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# Pulmonary vasoreactivity testing with inhaled iloprost in children with pulmonary hypertension related to congenital heart disease

## *Doğuştan kalp hastalığı ile ilişkili pulmoner hipertansiyonlu çocuklarda inhale iloprost ile pulmoner vazoreaktivite testi*

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***ABSTRACT***

***Background:*** This study aims to evaluate the acute hemodynamic effects of inhaled iloprost used to measure pulmonary vasoreactivity in congenital heart diseases with pulmonary hypertension.

***Methods:*** Between October 2005 and October 2012, a total of 51 patients (29 boys, 22 girls; mean age 4.9 years; range 4 months to 16 years) under follow-up with a diagnosis of pulmonary hypertension secondary to congenital heart disease who underwent vasoreactivity test with inhaled iloprost were retrospectively evaluated. Cardiac pressure and oxygen saturation values were obtained before and after iloprost inhalation, while flow ratio, pulmonary and systemic vascular resistances were calculated. A decrease greater than 10% in pulmonary vascular resistance, the mean pulmonary artery pressure, and resistance ratio were considered as positive responses to the vasoreactivity test.

***Results:*** Forty-four patients (86.3%) had ventricular septal defect, atrial septal defect, patent ductus arteriosus, and atrioventricular septal defect, while seven patients (23.7%) had complex heart diseases. Forty-two (82.4%) of the patients had positive vasoreactivity test results. In positive vasoreactivity test patients, the pre- and post-iloprost mean pulmonary artery pressure values were 59.7±13.4 mmHg and 53.3±13.7 mmHg ($p<0.05$), pulmonary vascular resistance was 12.2±7.6 Wood U/m$^2$ and 6.6±6 Wood U/m$^2$ ($p<0.05$), resistance ratio was (PVR/SVR) 0.6±0.5 and 0.3±0.3 ($p<0.05$), pulmonary flow (Qp) was 3.6±3.2 l/min and 7.2±9.6 l/min ($p<0.05$), flow ratio was (Qp/Qs) 2.3±1.5 and 6±4.8 ($p<0.05$), arterial oxygen saturation was 83.6% and 94.4% ($p<0.05$), respectively. None of the patients had any side effects associated with inhaled iloprost.

***Conclusion:*** Inhaled iloprost may be a good option as an effective and safe drug for pulmonary vasoreactivity testing in pediatric patients.

***Keywords:*** Inhaled iloprost; pulmonary hypertension; vasoreactivity testing.

***ÖZ***

***Amaç:*** Bu çalışmada pulmoner hipertansiyonlu doğumsal kalp hastalıklarında pulmoner vazoreaktiviteyi ölçmek amacıyla kullanılan inhale iloprostun akut hemodinamik etkileri değerlendirildi.

***Çalışma planı:*** Ekim 2005 - Ekim 2012 tarihleri arasında doğuştan kalp hastalığına sekonder pulmoner hipertansiyon tanısıyla izlenen ve inhale iloprost ile vazoreaktivite testi yapılan 51 hasta (29 erkek, 22 kız; ort. yaş 4.9 yıl; dağılım 4 ay-16 yıl) retrospektif olarak değerlendirildi. İnhale iloprost öncesi ve sonrasında kardiyak basınç ve oksijen satürasyon değerleri elde edildi; akım oranı, pulmoner ve sistemik vasküler dirençler hesaplandı. Pulmoner vasküler dirençte, pulmoner arter ortalama basıncında ve direnç oranında %10'dan fazla azalma olması vazoreaktivite testine pozitif yanıt olarak değerlendirildi.

