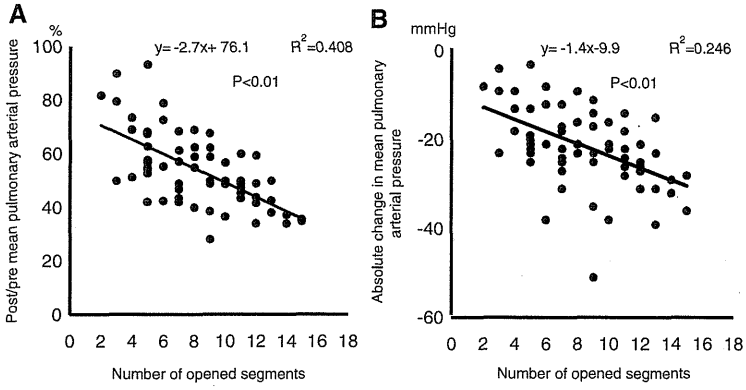

Figure 3. Correlation between the number of opened segments and the decrease in mean pulmonary arterial pressure. The relationships of reduction in mean pulmonary arterial pressure (**A**) and absolute change in mean pulmonary arterial pressure (**B**) with the number of segments of pulmonary arteries treated by balloon pulmonary angioplasty are shown. Values reflect the number of segments opened in all of the sessions, and the changes in pulmonary arterial pressure indicate changes from baseline to the last session. The more segments were dilated, the larger the decrease in mean pulmonary arterial pressure.

and II before BPA. Clinical and hemodynamic variables were remarkably improved after BPA. Six-minute walk distance and brain natriuretic peptide levels were significantly improved. Overall, mean pulmonary arterial pressure was significantly decreased ($P<0.01$) with an increased cardiac index after BPA, whereas there was no temporal change in systolic blood pressure (108.7±15.9 and 106.1±14.1 mm Hg). In addition, oxygenation was improved in all patients after BPA. The amount of oxygen to maintain peripheral oxygen saturation >95% was significantly decreased from 3.0±1.4 to 1.3±1.0 L/min ($P<0.01$).

Follow-up

During follow-up for 2.2±1.4 years after the final BPA, 1 patient died of pneumonia and the remaining 66 patients are alive. Fifty-seven patients underwent right heart catheterization at 1.0±0.9 years (0.3–7.0 years) after the final BPA. In these patients, mean pulmonary arterial pressure was 24.0±5.8 mm Hg at follow-up and improved hemodynamics were maintained (Figure 4). Angiographically, the pulmonary arteries where BPA was performed were even larger in diameter at follow-up (Figure 5). The improved hemodynamics were maintained even after significant reduction of medications for pulmonary hypertension. All of the 4 patients on long-term epoprostenol therapy before BPA were able to completely discontinue epoprostenol. The percentage of patients on other oral medications was significantly reduced (endothelin receptor antagonist: from 52% to 37%, $P<0.05$; phosphodiesterase-5 inhibitor: from 40% to 28%, $P<0.05$). At initial admission, all patients

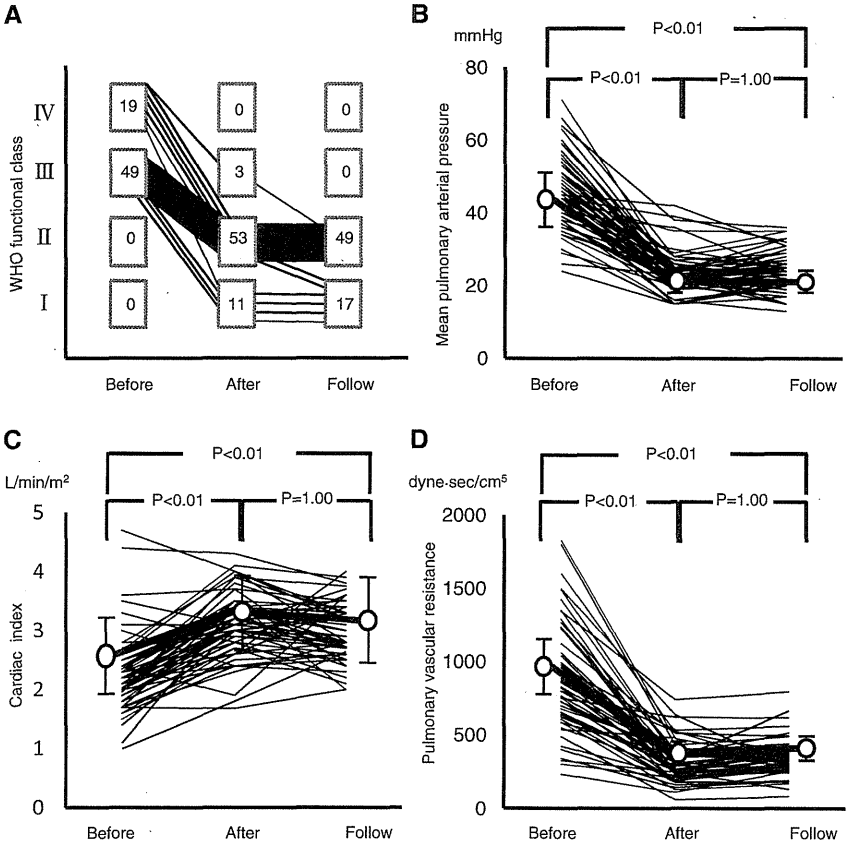

Figure 4. Change in parameters after balloon pulmonary angioplasty (BPA). Parameters before BPA (n=68), immediately after BPA (after) (n=67), and at follow-up (follow) (n=66 for **A** and 57 for **B–D**) were compared. World Health Organization (WHO) functional class (**A**), mean pulmonary arterial pressure (**B**), cardiac index (**C**), and pulmonary vascular resistance (**D**) were significantly improved immediately after BPA, and the improvement was maintained at follow-up.

