Trial Occlusion to Assess the Risk of Persistent Pulmonary Arterial Hypertension After Closure of a Large Patent Ductus Arteriosus in Adolescents and Adults With Elevated Pulmonary Artery Pressure

Duan-zhen Zhang, MD; Xian-yang Zhu, MD; Bei Lv, MD; Chun-sheng Cui, MD; Xiu-min Han, MD; Xiao-tang Sheng, MD; Qi-guang Wang, MD; Po Zhang, MD

Background—No method is available to predict whether patients with patent ductus arteriosus (PDA) and severe pulmonary arterial hypertension (PAH) will show persistent postprocedural PAH (PP-PAH) after PDA closure. This study evaluated the usefulness of trial occlusion for predicting PP-PAH after transcatheter PDA closure in patients with severe PAH.

Methods and Results—Trial occlusion was performed in 137 patients (age ≥12 years) with PDA and severe PAH. All patients undergoing trial occlusion had a mean pulmonary artery pressure ≥245 mm Hg, pulmonary:systemic flow (Qp/Qs) ratio >1.5, and pulmonary:systemic resistance (Rp/Rs) ratio <0.7. A total of 135 patients (98%) showing stable hemodynamics during occlusion trial underwent successful device closure. Linear correlation analysis revealed weak or moderate relationships between the baseline and post-trial pulmonary artery pressures and pulmonary:systemic pressure (Pp/Ps) ratios. Patients were followed up for 1 to 10 years (median: 5 years). PP-PAH (systolic pulmonary artery pressure >50 mm Hg by Doppler echocardiography) was detected in 17 patients (13%), who displayed no significant differences in sex and age compared with patients without PP-PAH. According to discriminant analysis, the strongest discriminators between patients with and without PP-PAH were the baseline left ventricular end-diastolic volume and the baseline and post-trial systolic Pp/Ps ratios. In particular, a post-trial systolic Pp/Ps ratio >0.5 correctly classified 100% of the PP-PAH and non-PAH patients.

Conclusions—Trial occlusion is a feasible method to predict PP-PAH in patients with PDA and severe PAH. A post-trial systolic Pp/Ps ratio >0.5 indicates a high risk of PP-PAH occurrence after device closure. (Circ Cardiovasc Interv. 2014;7:473-481.)

Key Words: ductus arteriosus, patent ▪ hypertension, pulmonary

The outcomes of defect closure in patients with congenital heart defects (CHDs) associated with pulmonary arterial hypertension (PAH) depend on the reversibility of pulmonary vascular changes. In the early, flow-dependent stage of PAH, closure of the shunt will normalize the shunt-induced PAH. Long-term systemic-to-pulmonary shunting may lead to irreversible pulmonary vascular changes because of prolonged exposure to high pulmonary pressure and increased flow. Once PAH develops into a bidirectional shunt, it can be difficult to decide whether the shunt should be closed. If the pulmonary vascular changes become irreversible, then the defect can function as a safety valve for unloading the right ventricle. In such cases, defect closure can lead to an increased mortality risk and a prognosis similar to that among patients with idiopathic PAH. However, the survival rate of patients with CHD-associated PAH is much higher than that of patients with idiopathic PAH. This fact underscores the importance of accurate decision making on operability in patients with CHDs and high pulmonary vascular resistance (PVR).

At present, no sufficiently sensitive and specific method is available for determining who will respond favorably to defect closure. Accordingly, physicians often use various criteria and their own experiences to determine whether a patient is a suitable candidate for defect closure. However, postoperative PAH is not rare. Previously, pulmonary biopsy had been used as a gold standard to determine the reversibility of PAH-associated histological changes in small pulmonary vessels. Despite reports showing a good correlation of biopsy results with postoperative hemodynamic parameters, the predictive value of lung biopsies in determining operability is limited. Lesions may be unequally distributed within the lungs, and thus, the degree of pulmonary vascular disease may be misinterpreted.

Right heart catheterization (RHC) is a common and useful method to determine the hemodynamics of patients with CHDs and PAH. However, early studies in the catheter laboratory have failed to establish clear cut offs for operability. Moreover, researchers observed that the preoperative pulmonary:systemic flow (Qp/Qs) and pulmonary:systemic resistance (Rp/Rs) ratio concluded that the usefulness of trial occlusion for predicting PP-PAH after transcatheter PDA closure in patients with severe PAH.

