sildenafil could solve several disadvantages of inhaled NO. First, although NO can be delivered to patients through an endotracheal tube and a specially designed nasal cannula, an appropriate scavenging system for harmful oxidants is also required. In contrast, with sildenafil there is no need for a special delivery system. Second, discontinuation of iNO often causes acute deterioration of the pulmonary circulation, leading to haemodynamic instability; the so-called ‘rebound’ effect [8,16], which often results in a requirement for resumption of iNO and an extended ICU stay. Rebound of PH did not occur after discontinuation of sildenafil in this study and has not been reported in the literature. Down-regulation of endogenous NO production by inhibition of NO synthase activity [20] and increased levels of plasma endothelin-1 [21] are considered to play a major role in the mechanism of rebound of PH following iNO withdrawal. In this context, sildenafil has been reported to facilitate withdrawal of iNO and prevent rebound PH in paediatric patients in weaning from iNO after congenital cardiac surgery [16]. In other words, pharmacological prophylaxis of rebound PH was achieved by oral sildenafil, as we also found in this study. The pharmacokinetic profile of sildenafil may be effective in balancing the changes in endogenous nitric oxide synthetase activity and intrinsic cGMP production that occur during weaning from iNO.

We found that Down’s syndrome patients were the majority of the sildenafil-treated cases in ventricular septal defect closure and atroventricular defect repair (27 out of 29) and sildenafil failed to relieve PH-related symptoms in two infants with Down’s syndrome. It is well known that the small PA is susceptible to high pressure in Down’s syndrome and that histological changes develop rapidly and severely at an earlier age, resulting in intimal and medial hypertrophy and eventually leading to vascular obstruction [22]. It is thought that endothelin-1 (ET-1) plays a major role in the proliferative changes of the PA in PH, through strong induction of proliferation, inflammation and vasoconstriction in arterioles [23]. In addition to the pathophysiological changes, persistently higher plasma circulating ET-1 levels after CPB have been shown to correlate significantly with a high incidence of postoperative acute PH crises in patients with Down’s syndrome, presumably because of strong vasoconstriction due to ET-1 compared to patients without Down’s syndrome [24]. These findings suggest that antagonism of ET-1 by bosentan may be useful as concomitant therapy with pulmonary vasodilation for enhancement of serum and local cGMP for postoperative severe PH in some infants with Down’s syndrome.

There are two limitations in this study. First, one difficulty with sildenafil is that absorption of the drug depends on the condition of the digestive system, which makes the plasma concentration unpredictable immediately after surgery. Therefore, in our protocol, sildenafil was administered in stepwise dose increments with careful monitoring of haemodynamics and adverse events. We observed no side effects after sildenafil administration. A large dose-finding and pharmacokinetic study of sildenafil in children with PH due to congenital heart disease is needed to validate the safety and efficacy of the dose range and interval used in this study and elsewhere [18].

Second, since this study was performed as a one-arm cohort trial and retrospectively reviewed, it is unclear whether the reduction in PA pressure and prevention of severe PH were induced by sildenafil or were part of the natural postoperative course in cardiac surgery. It also remains unclear whether the effects on systemic haemodynamics and oxygenation found in this study were directly associated with sildenafil because many other factors could have influenced haemodynamic and respiratory parameters in the early postoperative period. To answer this question, a large, multicentre, randomised controlled trial is warranted.
to validate the efficacy of sildenafil in comparison with placebo or other vasodilators. At present, two randomised control studies with small samples sizes were published and have shown a similar acute reduction in PA pressure and no significant influence on systemic haemodynamics and oxyge-

have shown a similar acute reduction in PA pressure and no

placebo or other vasodilators. At present, two randomised


[10] Leuchte HH, Schwaiblmair M, Baumgartner RA, Neurohr CF, Kolbe T, Behr 


[7] Miller OI, Tsang SF, Keech A, Celermajer DS. Rebound pulmonary hyper-


We thank Kaoru Suzuki, Department of Pharmacy, Osaka Medical College Hospital, for preparation of oral sildenafil.