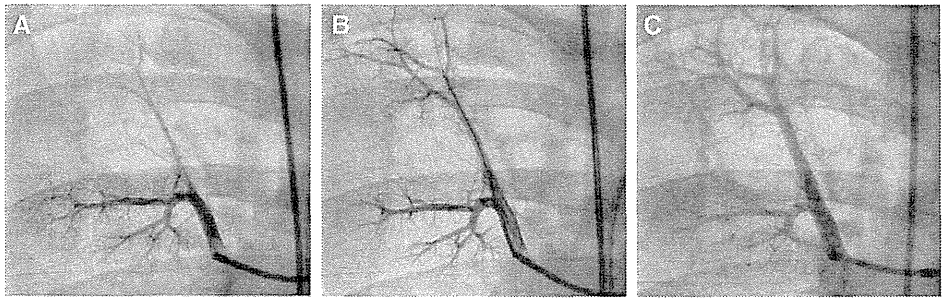

Figure 5. Representative pulmonary angiograms before balloon pulmonary angioplasty (BPA), after BPA, and at follow-up. Pulmonary angiograms before BPA (**A**), immediately after BPA (**B**), and at 1.5 years after the final BPA (**C**) are shown. The dose of epoprostenol was 5 ng/kg/min before and immediately after BPA. At follow-up, pulmonary arteries were dilated despite epoprostenol being discontinued.

required supplemental oxygen, whereas 26 patients were able to discontinue oxygen inhalation.

Complications Related to BPA

Reperfusion pulmonary injury was the major complication after BPA. It was confirmed by 3 methods, in the order of severity: hemo sputum; chest radiographic opacity in dilated segments and worsening of hypoxemia; or increased density of the dilated segment as shown by a chest CT scan taken 4 hours after BPA without any symptoms (Table 3). Patients were counted based on the methods by which pulmonary reperfusion injury was found and listed for only once. Chest-CT-only patients had chest CT findings without any other symptoms. When a patient had hemo sputum and radiographic findings, the patient was counted in the hemo sputum group. Intratracheal intubation was required in 3 patients with hemo sputum and 1 patient with increased radiographic opacity in a chest X-ray. Therefore, the incidence of severe reperfusion pulmonary injury that required intratracheal intubation was 6%. Among them, percutaneous cardiopulmonary support was required in 2 patients. One patient fully recovered and another patient died 28 days after BPA because of right-sided heart failure. None of the patients with reperfusion pulmonary injury detected only by chest CT required intratracheal intubation. Pulmonary artery perforation with a guide wire occurred in 5 patients, and 2 of them required emergent transcatheter coil embolization. The frequency of reperfusion pulmonary injury, particularly injury manifesting as hemo sputum, was significantly lower during the most recent half of our experience (127 procedures) than during the first half of our experience (128 procedures) ($P<0.01$, Table 3). Further details are provided in the online-only Data Supplement.

Table 3. Complications Related to BPA

	Diagnositic Criteria	Total	First 128 Sessions	Most Recent 127 Sessions	*P* Value
Reperfusion pulmonary injury	Hemo sputum	40	27	13	
	Chest X-ray or desaturation	36	19	17	
	Chest CT only	145	82	63	
	Total	221	128	93	<0.01
Pulmonary artery perforation		5	4	1	1.00

Data indicate the number of sessions. The incidence of complications was compared between the first 128 sessions (performed between November 2004 and October 2010) and the most recent 127 sessions (performed between November 2010 and September 2011).

CT indicates computed tomography.

No other procedural complications were experienced during BPA. There was no acute kidney injury caused by contrast medium. Interstitial pneumonitis in 1 patient and interstitial nephritis in 2 patients occurred after BPA. Non-steroidal anti-inflammatory drugs and radio-contrast medium were suspected to be the cause of these complications. All patients recovered after steroid pulse therapy.

Discussion

We found that our refined and comprehensive BPA strategy improved hemodynamics and clinical status of symptomatic patients with minimal serious adverse events. This is the first clinical trial to document that refined BPA can be a therapeutic option in inoperable patients with CTEPH who have no other treatment options.