Methods and Results—Trial occlusion was performed in 137 patients (age ≥12 years) with PDA and severe PAH. All patients undergoing trial occlusion had a mean pulmonary artery pressure ≥245 mm Hg, pulmonary:systemic flow (Qp/Qs) ratio >1.5, and pulmonary:systemic resistance (Rp/Rs) ratio <0.7. A total of 135 patients (98%) showing stable hemodynamics during occlusion trial underwent successful device closure. Linear correlation analysis revealed weak or moderate relationships between the baseline and post-trial pulmonary artery pressures and pulmonary:systemic pressure (Pp/Ps) ratios. Patients were followed up for 1 to 10 years (median: 5 years). PP-PAH (systolic pulmonary artery pressure >50 mm Hg by Doppler echocardiography) was detected in 17 patients (13%), who displayed no significant differences in sex and age compared with patients without PP-PAH. According to discriminant analysis, the strongest discriminators between patients with and without PP-PAH were the baseline left ventricular end-diastolic volume and the baseline and post-trial systolic Pp/Ps ratios. In particular, a post-trial systolic Pp/Ps ratio >0.5 correctly classified 100% of the PP-PAH and non-PAH patients.

Conclusions—Trial occlusion is a feasible method to predict PP-PAH in patients with PDA and severe PAH. A post-trial systolic Pp/Ps ratio >0.5 indicates a high risk of PP-PAH occurrence after device closure. (Circ Cardiovasc Interv. 2014;7:473-481.)

Key Words: ductus arteriosus, patent ▪ hypertension, pulmonary

The outcomes of defect closure in patients with congenital heart defects (CHDs) associated with pulmonary arterial hypertension (PAH) depend on the reversibility of pulmonary vascular changes. In the early, flow-dependent stage of PAH, closure of the shunt will normalize the shunt-induced PAH. Long-term systemic-to-pulmonary shunting may lead to irreversible pulmonary vascular changes because of prolonged exposure to high pulmonary pressure and increased flow. Once PAH develops into a bidirectional shunt, it can be difficult to decide whether the shunt should be closed. If the pulmonary vascular changes become irreversible, then the defect can function as a safety valve for unloading the right ventricle. In such cases, defect closure can lead to an increased mortality risk and a prognosis similar to that among patients with idiopathic PAH. However, the survival rate of patients with CHD-associated PAH is much higher than that of patients with idiopathic PAH. This fact underscores the importance of accurate decision making on operability in patients with CHDs and high pulmonary vascular resistance (PVR).

At present, no sufficiently sensitive and specific method is available for determining who will respond favorably to defect closure. Accordingly, physicians often use various criteria and their own experiences to determine whether a patient is a suitable candidate for defect closure. However, postoperative PAH is not rare. Previously, pulmonary biopsy had been used as a gold standard to determine the reversibility of PAH-associated histological changes in small pulmonary vessels. Despite reports showing a good correlation of biopsy results with postoperative hemodynamic parameters, the predictive value of lung biopsies in determining operability is limited. Lesions may be unequally distributed within the lungs, and thus, the degree of pulmonary vascular disease may be misinterpreted.

Right heart catheterization (RHC) is a common and useful method to determine the hemodynamics of patients with CHDs and PAH. However, early studies in the catheter laboratory have failed to establish clear cut offs for operability. Moreover, researchers observed that the preoperative pulmonary:systemic flow (Qp/Qs) and pulmonary:systemic resistance (Rp/Rs) ratio concluded that...
WHAT IS KNOWN

- There is no accurate method of determining whether patients with patent ductus arteriosus and severe pulmonary arterial hypertension (PAH) will show persistent postprocedural PAH after patent ductus arteriosus closure.
- The predictive value of lung biopsies in determining the success rate of defect closure is limited because of the unequal distribution of lesions in such patients.
- Right heart catheterization is a common and useful method for measuring hemodynamics in patients with congenital heart disease and PAH. However, preoperative pulmonary vascular resistance and pulmonary systolic/systemic flow and resistance ratios do not predict operative outcomes.