***Bulgular:*** Hastaların 44'ünü (%86.3) ventriküler septal defekt, atriyal septal defekt, patent duktus arteriozus ve atriyoventriküler septal defekt oluştururken, yedisini (%23.7) kompleks kalp hastalıkları oluşturuyordu. Hastaların 42'sinde (%82.4) vazoreaktivite testi pozitif bulundu. Vazoreaktivite testi pozitif bulunan hastalarda iloprost öncesi ve sonrası ortalama pulmoner arter basınçları sırasıyla 59.7±13.4 mmHg ve 53.3±13.7 mmHg ($p<0.05$), pulmoner vasküler direnç 12.2±7.6 Wood U/m$^2$ ve 6.6±6 Wood U/m$^2$ ($p<0.05$), dirençler oranı (PVR/SVR) 0.6±0.5 ve 0.3±0.3 ($p<0.05$), pulmoner akım (Qp) 3.6±3.2 l/dk. ve 7.2±9.6 l/dk. ($p<0.05$), akımlar oranı (Qp/Qs) 2.3±1.5 ve 6±4.8 ($p<0.05$), arter oksijen satürasyonu ise %83.6 ve %94.4 ($p<0.05$) idi. Hastaların hiç birinde inhale iloprost ile ilişkili yan etki görülmedi.

***Sonuç:*** Çocuk hastalarda pulmoner vazoreaktivite testinde inhale iloprost etkili ve güvenilir bir ilaç olarak iyi bir seçenek olabilir.

***Anahtar sözcükler:*** İnhale iloprost; pulmoner hipertansiyon; vazoreaktivite testi.

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Pulmonary arterial hypertension (PAH) rarely occurs in childhood, even in patients with congenital heart disease. It is a complex disorder with various etiologies according to the 2003 Venice Clinical Classification of Pulmonary Hypertension.[1] Pulmonary arterial hypertension is defined as having an elevated mean pulmonary artery pressure (mPAP) of more than 25 mmHg at rest, a normal pulmonary capillary wedge pressure (less than 15 mmHg) and a pulmonary vascular resistance (PVR) of more than 3 Wood units (WU).[2,3] One of the most common complications in congenital heart disease (CHD) is PAH because it causes a significant increase in morbidity and mortality and greatly affects the quality of life (QoL) in the affected individuals.

Pulmonary arterial hypertension is related to CHD, which used to be the most common form of PAH in children. However, the incidence rate of this disease has declined over the last decade due to early access to treatment and advances in congenital heart surgery. Unfortunately, patients with congenital heart diseases are exposed to long-term pulmonary hypertension, which can lead to pulmonary vascular disorders in countries with a poor socioeconomic status because of late access to treatment. Assessing pulmonary vasoreactivity remains an important tool for evaluating the pulmonary vascular beds as it helps to determine the best treatment option and prognosis.[4,5]

The aim of this study was to evaluate the acute hemodynamic effects of inhaled iloprost that was used to measure pulmonary vasoreactivity in congenital heart diseases in patients with pulmonary hypertension.

## PATIENTS AND METHODS

A total of 51 patients (29 boys and 22 girls; mean age 4.9 years; range 4 months-16 years) who were followed up at the Pediatric Cardiology Department of Dr. Sami Ulus Maternity and Pediatrics Training and Research Hospital between October 2005 and October 2012 and who were given a pulmonary vasoreactivity test with inhaled iloprost (Ventavis®, Bayer Healthcare Pharmaceuticals, Madrid, Spain) due to a diagnosis of pulmonary hypertension secondary to congenital heart disease were included in this study. The data from the patients' files and the cardiac catheterization findings were used in the evaluation process. Half an hour before the procedure, each patient was sedated with a cardiac cocktail (chlorpromazine, pethidine, and pheniramine), and then the femoral vein and artery were penetrated using vascular sheaths according to the age and body weight of the patient under local anesthesia. Both right and left heart catheterization and angiography were performed, but no additional oxygen was administered during the vasoreactivity test.