The prognosis of CTEPH has been reported to be poor when mean pulmonary arterial pressure is >30 mmHg,[13,14] and therefore, previously reported pulmonary arterial pressure after BPA >30 mmHg should be insufficient.[7] To achieve a sufficient decrease in mean pulmonary arterial pressure without increasing the risk of reperfusion pulmonary injury, pulmonary artery rupture, and perforation, it is necessary to achieve adequate dilation by selecting the appropriate size of balloons. In previous reports, balloon size was determined according to angiographic findings.[6,7] In our study, we evaluated pulmonary artery diameters by using IVUS, which provides information regarding the true size of the pulmonary artery lumen and wall thickness.[15] Furthermore, we selected a target artery by a soft-tipped 6F guiding catheter, which enabled us to select the smaller branches of pulmonary arteries with a reduced risk of causing dissection of arteries compared with a 7F custom made catheter used in a previous report.[7] We also used a thinner wire (0.014-inch) and a low profile balloon catheter, which potentiated the opening of completely obstructed lesions, with a lower risk of perforation. In a previous report,[7] a 7F pigtail catheter was modified by removing most of the curled tip. Our procedure requires only commercially available devices, and this procedure can be performed anywhere. We repeated these procedures until

a sufficient amount of stenoses were dissolved. The more segments were dilated, the larger the decrease in pulmonary arterial pressure was achieved. As a result, we succeeded in decreasing mean pulmonary arterial pressure by >20 mm Hg to achieve <25 mm Hg (Table 1).

Reperfusion pulmonary injury is the leading complication of pulmonary endarterectomy, and the incidence is reported to be 16% to 22%.[2,16] In our study, the incidence of clinically apparent reperfusion pulmonary injury was similar to that of a previous report (60% versus 61%).[7] With advanced examination, we found subclinical reperfusion pulmonary injury in 34% of patients, which indicated that occurrence of reperfusion pulmonary injury was essentially unavoidable in BPA. Feinstein et al[7] reported that development of reperfusion pulmonary injury is correlated with mean pulmonary arterial pressure before BPA >35 mm Hg. The reperfused area is anticipated to be exposed to a high perfusion pressure after BPA, resulting in severe reperfusion pulmonary injury. We expected that epoprostenol could dilate pulmonary arteries in the segments where BPA is not performed[17,18] and minimize the effect of pulmonary arterial pressure associated with pulmonary artery reperfusion. However, in our fully medicated patients, preoperative application of epoprostenol reduced mean pulmonary arterial pressure only by ≈3 mm Hg and a reduction <35 mm Hg could not be attained. We empirically used methylprednisolone to reduce pulmonary edema according to the procedure of pulmonary endarterectomy.[2] However, methylprednisolone failed to reduce lung injury after pulmonary endarterectomy,[19] and therefore, we stopped routinely using it after completion of this study. We attempted noninvasive positive airway pressure ventilation for at least 24 hours after BPA. Current studies suggest that noninvasive positive airway pressure ventilation does not show effectiveness in patients with acute lung injury.[20,21] We did not observe any difference in the frequency of reperfusion pulmonary injury compared with that reported by Feinstein et al.[7]

To reduce the size of the area of reperfusion pulmonary injury, we attempted to not dilate >2 vessels at the initial BPA and performed it in a staged fashion over multiple, separate procedures, as previously suggested.[7] In total, we performed more BPA sessions per patient compared with a previous report (4 [2–8] versus 3 [1–5] sessions/patient).[7] Performing BPA in limited vessels within a single lobe would reduce the extent of reperfusion pulmonary injury. With our best efforts, the incidence of severe reperfusion pulmonary injury that required intratracheal intubation was reduced to 6% compared with 17% reported in a previous study.[7] Notably, the incidence of complications was significantly reduced in recent sessions (Table 3), although we did not change other pharmacological prophylaxis to reduce reperfusion pulmonary injury. This finding indicated that the incidence of reperfusion pulmonary injury largely depended on the proficiency of operators performing BPA.

Considering the fact that reperfusion pulmonary injury is unavoidable in BPA despite best efforts, postprocedural intensive monitoring of hemodynamics and oxygenation is necessary, even if the patient appears to be free from pulmonary injury after BPA. On the other hand, a routine CT scan after BPA may be unnecessary, because no patients with pulmonary injury detected only by a CT scan required intratracheal intubation or percutaneous cardiopulmonary support.

Pulmonary endarterectomy is the only potentially curative treatment for CTEPH.[5,22] Although the University of California, San Diego pulmonary endarterectomy team has been publishing excellent outcomes, they are not applicable worldwide because of the complex surgical technique and requirement of experience. It was recently reported from Europe and Canada that over one third of patients are assessed as inoperable, with a large variation between countries (from 12.0% versus 60.9%).[4] Histopathological studies have confirmed the existence of small vessel changes in CTEPH, similar to those of idiopathic pulmonary arterial hypertension, and vasodilative agents have been attempted in patients with inoperable CTEPH.[23,24] Some of these therapies may play a role in improving exercise capacity in CTEPH to some extent, but a retrospective analysis of patients with CTEPH demonstrated that medical therapy has a minimal effect on hemodynamics.[25] All patients in our study were diagnosed as inoperable and suffered from increasing disability in spite of at least 1 specific drug to treat pulmonary hypertension at other experienced hospitals. Most of our patients were too old to undergo lung transplantation, and some of them were already in the end stage of right-sided heart failure. Considering the high mortality of these patients when untreated[13] and the difficulty of pulmonary endarterectomy, an alternative therapeutic option is required. Our data demonstrated that refined BPA successfully removed stenoses in distal arteries to obtain a substantial decrease in pulmonary arterial pressure in these patients. Therefore, our refined BPA procedure could be a treatment option for patients with inoperable CTEPH. Although the present results indicated the efficacy of BPA, it is clear that there is a learning curve in performing this procedure. To demonstrate sufficient safety and efficacy, acquirement of the BPA technique and experience of BPA are necessary, as well as comprehensive management of patients requiring expertise in pulmonary vascular diseases and respiratory and critical care medicine. In addition, our patient numbers are still too small to conclude that BPA is an alternative therapeutic option for inoperable patients with CTEPH. Therefore, further studies and clinical trials should be performed.