WHAT THE STUDY ADDS

- This study evaluated the usefulness of trial occlusion for identifying patients at high risk of persistent postprocedural PAH in patients with severe PAH undergoing transcatheter closure of the patent ductus arteriosus.
- This study suggests that a post-trial occlusion systolic pulmonary/systemic pressure ratio >0.5 may be a useful hemodynamic parameter for identifying patients with borderline PAH who have a high risk of postprocedural PAH after transcatheter patent ductus arteriosus closure.

resistance (Rp/Rs) ratios were not useful for predicting operative outcomes; instead, the PVR was the most reliable index of hemodynamics. Recent international consensus statements have recommended acute vasodilator testing as an important component when evaluating patients with PAH. Unfortunately, there is no evidence on the usefulness of such tests in predicting the response of the PAH to therapy at many centers. In patients with a large PDA, the patent ductus arteriosus (PDA) has become the first-choice defect closure.

Methods

Patient Population

This retrospective cohort study included consecutive patients aged ≥12 years with isolated PDA and severe PAH who were referred to the authors' institution for transcatheter device closure between January 2004 and March 2013. Severe PAH was defined as mean pulmonary artery pressure (PAP) ≥45 mm Hg, as measured by cardiac catheterization. The following exclusion criteria were applied: (1) PDA complicated with other CHDs, primary valvarular diseases, or identifiable causes for pulmonary hypertension, including pulmonary thromboembolic disease, acquired immune deficiency syndrome, portal hypertension, sleep apnea syndrome, and obstructive pulmonary disease; (2) a left ventricular (LV) ejection fraction <50% and pulmonary capillary wedge pressure >15 mm Hg before device closure; (3) a calculated Qp/Qs ratio ≤1.5 and Rp/Rs ratio >0.7 in patients with borderline PAH; and (4) treatment with PAH medications, including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, or prostacyclins, before device closure. Because ketamine can influence pulmonary hemodynamics, and as the individual response to it varies, patients who underwent cardiac catheterization under general anesthesia were also excluded from this study.

Echocardiographic Examination

Echocardiographers performed all of the echocardiographic examinations on a Philips iE33 system (Andover, MA). Comprehensive trans-thoracic echocardiograms, including M-mode, 2-dimensional, and Doppler echocardiograms, were obtained each time. The LV end-systolic and end-diastolic volumes were measured using M-mode echocardiograms on the parasternal long axis. This technique is observer independent, and patients with isolated PDA do not have regional LV wall motion abnormalities. The LV end-diastolic and end-systolic volumes were standardized by the body surface area, providing the LV end-diastolic-volume index (EDVI) and end-systolic-volume index, respectively. LV ejection fraction was calculated.

Procedure

The study was approved by the local institutional ethics committee. All patients or their parents/guardians signed appropriate informed consent forms for cardiac catheterization and trial occlusion before the procedure. The catheterization procedure was performed under local anesthesia. The heart rate, cardiac rhythm, and pulse oxygen saturation were continuously monitored during the procedure. Access was through the right femoral vein and the right femoral artery. Heparin (100 IU/kg) was administered intravenously after the vein and artery were cannulated.

Before trial occlusion, RHC was performed to determine whether device closure was indicated. Blood gas analysis was performed at each site. The pulmonary capillary wedge pressure and pressures at each cardiac chamber and great artery were measured. The oxygen content was calculated from the hemoglobin concentration and oxygen saturation. Oxygen consumption was estimated from the patient’s age and body surface area. Cardiac output was measured with Fick method, and the Qp/Qs ratio, PVR, and systemic vascular resistance were calculated with standard formulas.

As patients with a Qp/Qs ratio ≤1.5 were excluded, vasodilator testing was not performed before or after device closure. Descending aortography was performed in the lateral and right anterior oblique views with a 6F pigtail catheter (Cordis, Miami, FL) to define the PDA anatomy. The diameter at the pulmonary and aortic ends and the length of the PDA were measured. The duct size was described according to the diameter at the pulmonary end. The device chosen for closure had a diameter at the aortic end that was twice the duct diameter.