The inhaled iloprost (0.5 mcg/kg) was given for 10 minutes using a facial mask, and an OMRON NE-C28 CompAIR Nebulizer (OMRON Healthcare, Inc., Lake Forest, IL, USA) was used to administer the drug via 3 μm particles during the vasoreactivity test. The hemodynamic measurements were repeated 10 minutes after the inhalation was completed, and the right atrium, left atrium and/or pulmonary capillary wedge pressures, pulmonary artery pressure (PAP), and systolic, diastolic and mean aortic pressures were recorded before and after inhaling the iloprost. Cardiac output (CO) was measured by applying the Fick principle.[6] The pulmonary vascular resistance (PVR) was calculated as the mPAP - the pulmonary wedge pressure (PCWP)/CO, and the systemic vascular resistance (SVR) was calculated as the mean systemic blood pressure (SBP) - the right atrial pressure/CO. A 10% decrease in the mPAP, PVR and PVR/SVR ratio after iloprost administration compared to the pre-iloprost values indicated a positive response to the test.[7,8] In addition, the patients were followed up for any possible side effects for a period of 24 hours after they inhaled the iloprost.

### Statistical analysis

Statistical analyses were performed using the SPSS version 16.0 software program (SPSS Inc., Chicago, IL, USA). The patient distribution was normal, and a paired samples t-test was used to compare the pre- and post-treatment mean values. A $p$ value of $<0.05$ were considered to be statistically significant.

## RESULTS

In terms of concomitant heart diseases, 19 patients (37.3%) had a ventricular septal defect (VSD), five (9.8%) had a VSD and an atrial septal defect (ASD), three (5.9%) had VSD and patent ductus arteriosus (PDA), five (9.8%) had PDA, and 12 (23.5%) had an atrioventricular septal defect (AVSD). In addition, six others (11.8%) had cyanotic heart disease and one (2%) had an aortopulmonary window (Table 1).

Among the 30 patients who underwent surgery, eight (26.6%) had persistent pulmonary hypertension during the postoperative period. Four of the eight were girls, and four were boys, and the mean age of these eight patients was 8.3±5.1 years (range 1-15 years). Four of these patients received treatment with inhaled iloprost while the other four received treatment with both inhaled iloprost and bosentan. The patients were followed up for a mean duration of 23.9±19.7 months,

**Table 1. Distribution of diagnoses among patients who underwent a vasoreactivity test**

| Diagnosis | n | % |
|---|---|---|
| Ventricular septal defect | 19 | 37.3 |
| Ventricular septal defect + atrial septal defect | 5 | 9.8 |
| Ventricular septal defect + patent ductus arteriosus | 3 | 5.9 |
| Patent ductus arteriosus | 5 | 9.8 |
| Atrioventricular septal defect | 12 | 23.5 |
| Aortopulmonary window | 1 | 2 |
| Transposition of the great arteries, ventricular septal defect, and patent ductus arteriosus | 2 | 3.8 |
| Truncus arteriosus type 1 + ventricular septal defect | 1 | 1.95 |
| Truncus arteriosus type 2 + ventricular septal defect | 1 | 1.95 |
| Double outlet right ventricle + patent ductus arteriosus | 1 | 1.95 |
| Double inlet right ventricle, ventricular septal defect, and hypoplastic right ventricle | 1 | 1.95 |
| *Total* | 51 | 100 |

and the PAP returned to normal values with medical treatment in three of the patients, whereas in the other five, the PAP was lower but did not return to normal values.

The patients' baseline hemodynamic parameters and their responses to the inhaled iloprost are shown in Table 2 and Figures 1-4. Forty-two (82.4%) of the patients had a positive response to the iloprost inhalation test and the pre- and post-iloprost values for those were as follows respectively: mPAP values of 59.7±13.4 mmHg and 53.3±13.7 mmHg ($p<0.05$), PVR of 12.2±7.6 Wood U/m$^2$ and 6.6±6 Wood U/m$^2$ ($p<0.05$), a PVR/SVR ratio of 0.6±0.5 and 0.3±0.3 ($p<0.05$), a Qp of 3.6±3.2 l/min and 7.2±9.6 l/min ($p<0.05$), a Qp/Qs ratio of 2.3±1.5 and 6±4.8 ($p<0.05$), and an aortic oxygen saturation rate of 83.6±16% and 94.4±5% ($p<0.05$.