Limitations

There are some limitations to this study. We do not have results of long-term follow-up of >7 years. There might be cases with restenosis or persistent pulmonary hypertension after BPA similar to that found in patients after pulmonary endarterectomy. To date, we have not experienced patients with angiographically documented restenosis after BPA. Second, a randomized and controlled direct comparison of BPA and medical therapy is necessary, and cost analysis is required because of the long duration of hospitalization with repeated BPA.

Disclosures

Dr Matsubara received lecturer fees from GlaxoSmithKline, Actelion Pharmaceuticals Japan, and Nippon Shinyaku.

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SUPPLEMENTAL MATERIAL

(1) Reperfusion pulmonary injury

Supplemental Methods

We assessed the site where reperfusion pulmonary injury occurred and how long the pulmonary injury lasted. Univariate logistic regression analysis (using a $P < 0.05$) was used to evaluate associations between clinically apparent reperfusion pulmonary injury and factors of baseline characteristics, laboratory data, and parameters related to BPA procedure.

Supplemental Results

Reperfusion pulmonary injury occurred at the area where pulmonary arteries were dilated. Reperfusion injuries found on chest X-ray disappeared in a median of 4 days. None of the parameters analyzed, including maximum inflation pressure (14 atm in all sessions) and the inflation time (2 seconds in all sessions), were associated with the occurrence of clinically apparent reperfusion pulmonary injury (Supplemental Table).

Patients with extreme pulmonary hypertension manifest a higher rate of postoperative reperfusion edema after pulmonary endarterectomy[1]. We pay special attention as described below when pulmonary arterial pressure is high, and this could be the reason why none of the hemodynamic parameters was significantly associated with the occurrence of clinically apparent reperfusion pulmonary injury.

(2) Learning curve

In the first 128 and the most recent 127 procedures, there were 42 and 26 initial procedures, respectively. More initial procedures were included in the first 128 procedures. However, there was no significant association in the occurrence of pulmonary injury and initial session vs. follow-up session. We attempted to avoid injury of the pulmonary artery by passing the

targeted lesion without vigorously pushing the guide wire or balloon catheter, and by placing the wire tip within the angiographically visible area, along with evaluating accurate diameters with IVUS throughout the targeted lesion and inflating the balloon just at the targeted lesion. Because there was a large amount of swinging of the tip of the guiding catheter along with the heart beat, placing and holding a guiding catheter at the appropriate position is most difficult, but it is important to complete these simple and ordinary tasks. After a learning curve, we were able to safely select each segmental pulmonary artery by the guiding catheter and place the tip of the catheter at the appropriate site just proximal to the targeted lesions coaxially.

Supplemental Table. Baseline characteristics and procedure-related parameters had no association with clinically apparent reperfusion pulmonary injury

	Odds ratio (95% confidence interval)	P
Baseline characteristics		
Sex	1.03 (0.52-2.02)	0.89
Age	1.02 (0.99-1.05)	0.07
Body mass index	0.99 (0.90-1.08)	0.46
6-minute walk distance	0.99 (0.99-1.00)	0.09
Baseline laboratory data		
Brain natriuretic peptide	0.99 (0.98-1.00)	0.08
White blood cell counts	1.00 (1.00-1.00)	0.75
Hemoglobin levels	0.93 (0.73-1.19)	0.09
Platelet counts	0.98 (0.94-1.03)	0.46
Creatinine levels	2.20 (0.52-0.94)	0.29
Uric acid levels	1.01 (0.88-1.06)	0.45
C-reactive protein	0.86 (0.65-1.13)	0.29
Baseline hemodynamic parameters		
Systolic systemic blood pressure	1.01 (0.97-1.01)	0.79
Right atrial pressure	1.06 (0.99-1.13)	0.12
Systolic pulmonary arterial pressure	1.01 (0.97-1.01)	0.79
Mean pulmonary arterial pressure	0.99 (0.92-1.05)	0.67
Cardiac index	0.97 (0.87-1.07)	0.51
Pulmonary vascular resistance	0.99 (0.98-1.00)	0.29

BPA procedure-related parameters		
Initial vs. follow-up sessions	1.15 (0.47-2.81)	0.41
Maximum diameter of balloon/session	0.88 (0.74-1.05)	0.16
Number of balloon inflation/session	1.01 (0.97-1.04)	0.74
Number of dilated vessels/session	0.98 (0.80-1.18)	0.81
Number of balloons/session	1.07 (0.94-1.22)	0.29

BPA: balloon pulmonary angioplasty.