Two types of occluders (Shanghai Shape Memory Alloy Ltd, China) were used: a duct occluder and a muscular ventricular septal defect occluder. Both devices have been approved by the China Food and Drug Administration for the treatment of CHD. The muscular ventricular septal defect occluder was used to close the large tubular and window-like PDA. The designs of these 2 types of devices have been described in detail in previous reports. The device was placed into the PDA.
while still attached to the cable. The PAP and aortic pressure (AP) were continuously measured by saline-filled catheters until the device was released. The device was withdrawn if (1) the patient had symptoms (eg, chest pain, shortness of breath), (2) the AP decreased more than the PAP did after device placement, or (3) device closure did not result in decreased PAP compared with before device placement.

Descending aortography was repeated 5 to 15 minutes after device placement. The post-trial residual shunt was classified as follows (as described by Gamboa et al): trace, if the contrast was slightly opaque at the ductal pulmonary end; mild, if the pulmonary artery was stained without outlining its valve; and moderate, if the whole valvular plane was outlined. The PAP and AP were recorded, and the device was released only when the PDA was closed without shunt or with trace shunt.

Follow-Up
Patients underwent serial follow-up examinations at 24 hours, 3, 6, and 12 months, and then yearly after the procedure. Follow-up studies included clinical examination, ECG, and transthoracic echocardiogram. In patients with suspected clinical or echocardiographic signs of PAH, the tricuspid regurgitation peak velocity was measured by continuous wave Doppler echocardiography. The peak pressure gradient between the right ventricle and right atrium was calculated with the simplified Bernoulli equation, as $4v^2 +$ right atrial pressure. The velocities in the tricuspid regurgitant jet were obtained from the apical 4-chamber view. Postprocedural PAH was defined as a calculated systolic PAP $\geq 50$ mm Hg.

Statistical Analysis
Data were expressed as the frequency (n) or percentage (%) for categorical variables and as the mean±SD for continuous variables. The pulmonary:systemic artery pressure (Pp/Ps) ratio was calculated as PAP/AP. Statistical analyses were performed with the SPSS 15.0 software package. A 2-sided $P<0.05$ was considered statistically significant.

Differences in PAP and the Pp/Ps ratio between baseline and post-trial occlusion were compared with paired Student $t$ test. Correlation analyses were conducted to assess the strength and magnitude of the linear relationship, and simple linear regressions were used to find the best-fit line between the baseline and post-trial PAPs and the Pp/Ps ratios. According to the follow-up outcomes, patients were divided into 2 groups: patients without (non-PAH group) and patients with (PAH group) PP-PAH. Qualitative data were compared between groups by the $\chi^2$ test, and continuous data were compared by independent $t$ test.

Linear discriminant analysis was used to generate 2 predictive models of PP-PAH. The first model was generated from the linear combination of the patient age, PDA size, baseline ventricular size and function, and baseline hemodynamic parameter values that were different between groups by Student $t$ test. The second model was generated from the linear combination of the post-trial PAP, post-trial Pp/Ps ratio, and the postcatheterization ventricular size and function. Linear discriminant analysis was performed by the Fisher method. To identify the strongest discriminators and the cut off points in predictive variables for PP-PAH, stepwise linear discriminate analysis was performed with an $F$ value entry probability of 0.05 and removal probability of 0.10.

Results

Baseline Characteristics
Of the 718 patients aged $\geq 12$ years undergoing attempted transcatheter closure of PDA, 147 patients had mean PAP $\geq 45$ mm Hg and a Qp/Qs ratio $>1.5$. Ten were excluded because of general anesthesia use (n=1), combined atrial septal defect (n=2), combined ventricular septal defect (n=6), or treatment with PAH medication before the procedure (n=1). Finally, 137 patients (24 men; age range, 12–60 years) were recruited into this study.

The baseline characteristics of the recruited patients are summarized in Table 1. Of the 137 patients, 23 had severe heart failure (New York Heart Association grade III and IV in 19 and 4 patients, respectively) at admission. After treatment with intravenous diuretics and inotropic agents, the cardiac function was restored to grade New York Heart Association I or II before cardiac catheterization. LV ejection fraction $>50\%$ and pulmonary capillary wedge pressure $\leq 15$ mm Hg were observed in all patients. RHC showed that the minimum Qp/Qs ratio was 1.51, and the maximum Rp/Rs ratio was 0.65.