Among the patients who had no response to the iloprost inhalation test, the pre- and post-iloprost values for those were as follows respectively: mPAP values of 63.3±16.9 mmHg and 67.9±20.9 mmHg, PVR of 12.2±4.3 Wood U/m$^2$ and 14.3±6 Wood U/m$^2$, a PVR/SVR ratio of 1±0.6 and 0.8±0.5, a Qp of 3.3±1.9 l/min and 3.3±1.6 l/min, a flow ratio of 1.2±0.5 and 1.6±0.7, and an aortic oxygen saturation rate of 87.8±7.3% and 98±1.2%. Six of the boys and three of the girls were deemed to be unsuitable candidates for surgery, and their mean age was 5.1±4.7 years (range 6 months-13 years). In addition, six patients were diagnosed with VSD, three with AVSD, and one with truncus arteriosus. Anti-pulmonary hypertension medicines were initiated for these pateints, and follow-up was started. Furthermore, they were also scheduled to undergo catheter angiography.

For 30 of the 42 patients in our study, we made the decision that surgery was necessary, and this successfully corrected the congenital heart defects. All of these patients had a PVR of <6 Wood U/m$^2$ and an Rp/Rs ratio of <0.3 as well as a positive response to the vasoreactivity test.

**Table 2. Hemodynamic parameters before and after the vasoreactivity test**

| | Positive vasoreactivity | | | Negative vasoreactivity | | |
|---|---|---|---|---|---|---|
| | Pre-iloprost | Post-iloprost | | Pre-iloprost | Post-iloprost | |
| | Mean±SD | Mean±SD | *p* | Mean±SD | Mean±SD | *p* |
| Mean PAP (mmHg) | 59.7±13.4 | 53.3±13.7 | <0.05 | 63.3±16.9 | 67.9±20.9 | >0.05 |
| Systolic PAP (mmHg) | 83.2±16.2 | 77±15.4 | <0.05 | 83.5±13.4 | 83±15.6 | >0.05 |
| Diastolic PAP (mmHg) | 40.8±15.6 | 34.2±16 | <0.05 | 40.4±11.9 | 41±16.6 | >0.05 |
| PVR (Wood U/m$^2$) | 12.2±7.6 | 6.6±6 | <0.05 | 12.2±4.3 | 14.3±6 | >0.05 |
| PVR/SVR | 0.6±0.5 | 0.3±0.3 | <0.05 | 1±0.6 | 0.8±0.5 | >0.05 |
| Qp (l/min) | 3.6±3.2 | 7.2±9.6 | <0.05 | 3.3±1.9 | 3.3±1.6 | >0.05 |
| Qp/Qs | 2.3±1.5 | 6±4.8 | <0.05 | 1.2±0.5 | 1.6±0.7 | >0.05 |
| Arterial oxygen saturation | 83.6±16 | 94.4±5 | <0.05 | 87.8±7.3 | 98±1.2 | >0.05 |

Pre: Preoperative; Post: Postoperative; SD: Standard deviation; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance; Qp: Pulmonary blood flow; Qs: Systemic blood flow ratio.

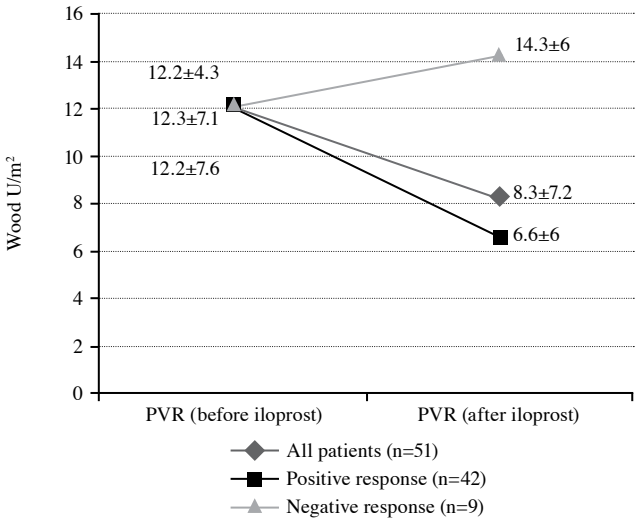


**Figure 1.** Distribution of the patient's pulmonary vascular resistance (PVR) values before and after iloprost inhalation.