Supplemental Reference

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STRUCTURAL HEART DISEASE

Long-Term Effects of Transcatheter Closure of Atrial Septal Defect on Cardiac Remodeling and Exercise Capacity in Patients Older than 40 Years with a Reduction in Cardiopulmonary Function

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Background: *Although it has been demonstrated that cardiac remodeling and exercise capacity improve after transcatheter closure of atrial septal defect (ASD), little is known about long-term benefits in middle-aged and elderly patients with a reduction in cardiopulmonary function.*
Objectives: *To evaluate long-term extent and time course of improvements in cardiac remodeling and exercise capacity in those patients.*
Methods: *Twenty ASD patients ≥ 40 years of age with a reduction in cardiopulmonary function (predicted peak oxygen uptake [VO_2] < 65%) were enrolled. Transthoracic echocardiography and cardiopulmonary exercise testing were performed at baseline and at 1 month, 3 months, 6 months, and >12 months after the procedure.*
Results: *At 1 month after the procedure, significant decreases in right ventricular (RV) end-diastolic diameter (38.2 ± 4.4 to 31.9 ± 4.4 mm; P < 0.001) and RV/left ventricular end-diastolic diameter ratio (0.95 ± 0.17 to 0.71 ± 0.13; P < 0.001) occurred, and they were maintained during the follow-up period. Normal RV size was achieved in 11 of 18 patients with RV enlargement. Predicted peak VO_2 did not change at 1 month and 3 months, but it improved significantly after 6 months (53.6 ± 6.5 to 62.1 ± 12.6%; P < 0.01). Sixteen of the 20 patients showed improved predicted peak VO_2.*
Conclusions: *Cardiac remodeling and exercise capacity could be improved over the long-term period after transcatheter closure of ASD in middle-aged and elderly patients with a reduction in cardiopulmonary function. There were differences in the time course of improvement between cardiac remodeling and exercise capacity in those patients.* (J Interven Cardiol 2013;26:195–199)

Introduction

Atrial septal defect (ASD) of secundum type is one of the most common forms of congenital heart disease in adults. Many patients with ASD are usually asymptomatic in early life, but clinical symptoms such as fatigue and dyspnea develop frequently in the course of time.[1,2] The development of clinical symptoms, echocardiographic signs of shunt volume or shunt-related pulmonary hypertension are widely accepted indications for closure of ASD. It is well known that surgical closure of ASD leads to long-term functional benefits in middle-aged and elderly symptomatic patients.[3–6] In recent years, transcatheter closure of ASD has been established as a secure and effective treatment, and it has become an important alternative to surgical repair for ASD.[7,8] A few studies

Conflict of interest: None

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have shown short-term benefits of transcatheter closure of ASD on cardiac remodeling and exercise capacity in middle-aged and elderly patients.[9,10] However, little is known about long-term results. Furthermore, the extent and time course of functional improvements after the procedure in middle-aged and elderly patients with a marked reduction in cardiopulmonary function remains unclear. Therefore, the aim of this study was to investigate the long-term extent and time course of improvements in cardiac remodeling and exercise capacity after transcatheter closure of ASD in those patients.

Methods

Study Population. From June 2006 to April 2009, 20 consecutive ASD patients $\geq$ 40 years of age with a moderate or severe reduction in cardiopulmonary function who underwent transcatheter closure of secundum ASD were enrolled. We defined moderate reduction in cardiopulmonary function as 50% $\leq$ predicted peak oxygen uptake (VO_2) < 65%, and we defined severe reduction as predicted peak VO_2 < 50%. The indications for ASD closure in all patients were significant left-to-right shunt detected by echocardiography, presence of right ventricular (RV) volume overload, shunt-related symptoms, or pulmonary hypertension. Exclusion criteria included pulmonary vascular resistance > 8 wood units on 100% O_2 and transesophageal maximal ASD diameter > 40 mm. The Okayama University Ethics Committee approved this study, which was performed in accordance with the Helsinki declaration, and all patients provided written informed consent before participation in this study.

Transcatheter Closure of ASD. Transesophageal echocardiography was performed in all patients before the procedure, and left atrial thrombi were not detected in any of the patients. Coronary angiography was performed in all patients, and there was no significant coronary stenosis. Transcatheter closure of ASD using an AMPLATZER septal occluder device (AGA Medical Corporation; Plymouth, MN, USA) was performed under general anesthesia with the assistance of transesophageal echocardiography. Hemodynamic evaluation was performed just before ASD closure. With oxygen uptake measured at rest, the pulmonary to systemic flow ratio was calculated by oxymetry using the Fick principle. If the pulmonary wedge pressure increased > 5 mmHg from baseline, the procedure was abandoned.

Echocardiography. Transthoracic echocardiography was performed at baseline and at 1 month, 3 months, 6 months, and >12 months after the procedure using a 3.5 MHz transducer (Aplio, Toshiba, Otawara, Japan). Left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, and RV end-diastolic diameter were measured by M-mode parasternal echocardiography, and RV/LV end-diastolic diameter ratio was calculated. LV ejection fraction was derived using Teichholz's formula. These measurements were done at least three times and averaged to obtain mean values by 2 independent experienced investigators who were blinded to the data of treatment.

Cardiopulmonary Exercise Testing. Cardiopulmonary exercise testing was performed at baseline and at 1 month, 3 months, 6 months, and >12 months after the procedure. All patients underwent symptom-limited exercise tests on an upright bicycle ergometer using a ramp protocol (15 W/min) with simultaneous respirator gas analysis. Patients were encouraged to exercise to exhaustion or to a respiratory exchange ratio $\geq$ 1.09. Blood pressure and heart rate were measured every minute. A 12-lead electrocardiogram was continuously monitored during exercise testing. Breathed gas was continuously collected to analyze VO_2, carbon dioxide production, and minute ventilation with a gas analyzer. Peak VO_2 was defined as the highest VO_2 value achieved at peak exercise after reaching the respiratory compensation point, and predicted peak VO_2 was expressed according to age, sex, weight, and height. VO_2 to work rate ratio ($\Delta VO_2/\Delta WR$) was determined. A spirometric measurement was performed to assess vital capacity and forced expiratory volume in 1 second. These analyses were done by 2 independent experienced investigators who were blinded to the data of treatment.