Procedural Details
The average diameter of the PDAs was $10\pm 3$ mm. The devices used for trial occlusion were duct occluders (n=122) and muscular ventricular septal defect occluders (n=15), with sizes of $21\pm 3$ mm and $23\pm 4$ mm, respectively. During the procedure, no cases of thromboembolic disease because of device retrieval, flow obstruction by the devices in the left pulmonary artery or descending thoracic aorta, recurrent laryngeal nerve injury after device closure, or death were observed.

Two patients failed to pass the trial occlusion. The first patient, with a PDA diameter of 11 mm had, a baseline Qp/Qs ratio of 1.53 and a baseline Rp/Rs ratio of 0.65. An 18-mm muscular ventricular septal defect occluder was used for trial occlusion. The PAP decreased from 98/56 mm Hg at baseline to 74/38 mm Hg 10 minutes after device closure. The patient complained of chest pain, and the aortic angiogram showed a marked residual shunt. In the second patient, the baseline Qp/Qs ratio was 1.54 and the Rp/Rs ratio was 0.51. After device deployment, she complained of shortness of breath. The AP decreased from 120/75 mm Hg at baseline to 70/50 mm Hg, and the heart rate decreased from 110 to 75 beats/min. In both cases, the devices were withdrawn immediately, and

Table 1. Baseline Characteristics of Patients Undergoing Cardiac Catheterization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female), n (%)</td>
<td>113 (82)</td>
</tr>
<tr>
<td>Age, y</td>
<td>31±14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>46±11</td>
</tr>
<tr>
<td>Heart function (New York Heart Association grade) at admission, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>81 (59)</td>
</tr>
<tr>
<td>II</td>
<td>33 (24)</td>
</tr>
<tr>
<td>III</td>
<td>19 (14)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Cardiotoracic ratio</td>
<td>0.62±0.06</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>67±7</td>
</tr>
<tr>
<td>Ductus size, mm</td>
<td>10±3</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg), 95% CI</td>
<td>68±14 (65–70)</td>
</tr>
<tr>
<td>Pulmonary:systemic flow ratio, 95% CI</td>
<td>2.34±0.78 (2.18–2.45)</td>
</tr>
<tr>
<td>Pulmonary:systemic vascular resistance ratio, 95% CI</td>
<td>0.34±0.11 (0.33–0.37)</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD. CI indicates confidence interval.
dopamine was infused. The AP returned to normal, and the procedures were ceased.

A total of 135 patients underwent successful trial occlusion and device closure. PDAs were completely closed in 110 patients and closed with trace residual shunt in 25 patients by 5 to 15 minutes after trial occlusion. After trial occlusion, the PAPs and the Pp/Ps ratios were markedly decreased (Table 2). Correlation analyses showed significant positive correlations between the baseline and post-trial PAPs and the Pp/Ps ratios, with correlation coefficients ranging from 0.413 to 0.641 (Figure 1).

Follow-Up Results

The median duration of follow-up after PDA closure was 5 years (range, 1–10 years). All patients underwent an echocardiographic examination at the last follow-up visit. No patient deaths occurred during the follow-up period. Tricuspid regurgitation was detected in all patients suspected of post-procedural PAH. A systolic PAP >50 mm Hg was detected by continuous wave Doppler ultrasound in 27 patients at 3 months postprocedure, but the PAP and chamber size were restored to normal values in 10 of these patients by 6 months postprocedure (Figure 2).

Seventeen patients (13%) showed PP-PAH during the follow-up period (Figure 3). Two of these patients received RHC because of PAH progression at 3.5 and 8 years after PDA closure, respectively. Their PAPs were 112/60 and 129/76 mm Hg, respectively. Five patients received medicine therapy for PAH: 3 patients received medication immediately after the procedure and 2 patients received medication at 2 and 8 years after the procedure, respectively. None of the 5 patients had a normal PAP during the follow-up. At the last follow-up, the mean systolic PAP estimated by Doppler echocardiography was 86±29 mm Hg among the patients with PP-PAH (Figure 4).