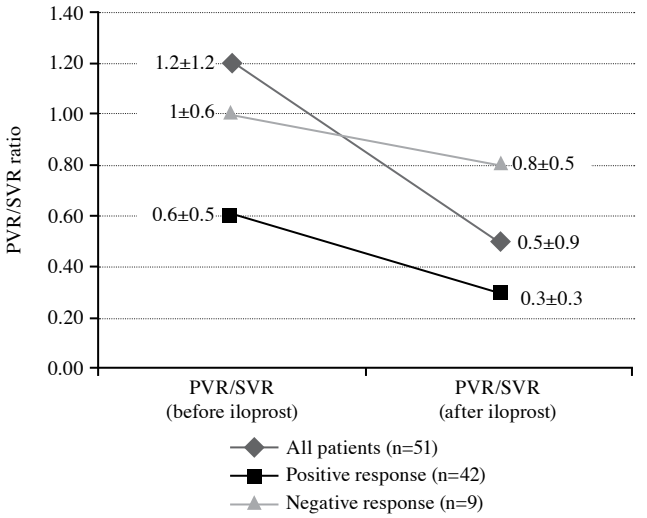


**Figure 2.** Distribution of the patients' pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) ratios before and after iloprost inhalation.

The patients were followed for 24 hours after the administration of the inhaled iloprost, and no side effects were observed.

## DISCUSSION

Pulmonary hypertension is a complex, multidisciplinary disorder characterized by abnormally high pulmonary vascular pressure, and it is usually idiopathic in adults. In developing countries like Turkey, pediatric patients without access to surgery are exposed to long-term pulmonary hypertension. Consequently, pulmonary vascular disease develops in these patients. Thus, cardiologists are faced with a tough decision regarding whether surgery is necessary for patients with suspected pulmonary vascular disease, and pulmonary vasoreactivity remains an important tool for evaluating the pulmonary vascular beds because it helps define the best treatment option and prognosis.

The 2009 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PAH in adults state that the vasoreactivity test should be used to detect patients who are likely to benefit from long-term treatment with calcium channel blockers.[2]

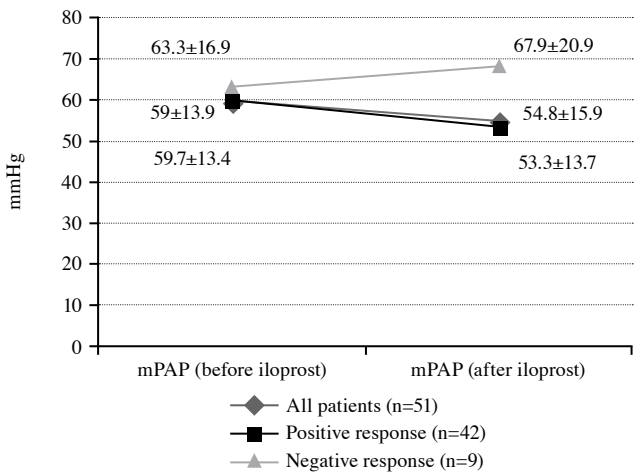


**Figure 3.** Distribution of the patients' mean pulmonary artery pressure (mPAP) values before and after iloprost inhalation.

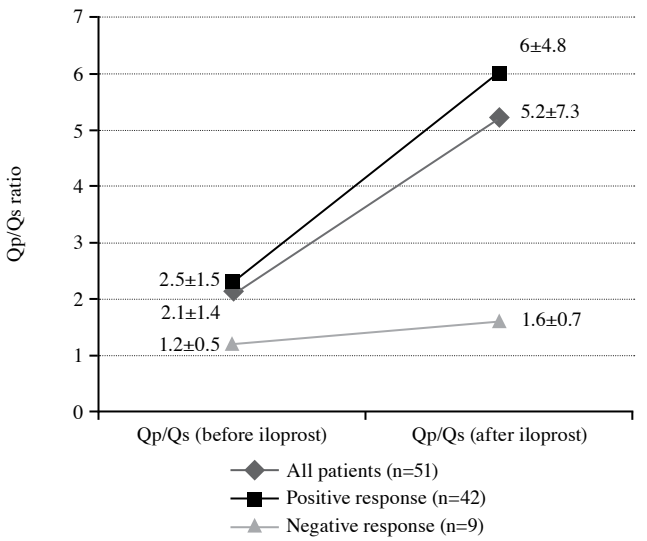


**Figure 4.** Distribution of the patients' pulmonary blood flow (Qp)/systemic blood flow (Qs) ratios before and after iloprost.