Statistical Analysis. Variables are expressed as means $\pm$ standard deviation or percentage. Statistical analysis was performed by Wilcoxon's matched-pairs test. A P value < 0.05 was considered to be statistically significant.

Results

Study Population. Patient clinical characteristics are summarized in Table 1. Mean age at transcatheter closure of ASD was 54.5 $\pm$ 10.9 years (range, 40–78 years). Fourteen patients (70%) were female. ASD diameter measured by transesophageal echocardiography was 17.8 $\pm$ 4.3 mm. Pulmonary to

Table 1. Patient Clinical Characteristics

Variables	
Age (years)	54.5 ± 10.9
Female (%)	70
Smoking (%)	25
Lung disease (%)	15
Hypertension (%)	25
Diabetes mellitus (%)	10
Stroke (%)	5
Atrial septal defect diameter (mm)	17.8 ± 4.3
Device size (mm)	21.7 ± 4.7
Pulmonary to systemic flow ratio	2.6 ± 0.6
Mean pulmonary artery pressure (mmHg)	14.5 ± 4.0
Vital capacity (l)	2.9 ± 0.6
Forced expiratory volume in 1 second (l/second)	2.3 ± 0.6

Data are presented as mean ± standard deviation or percentage.

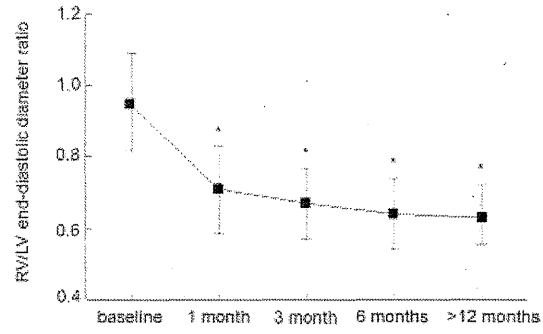

Figure 1. Time course of data on RV/LV end-diastolic diameter after transcatheter closure of atrial septal defect. *P < 0.001 versus baseline. RV = right ventricular; LV = left ventricular.

systemic flow ratio was 2.6 ± 0.6, and mean pulmonary artery pressure under general anesthesia was 14.5 ± 4.0 mmHg. Transcatheter closure of ASD was performed successfully in all patients using an AMPLATZER septal occluder device. All patients were followed up for a mean period of 25.2 ± 10.5 months (range, 12.0–40.8 months). There were no complications including thromboembolic events in the procedural and follow-up period.

Cardiac Remodeling and Exercise Capacity. Time courses of data obtained by transthoracic echocardiography and cardiopulmonary exercise testing at baseline and after the procedure are summarized in Table 2. At baseline, RV enlargement (RV end-diastolic diameter >30 mm) was present in 18 patients (90%). After the procedure, a significant decrease in RV end-diastolic diameter was observed at 1 month, and it was maintained during the follow-up period. Eleven of 18 patients with RV enlargement (61%) achieved a normal RV size (RV end-diastolic diameter <30 mm). In addition, LV end-diastolic diameter increased significantly. Therefore, cardiac remodeling resulted in a decrease in RV/LV end-diastolic diameter ratio at 1 month (Fig. 1). LV ejection fraction and LV end-systolic diameter did not change from baseline. At baseline, 13 patients (65%) had a moderate reduction in cardiopulmonary function and 7 patients (35%) had a severe reduction. After the procedure, predicted peak VO_2 did not change at 1 month and 3 months, but it improved significantly after 6 months (Fig. 2). Predicted peak VO_2 increased overall by 15%, and 16 of the 20 patients (80%), including 10 of the 13 patients with a moderate reduction in cardiopulmonary function and 6 of the 7 patients with a severe reduction in cardiopulmonary function, showed improved predicted peak VO_2 in the follow-up period. In addition, a

Table 2. Transthoracic Echocardiography and Cardiopulmonary Exercise Testing at Baseline and After Transcatheter Closure of Atrial Septal Defect

Variables	Baseline	1 month	3 months	6 months	>12 months
LV end-diastolic diameter (mm)	40.7 ± 5.0	45.7 ± 5.3**	46.1 ± 4.7**	46.5 ± 5.3**	46.6 ± 5.2***
LV end-systolic diameter (mm)	24.4 ± 3.9	26.9 ± 3.7	26.2 ± 3.1	26.8 ± 3.9	26.8 ± 3.6
LV ejection fraction (%)	71.2 ± 5.2	72.3 ± 4.0	74.0 ± 4.4	73.4 ± 5.4	73.6 ± 4.7
RV end-diastolic diameter (mm)	38.2 ± 4.4	31.9 ± 4.4***	30.5 ± 3.5***	29.6 ± 3.2***	29.3 ± 2.9***
RV/LV end-diastolic diameter ratio	0.95 ± 0.17	0.71 ± 0.13***	0.67 ± 0.10***	0.64 ± 0.10***	0.63 ± 0.08***
Predicted peak oxygen uptake (%)	53.6 ± 6.5	55.8 ± 11.5	56.8 ± 9.7	62.1 ± 12.6**	61.8 ± 9.7**
Peak oxygen uptake (ml/min/kg)	15.4 ± 2.3	16.3 ± 3.7	16.0 ± 2.9	17.6 ± 3.9*	17.5 ± 3.5*
Oxygen uptake to work rate ratio	7.3 ± 1.8	6.9 ± 1.6	7.9 ± 1.6	8.1 ± 1.7	8.3 ± 1.4*

Data are presented as mean ± standard deviation.
*P < 0.05 versus baseline, ** P < 0.01 versus baseline, *** P < 0.001 versus baseline.
LV = left ventricular; RV = right ventricular.