Factors Associated With PP-PAH

Table 3 shows the baseline characteristics, as well as the echocardiographic and hemodynamic parameter values of patients with and without PP-PAH. No differences in sex, age, and baseline and postclosure LV ejection fraction were observed between patients with and without PP-PAH. Stepwise discriminant analyses revealed that the baseline LV EDVI (Wilks λ=0.649; F=13.788; P<0.001) and the baseline systolic Pp/Ps ratio (Wilks λ=0.591; F=11.558; P<0.001) were the strongest discriminators in the first model. The combination of the 2 discriminators identified 93% of the originally grouped cases correctly, with a sensitivity of 96% and specificity of 71%. The post-trial systolic Pp/Ps ratio, as the sole discriminator of PP-PAH in the second model, classified 100% of the originally grouped cases correctly (Wilks λ=0.316; F=288.196; χ²=152.739; P<0.001; Figure 5). The cut off point of the post-trial systolic Pp/Ps ratio was 0.5.

Discussion

In the present study, we evaluated the usefulness of trial occlusion in predicting PP-PAH. The post-trial systolic Pp/Ps ratio

<table>
<thead>
<tr>
<th>Table 2. Comparisons Between Baseline and Post-Trial Pressure Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Systolic PAP, mm Hg</td>
</tr>
<tr>
<td>Diastolic PAP, mm Hg</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
</tr>
<tr>
<td>Systolic Pp/Ps ratio</td>
</tr>
<tr>
<td>Diastolic Pp/Ps ratio</td>
</tr>
<tr>
<td>Mean Pp/Ps ratio</td>
</tr>
</tbody>
</table>

PAP indicates pulmonary artery pressure; and Pp/Ps, pulmonary:systemic pressure.

Figure 1. Relationship between baseline and post-trial pressure parameters. A, Systolic pulmonary artery pressure (sPAP). B, Diastolic pulmonary artery pressure (dPAP). C, Mean pulmonary artery pressure (mPAP). D, Systolic pulmonary:systemic pressure (sPp/Ps) ratio. E, Diastolic pulmonary:systemic pressure (dPp/Ps) ratio. F, Mean pulmonary:systemic pressure (mPp/Ps) ratio.
was identified as a sensitive and specific parameter that could predict the presence of PP-PAH, and a post-trial systolic Pp/Ps ratio >0.5 suggested inevitable PP-PAH.

**Usefulness of Trial Occlusion in Assessing the PAH Response After Defect Closure**

Isolated PDA accounts for 6% to 11% of all CHD cases. Because of its relatively asymptomatic nature, isolated PDA often escapes clinical detection until adulthood when PAH or congestive heart failure develops. For this reason, many patients do not undergo PDA closure until they develop severe PAH.

Trial occlusion has been reported to be a useful method to establish whether the defect is operable in patients with CHDs and severe PAH. Sánchez-Recalde et al assessed the usefulness of temporary balloon trial occlusion for predicting the pulmonary resistance and the response to surgery in patients with atrial septal defects and severe PAH. They successfully used temporary balloon trial occlusion to assess the PAH response after definitive closure, identifying a ≥25% reduction in the mean PAP relative to baseline values as a criterion for device closure. In 1957, Keszdi et al found that temporary obstruction of the ductus with a balloon during cardiac catheterization was useful for evaluating the indication for surgical closure.

Transient balloon occlusion of the PDA was also useful for predicting the hemodynamic response after transcatheter closure of the PDA in patients with borderline PAH. Because the balloon obstruction-based approach is time consuming and inconvenient, Yan et al described a simple method to assess the PAH response, in which the balloon was replaced with a self-expandable occluder for trial occlusion. In this study, we found that trial occlusion was useful in predicting PP-PAH after transcatheter closure of the PDA in patients with borderline PAH.

**Definition of PP-PAH in Patients With PDA**

A large PDA commonly leads to a substantial systemic-to-pulmonary shunt. This condition increases the LV volume load and right ventricular pressure load simultaneously, leading to LV dilatation with possible LV dysfunction and right ventricular hypertrophy. Even after the PDA is closed, recovery of the pulmonary endothelial injury, pulmonary in situ thrombosis, and LV failure can take a long time, leaving the PAP suspended at a high level. However, no study has demonstrated how long it takes to return to normal. Moreover, no exact definition has been provided for PP-PAH in patients undergoing transcatheter closure of CHDs.
In the present study, 10 patients showed an elevated PAP at 3 months but a normal PAP at 6 months after the procedure. The PAH was persistent if the PAP did not resolve to a normal level by 6 months after the procedure. Therefore, in patients with severe PAH who undergo treatment to close the PDA, we propose that it is reasonable to define PP-PAH as a higher-than-normal PAP at 6 months after the procedure.