The rationale for pulmonary vasoreactivity testing in children with PAH is associated with two issues: management options and prognosis. This test evaluates the operability of the cardiac lesion in children with severe PAH secondary to CHD and can also predict whether a postoperative pulmonary hypertensive crisis is likely to show a favorable response to a pharmacological agent.[4] If the vasoreactivity test is positive when right heart catheterization is performed and if the hemodynamic parameters are convenient, the patient should undergo surgery before the development of pulmonary vascular obstructive disease.[9,10]

The agent used for the vasoreactivity test should be short-acting and safe, provide ease of use, and have limited or no systemic effects. These agents should be specific to the pulmonary vessels and have a rapid onset and offset of action. Oxygen, inhaled nitric oxide (iNO), inhaled iloprost, intravenous (i.v.) adenosine, and i.v. prostacyclin can be used for this purpose,[4,11] but oxygen and iNO are most commonly used in children.[2,12] In patients with CHD, pure oxygen is initially used for pulmonary vasoreactivity testing because it is readily available and easy to administer. Although oxygen has been widely used to assess pulmonary vasoreactivity in children with CHD, dissolved oxygen must be taken into account in order to avoid false positive results. The disadvantages of i.v. prostacyclin include the need for vascular access, systemic side effects, hypotension, and gas-exchange disturbances while i.v. adenosine has a rapid onset of action that can lead to systemic hypotension as well as bradycardia. Furthermore, iNO has been demonstrated to be an effective pulmonary vasodilator in children.[13] Moreover, Balzer et al.[14] showed an increased rate of sensitivity in defining the candidates for corrective surgery with the combination of oxygen and iNO, and although iNO is a commonly used agent, it may cause rebound pulmonary hypertension in some cases. Thus, as an alternative to iNO, the use of inhaled iloprost has increased in recent years,[15,16] and many centers have started using it for vasoreactivity testing, particularly in adult patients. For example, a recent study by Jing et al.[17] showed for the first time that aerosolized iloprost could be used for pulmonary vasoreactivity testing, and Opitz et al.[18] found that inhaled iloprost demonstrates pulmonary selectivity in contrast to intravenous prostacyclin. In addition, it was found to be a more potent pulmonary vasodilator than iNO in studies conducted on adults.[19,20] Hoeper et al.[19] also used inhaled iloprost for pulmonary vasoreactivity testing. However, there are only a limited number of relevant studies that have focused on the use of this agent in pediatric patients.[4,7,12,17]

Iloprost is a selective, short-acting vasodilator and a prostacyclin analogue with a stable structure. It has a half-life of 20-30 minutes and is readily available in many countries. Furthermore, it is an inexpensive, unlike iNO. The most common side effects of iloprost are coughing, headaches, flushing, and jaw pain,[21] but rashes and bronchoconstriction have also been reported in a few cases.[22-24] The primary rationale for using this agent instead of iNO is that it offers a comparable clinical effect while also being cheaper, and it can be more easily administered. Thus, inhaled iloprost is more likely to be used in poorer countries. Moreover, iNO therapy is not available in many countries.