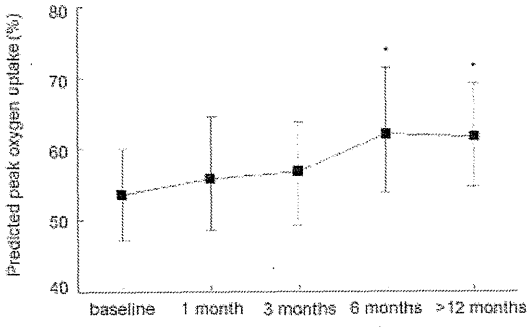

Figure 2. Time course of data on predicted peak oxygen uptake after transcatheter closure of atrial septal defect. *P < 0.01 versus baseline.

significant improvement in $\Delta VO_2/\Delta WR$ was observed at > 12 months after the procedure.

Discussion

In this study, we evaluated long-term functional benefits of transcatheter closure of ASD in middle-aged and elderly patients with a marked reduction in cardiopulmonary function, and we found significant improvements in cardiac remodeling and exercise capacity. Decrease or even normalization of RV size and RV/LV end-diastolic diameter ratio occurred early after the procedure, and they were maintained during the long-term period. Exercise capacity measured by cardiopulmonary exercise testing did not change early, but it improved during the long-term period. We also found the time delay of improvement in exercise capacity compared with cardiac remodeling in those patients. The severity of functional limitation increases with advancing age in the majority of patients with ASD.[1,2] The clinical courses and long-term results after surgery depend mainly on the patient's preoperative clinical status. In the past, controversy existed as to whether middle-aged and elderly patients benefit from surgery. Murphy et al.[11] proved that symptomatic patients who undergo surgery after the age of 40 years were at increased risk for postoperative cardiovascular complications, whereas young adults had an excellent prognosis. However, several studies have demonstrated long-term benefits of surgical ASD closure in middle-aged and elderly symptomatic patients.[3–6] Konstantinides et al.[3] showed that surgical ASD closure in symptomatic patients over the age of 40 years increased long-term survival and prevented deterioration of New York Heart Association (NYHA) functional class during a follow-up period of 8.9 years. Jemielity et al.[4], in patients aged 40–62 years and followed for 6.9 years, also found a significant improvement in functional class with 61.8% patients in NYHA functional class III and IV before surgery compared with 82.4% in NYHA functional class I and II after surgery. These studies indicated that surgical ASD closure benefits many or most middle-aged and elderly symptomatic patients in the long-term period and therefore it is widely recommended for those patients. Recently, transcatheter closure of ASD has been performed safely and effectively, and it has become an alternative to surgical ASD closure.[7,8] Similar to surgical repair, several studies have demonstrated functional benefits of transcatheter closure of ASD in adult patients.[12–15] Giardini et al.[12] evaluated long-term impacts of transcatheter closure of ASD on RV remodeling and exercise capacity in asymptomatic patients, and they found a significant decrease in RV diameter and a significant improvement in peak VO_2. In comparison with this study, their study population was younger and had less severe cardiopulmonary function at the time of the procedure. Our study population consisted of only patients ≥ 40 years of age with a marked reduction in cardiopulmonary function to investigate patients considered at higher risk for functional recovery after the procedure. Regarding middle-aged and elderly patients, Brochu et al.[9] investigated results in asymptomatic or mildly symptomatic patients over the age of 40 years, and they showed that peak VO_2 was increased significantly at 6 months after the procedure. Jategaonkar et al.[10] reported a significant decrease in RV end-diastolic diameter and significant improvements of NYHA functional class and peak VO_2 at 3 months after the procedure even in patients over the age of 60 years. However, little is known about long-term results in those patients. Furthermore, although impaired exercise capacity is a predictive parameter in terms of mortality in congenital heart disease,[16,17] limited information is available for long-term extent of functional improvement in middle-aged and elderly patients with markedly reduced cardiopulmonary function. The recently published study of Khan et al.[18] showed significant improvements in cardiac remodeling and 6-min walk test at 12 months after the procedure in patients over the age of 40 years. Our results are similar to their findings. However, we also evaluated the time course of functional improvements, and we revealed that an improvement in exercise capacity was delayed compared with cardiac remodeling in middle-aged and elderly patients with a marked reduction in cardiopulmonary function. The mechanism leading to improved exercise capacity after the

procedure has been clarified. ASD closure with abolishment of left-to-right shunt leads to augmented LV filling by increased preload and therefore to improved stroke volume.[14] The rise in cardiac output may explain the increase of exercise capacity. In this study, we found the time delay of improvement in exercise capacity compared with cardiac remodeling. In addition, even if RV size was normalized in more than half of all patients, mean exercise capacity continued to be at least moderately reduced. Exercise capacity is influenced by several factors, not only cardiac output but also noncardiac factors such as pulmonary function and skeletal muscle function. We speculated that the delay of improvement in exercise capacity could be related to the time needed for the recover of skeletal muscle function after transcatheter closure of ASD in middle-aged and elderly patients with a marked reduction in cardiopulmonary function, but not the time needed for the recover of cardiac function. Similar to our results, Helber et al.[19] showed the lack of improvement in exercise capacity early after surgical ASD closure in patients over the age of 40 years, and they suggested that the improvement in exercise capacity took place after 1–2 years after the procedure. Thus, exercise training after the procedure may be needed to recover the pulmonary function and skeletal muscle function early in those patients.