Factors Identifying PP-PAH
In the literature, several criteria have been used to define the PAH severity, according to the PAP, Pp/Ps ratio, and Rp/Rs ratio. However, these criteria have failed to establish a clear cut off for PP-PAH. Evidence on which pulmonary hemodynamic parameters correlate with the best patient outcomes is lacking.

Clinically, in patients with PDA (especially with a large PDA), interruption of the systemic-to-pulmonary shunt will markedly decrease the PAP and lead to elevation of the systemic blood pressure because of the increased systemic flow. However, the systemic-to-pulmonary shunt depends not only on the PDA size but also on the systemic-to-pulmonary pressure gradient. The impact of PDA closure on the PAP and the systemic blood pressure is decreased in cases of high baseline PAP because of the decreased systemic-to-pulmonary shunt. This finding suggests that the Pp/Ps ratio may be more important than the PAP in reflecting the severity of PAH.

In fact, Barst et al proposed that it was more appropriate to define PAH according to the Pp/Ps ratio in patients with CHD than according to the PAP because the latter ignores the variance of the systemic pressure in different patient populations. Although important for assessing the reversibility of PAH, the PVR and Rp/Rs ratio were not significantly associated with PP-PAH according to stepwise discriminant analysis. Instead, the strongest discriminator among the baseline hemodynamic parameters was the systolic Pp/Ps ratio. It may be that the accuracy of PVR and the Rp/Rs ratio was affected by the unavoidable error in the oxygen content of the pulmonary blood sample. Furthermore, the mean PAP can be underestimated in the presence of pulmonary regurgitation.
Discriminant analysis also identified the baseline LV EDVI as a discriminator of PP-PAH. This finding may be a special phenomenon of a large PDA, which commonly leads to a substantial systemic-to-pulmonary shunt and results in marked LV dilation. With the elevation of PAP, the LV EDVI will decrease because of the fall of the systemic-to-pulmonary shunt. Although the baseline LV EDVI and systolic Pp/Ps ratio were the strongest discriminators of PP-PAH, the combination of these 2 parameters only correctly identified 93% of the originally grouped cases. Compared with these 2 parameters, the post-trial systolic Pp/Ps ratio was a more valuable variable in the prediction of PP-PAH, as it identified 100% of the originally grouped cases correctly. A post-trial systolic Pp/Ps ratio >0.5 was associated with inevitable PP-PAH in patients with PDA and severe PAH. This finding emphasizes the importance of measuring PAP and AP simultaneously before releasing the device in patients with PDA and severe PAH, especially in those with borderline PAH.

**Management of Patients With Borderline PAH**

Clinicians and researchers continue to investigate how best to manage patients with CHDs and borderline PAH. With the development of PAH medications, 2 treatment options are currently available: (1) PAH medications can be administered first, and the hemodynamics reassessed to see whether the patient is a candidate for defect closure; or (2) defect closure can be performed first to assess the PAH response, followed by the use of PAH medications if the hemodynamic response is unfavorable. Considering the cost, efficacy, and safety of the medications and closure procedure, each option has certain advantages over the other.

Theoretically, treatment with PAH medication followed by device closure is safer than the reverse approach. In this study, although 2 patients failed to pass the trial occlusion because of adverse events, there were no major adverse events (eg, thromboembolic diseases or deaths). This result suggests that trial occlusion is safe in patients with a mean PAP ≥45 mmHg, Qp/Qs ratio >1.5, and Rp/Rs ratio <0.7. Moreover, a significant improvement in hemodynamics after treatment with PAH medications does not mean that the PDA can be closed without PP-PAH. Because of the lack of definite indications for defect closure in patients already treated with PAH medications, trial occlusion is still necessary to assess the postclosure PAH response.