The definition of a "positive" response is debatable. Diagnosis and treatment guidelines of the cardiology societies in Europe and the United States define it as a decrease of 10 mmHg or more in mPAP values in the setting of increased or stable cardiac output plus an absolute PAP value of 40 mmHg or less.[2,3] The supporting rationale for this definition is based on the clinical outcomes of a retrospective analysis by Badesch et al.[3] in which 557 patients were treated with high-dose calcium channel blockers. However, these guidelines can only be applied to adults. No guidelines currently exist for pediatric patients. Several parameters have been used as the criteria for vasoreactivity test positivity in various studies.[2,7,8,16,25] Berner et al.[8] used the simultaneous decrease of more than 10% in PVR and the PVR/SVR ratio while Rosenzweig et al.[16] added more specific criteria to define positivity among children with idiopathic PAH by including an mPAP of 40 mmHg or less and a decrease of at least 20% in the PVR index. In our study, positivity required a decrease of 10% in the PVR and the PVR/SVR ratio, which yielded a positive response to the pulmonary vasoreactivity testing in 42 of the 51 patients.

In the studies by Bush et al.[26] and Limsuwan et al.,[7] the decision regarding whether or not to operate on children with severe PAH was based on an actual PVR value of less than 6 Wood U/m$^2$ or a pulmonary-systemic resistance ratio of less than 0.3 following the acute vasodilator test. Furthermore, Balzer et al.[14] used an Rp/Rs ratio of less than 0.33 and a 20% decrease in this ratio compared with the baseline as the criteria for operability in their preoperative study group for iNO.

According to various studies in this field, a consensus has been reached to perform surgical correction in patients with a PVR of <6 Wood U/m$^2$ and a PVR/SVR ratio of <0.3.[7,26] In our study, 41 patients had a positive response to the vasoreactivity test;

however, only the 30 whose PVR and PVR/SVR ratios agreed with this consensus were scheduled for surgery. Limsuwan et al.[7] found that 13 out of 22 pediactric patients with congenital heart disease in conjunction with severe pulmonary hypertension and left-right shunt had a positive response to inhaled iloprost vasoreactivity testing, and they reported persistent pulmonary hypertension in two of these patients during the postoperative period. After the corrective surgery was performed on 30 of our patients, persistent pulmonary hypertension was observed in only eight of them postoperatively. In addition, none experienced a hypertensive crisis and all of them survived.

No adverse effects have been reported when inhaled iloprost has been used for vasoreactivity testing.[12,27] In a study that featured both pediatric and adult patients, i.v. adenosine and inhaled iloprost were used for vasoreactivity testing in patients with idiopathic pulmonary hypertension. While non-inferiority was shown for both agents in terms of efficacy, the iloprost was found to be safer with regard to side effects. In fact, only two out of the 74 patients in the study had side effects (a cough and hypotension) that could be attributed to this agent,[17] and in our study, no adverse effects were associated with iloprost.

Our study was retrospective in nature and was performed at a single center with a small cohort. Therefore, we were not able to compare the efficacy of inhaled iloprost with other drugs. In addition, the duration of the postoperative follow-up was insufficient. Therefore, we recommend that a prospective, multi-center clinical study with a larger sample size be conducted to verify our findings.

### Conclusion

Pulmonary vasoreactivity testing is an important tool that can be used to assess the pulmonary vascular bed in pediatric patients with pulmonary hypertension, and it can aid in determining the best treatment option. While various vasodilator agents have been used for pulmonary vasoreactivity testing in children, we would like to emphasize that iloprost, which has been highlighted in many recent studies, is probably the best option because of its rapid onset and offset of action, selectivity for the pulmonary bed, and good safety profile with limited side effects.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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## REFERENCES