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Appendix A. Conference discussion

Dr A. Bogers (Rotterdam, Netherlands): This presentation and the accompanying manuscript claim to assess the benefit of oral sildenafil for persistent pulmonary hypertension early after congenital cardiac surgery in paediatric patients. One hundred patients are included and divided into six age groups.

You conclude that oral sildenafil treatment in this regard is safe, simple, and effective, but in your manuscript you give the advice that careful long-term follow-up should be continued, and a double-blind clinical trial should be conducted.

I’m not sure that you can keep up these conclusions, and I have at this time three items to comment on. The first one is on methodology. No data are provided on the selection of patients and the background population, and no data are provided on the decision tree to start sildenafil. Sixty-six patients in your group were already treated with nitric oxide, and only 34 patients, you state in your manuscript, got continuous pulmonary artery pressure measurement. No difference was made between rebound pulmonary artery hypertension, pulmonary vascular reactivity, or persistent pulmonary hypertension in the indications for treatment. Moreover, sildenafil treatment was given, as you showed us, in five patients with either PCP or TPCC who definitely do not meet the inclusion criteria for this study. It seems that a retrospective description is made of your clinical experience and not a systematic clinical trial. Could you elaborate on this and demonstrate to us your inclusion criteria to start with?

The second question is on pharmacology. Take-up and effect of medication through the gastrointestinal system early after surgery may be unpredictable and differs in different age groups. No pharmacological data studies are provided in your manuscript or in your presentation. Do you think that your data validate your conclusions in this regard, and do they comply with the standards of pharmacological studies?

And the third one is on clinical practice, especially postoperative care. You did not include a control population, therefore, you cannot exclude that observations on the regular postoperative course are being made in your study. And, therefore, you cannot exclude that your sildenafil treatment is overtreatment that may be not necessary but still results in prolonged length of stay. Can you comment on this possible overtreatment?

Dr Nemoto: First of all, regarding inclusion criteria of sildenafil. Maybe I need to say that in the conclusion, because we didn’t bring objective scientific methods and more precise criteria such as, let’s say, if you use inhaled nitric oxide, wait 6 hours, then give sildenafil, those kind of things. We don’t have these kind of clear criteria. This is maybe a kind of initial study to figure out those kind of criteria. That’s what the first step.

Secondly, regarding pharmacology. There were so many difficulties in obtaining data; we even asked the company, but no definitive data was available. Therefore, what we were able to do was just to review all the
published data. So that's why we finally reached this protocol. Fortunately, this protocol has already been used in some centers in Europe; it is like a prototype protocol.

And the third one is a question I always get from an audience, whether it is a natural cause or an effect of sildenafil. We still don't know. But the effect was clearly seen when we watched the pulmonary artery pressure. When we gave the maximum dose, maybe usually 1 to 3 hours, you see that the pressure comes down. And also, when patients woke up, we usually saw that the pulmonary pressure hit more than the blood pressure. But the phenomenon had gone after sildenafil administration.

That's why we believe that sildenafil is working okay, but we still need to have a double-blind study in the future.

Dr. Bogers: Are you going to do that?

Dr. Nemoto: Yes. I need to call colleagues in Japan, or maybe those kind of studies can be done in Europe I guess.

Dr. M. Danton (Glasgow, UK): Just to continue that question, I agree that the flaw of this study is the lack of control group, and because of that I think the conclusions are relatively meaningless. We have performed a similar, but randomized controlled study of sildenafil versus placebo administered preoperatively in a defined patient group, those at risk of postoperative pulmonary hypertensive complications, i.e., those with high flow pulmonary circulations — AVSD. And whilst I am unable to expand on results at the moment, I think it’s important that you consider other parameters including ventricular function and oxygenation index. These indices have been reported in the literature to be adversely affected by the use of sildenafil.

Dr. Nemoto: That is a good comment. We already know, and there is a paper from the States, that in the hypertrophied right ventricle, the phosphodiesterease-5 increased leading to cAMP suppression. Then when they gave the sildenafil, those kind of phosphodiesterase-5 inhibition was working and led to cyclic GMP increment to pump up the right heart better. So that’s why we believe sildenafil works as a pulmonary vasodilator as well as an inotropic agent for the right ventricle.

Dr. Danton: I'm not implying that sildenafil has a positive effect on ventricular function.