In addition to offering a useful way to differentiate patients with PP-PAH, this study provides an important reference for determining how to manage patients with borderline PAH. In patients with a post-trial systolic Pp/Ps ratio >0.5, treatment with PAH medications is justified because PP-PAH is inevitable. Otherwise, PAH medications should be administered immediately after the procedure even if the PDA is closed.
with a marked decrease in PAP. However, whether the combined use of PDA closure and medical therapy for PAH can improve the prognosis more than medical therapy for PAH alone is still a matter of debate.

Technical Details of Trial Occlusion
Several details about the trial occlusion approach must be considered. First, use of an oversized device is preferred in patients with severe PAH undergoing transcatheter closure of the PDA. In patients with borderline PAH, the PDA size is likely to be underestimated by echocardiogram or aortic angiogram because the systemic-to-pulmonary shunt through the ductus decreases with increasing PAP. Second, the hemodynamic parameters, including PAP, AP, and heart rate, should be monitored continuously during trial occlusion. As demonstrated in this study, the AP and heart rate will decrease sharply in some patients after PDA closure. Third, the PAP must be recorded after the PDA is completely closed or closed with trace residual shunt. Otherwise, the post-trial PAP will be inaccurate, leading to misjudgment of the prognosis. Severe PAH is commonly associated with a large PDA. As the device size increases, the time to close the ductus also increases accordingly. In our experience, 5 to 6 minutes are sufficient to close a small PDA completely, but 10 to 15 minutes are usually needed for a large PDA.

Limitations
The major limitation of the present study was that nearly all the patients were followed up clinically and by echocardiography. Only 2 patients received RHC, several years after the procedure, because of PAH progression. Continuous wave Doppler echocardiography is the most commonly used noninvasive method of measuring PAP. Tricuspid regurgitation has been demonstrated in this study, the AP and heart rate will decrease sharply in some patients after PDA closure. However, whether closure is actually the best therapy in these patients requires further exploration. Third, the number of patients with PP-PAH was still relatively small, particularly at the later follow-up time points. Therefore, the findings should be considered as preliminary. Moreover, the data were relatively short-term and may not reflect the long-term progression of PAH, which can occur much later than 1 to 10 years after the procedure.41 Hence, whether closure is actually the best therapy in these patients requires further exploration. Third, this was a retrospective study performed at a single institution, which may decrease the generalizability of the results to other settings. However, this study provides some evidence on the criteria of PDA closure in patients with borderline PAH.

Conclusions
In conclusion, 13% of patients with a mean PAP ≥45 mmHg and an R/PrRs ratio <0.7 who underwent transcatheter closure of the PDA had PP-PAH, although they showed a baseline Qp/Qs ratio >1.5 and a significantly decreased PAP after PDA closure. The post-trial systolic Pp/Ps ratio is a sensitive and specific parameter to identify PP-PAH, and a post-trial systolic Pp/Ps ratio >0.5 suggests inevitable PP-PAH.

Disclosures
None.

References


Trial Occlusion to Assess the Risk of Persistent Pulmonary Arterial Hypertension After Closure of a Large Patent Ductus Arteriosus in Adolescents and Adults With Elevated Pulmonary Artery Pressure

Duan-zhen Zhang, Xian-yang Zhu, Bei Lv, Chun-sheng Cui, Xiu-min Han, Xiao-tang Sheng, Qi-guang Wang and Po Zhang

_Circ Cardiovasc Interv._ 2014;7:473-481; originally published online August 5, 2014; doi: 10.1161/CIRCINTERVENTIONS.113.001135

_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/7/4/473

An erratum has been published regarding this article. Please see the attached page for:
/content/7/5/731.full.pdf

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Interventions_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation: Cardiovascular Interventions_ is online at:
http://circinterventions.ahajournals.org/subscriptions/
Correction


Correspondence should be directed to Xian-yang Zhu, MD:

Correspondence to Xian-yang Zhu, MD, Department of Congenital Heart Disease, General Hospital of Shenyang Military Area Command, Shenyang 110840, People’s Republic of China. E-mail xyangz2011@163.com

This correction has been made to the online version of the article, which is available at http://circinterventions.ahajournals.org/content/7/4/473.