1. Gabbay E, Yeow W, Playford D. Pulmonary arterial hypertension is an uncommon cause of pulmonary hypertension in an unselected population: the Armadale echocardiography study. Am J Respir Crit Care Med 2007:175;A713.
2. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493-537.
3. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:35S-62.
4. Limsuwan A, Khowsathit P. Assessment of pulmonary vasoreactivity in children with pulmonary hypertension. Curr Opin Pediatr 2009;21:594-9.
5. Friedman WF. Proceedings of National Heart, Lung, and Blood Institute pediatric cardiology workshop: pulmonary hypertension. Pediatr Res 1986;20:811-24.
6. Friedman WF. Proceedings of National Heart, Lung, and Blood Institute pediatric cardiology workshop: pulmonary hypertension. Pediatr Res 1986;20:811-24.
7. Limsuwan A, Khosithseth A, Wanichkul S, Khowsathit P. Aerosolized iloprost for pulmonary vasoreactivity testing in children with long-standing pulmonary hypertension related to congenital heart disease. Catheter Cardiovasc Interv 2009;73:98-104.
8. Berner M, Beghetti M, Spahr-Schopfer I, Oberhansli I, Friedli B. Inhaled nitric oxide to test the vasodilator capacity of the pulmonary vascular bed in children with long-standing pulmonary hypertension and congenital heart disease. Am J Cardiol 1996;77:532-5.
9. Blackstone EH, Kirklin JW, Bradley EL, DuShane JW, Appelbaum A. Opitmal age and results in repair of large ventricular septal defects. J Thorac Cardiovasc Surg 1976;72:661-79.
10. Friedli B, Kidd BS, Mustard WT, Keith JD. Ventricular septal defect with increased pulmonary vascular resistance. Late results of surgical closure. Am J Cardiol 1974;33:403-9.
11. Ghofrani HA, Wilkins MW, Rich S. Uncertainties in the diagnosis and treatment of pulmonary arterial hypertension. Circulation 2008;118:1195-201.
12. Gorenflo M, Bettendorf M, Brockmeier K, Ulmer HE. Pulmonary vasoreactivity and vasoactive mediators in children with pulmonary hypertension. Z Kardiol 2000;89:1000-8.
13. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers

in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.
14. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, et al. Inhaled Nitric Oxide as a Preoperative Test (INOP Test I): the INOP Test Study Group. Circulation 2002;106:I76-81.
15. Rimensberger PC, Spahr-Schopfer I, Berner M, Jaeggi E, Kalangos A, Friedli B, et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation 2001;103:544-8.
16. Rosenzweig EB, Morse JH, Knowles JA, Chada KK, Khan AM, Roberts KE, et al. Clinical implications of determining BMPR2 mutation status in a large cohort of children and adults with pulmonary arterial hypertension. J Heart Lung Transplant 2008;27:668-74.
17. Jing ZC, Jiang X, Han ZY, Xu XQ, Wang Y, Wu Y, et al. Iloprost for pulmonary vasodilator testing in idiopathic pulmonary arterial hypertension. Eur Respir J 2009;33:1354-60.
18. Opitz CF, Wensel R, Bettmann M, Schaffarczyk R, Linscheid M, Hetzer R, et al. Assessment of the vasodilator response in primary pulmonary hypertension. Comparing prostacyclin and iloprost administered by either infusion or inhalation. Eur Heart J 2003;24:356-65.
19. Hoeper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. J Am Coll Cardiol. 2000;35:176-82.
20. Leuchte HH, Schwaiblmair M, Baumgartner RA, Neurohr CF, Kolbe T, Behr J. Hemodynamic response to sildenafil, nitric oxide, and iloprost in primary pulmonary hypertension. Chest 2004;125:580-6.
21. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.
22. Olschewski H, Rohde B, Behr J, Ewert R, Gessler T, Ghofrani HA, et al. Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension. Chest 2003;124:1294-304.
23. Feito Rodríguez M, Floristan U, de Lucas Laguna R. A curious but non-serious local side effect of inhaled iloprost: sudden linear erythematous facial rash. Clin Exp Dermatol 2009;34:1014.
24. Ivy DD, Doran AK, Smith KJ, Mallory GB Jr, Beghetti M, Barst RJ, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol. 2008;51:161-9.
25. Oliveira EC, Amaral CF, Moura MA, Campos FT, Pauperio HM. Testing pulmonary vasoreactivity. J Bras Pneumo 2008;34:838-44.
26. Bush A, Busst CM, Haworth SG, Hislop AA, Knight WB, Corrin B, et al. Correlations of lung morphology, pulmonary vascular resistance, and outcome in children with congenital heart disease. Br Heart J 1988;59:480-5.
27. Zhang HL, Liu ZH, Wang Y, Xiong CM, Ni XH, He JG, et al. Acute responses to inhalation of Iloprost in patients with pulmonary hypertension. Chin Med J (Engl) 2012;125:2826-31.