Study Limitations. This study had some limitations. First, the current findings need confirmation in large studies because this study included only 20 patients from a single center. Second, exercise capacity is also influenced by noncardiac factors, but measurements of those factors are lacking. Finally, the evaluation of RV function using two-dimensional strain echocardiography, three-dimensional echocardiography, or tricuspid annular plane systolic excursion should be preferable to demonstrate RV remodeling after transcatheter closure of ASD.

Conclusion

Transcatheter closure of ASD in patients $\geq$ 40 years of age with markedly reduced cardiopulmonary function resulted in significant long-term improvements of cardiac remodeling and functional capacity. There were differences in the time course of improvement between cardiac remodeling and exercise capacity after the procedure in those patients.

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IMAGES IN CARDIOLOGY

Combined Subaortic and Mid-ventricular Obstruction With Significant Aortic Stenosis Diagnosed by Triphasic Doppler Flow Pattern

Multiple Levels of Left Ventricular Outflow Tract Obstruction

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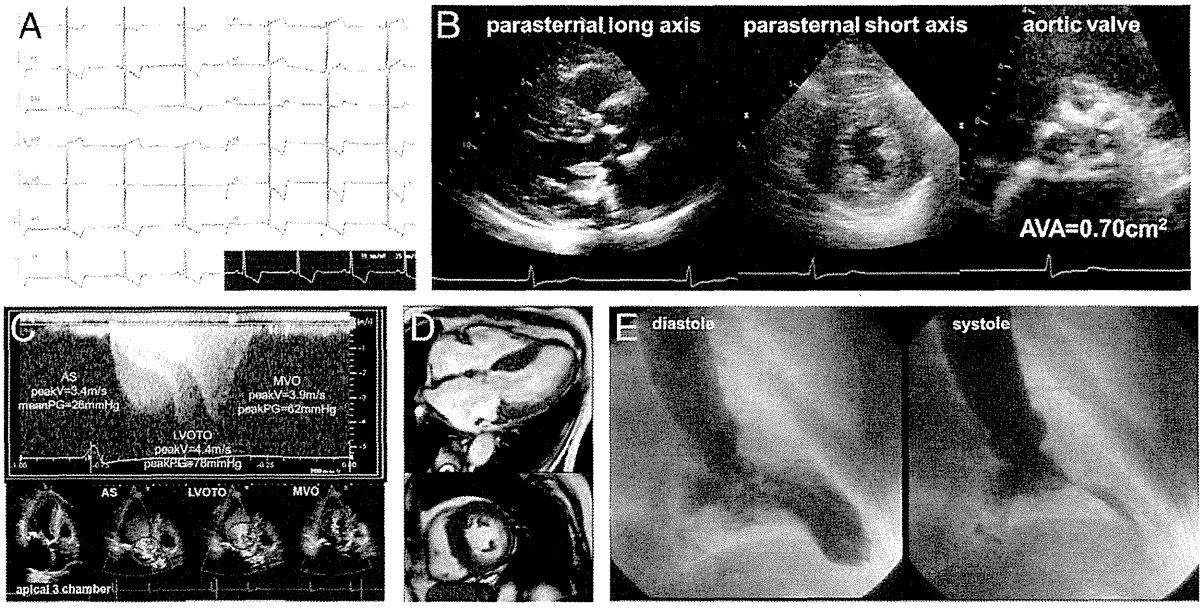
Okayama, Japan



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A 74-year-old woman was referred to our hospital for evaluation of increasing dyspnea and fatigue. Her electrocardiogram showed marked left ventricular (LV) hypertrophy and T-wave inversion over leads V_3 to V_6 **(A)**. Transthoracic echocardiography demonstrated significant aortic stenosis (AS) and gross asymmetrical LV hypertrophy **(B**, Online Videos 1, 2, and 3), which caused combined subaortic and mid-ventricular obstruction. Doppler echocardiography demonstrated triphasic severe pressure gradients through the LV outflow tract (LVOT), mid-peaking symmetric velocity, and 2 asymmetric late-peaking "dagger-shaped" velocities. The subaortic gradient reached a peak in mid-systole, and the mid-ventricular gradient reached a peak in late systole and persisted to early diastole (**C**, Online Videos 4 and 5). Cardiac magnetic resonance imaging showed marked asymmetrical LV hypertrophy **(D)**. A left ventriculogram also revealed dynamic mid-cavity and LVOT obliteration **(E)** (Online Video 6). Coronary angiography showed normal vessels.

The patient was diagnosed with multiple levels of LVOT obstruction with significant AS. Septal myectomy and aortic valve replacement were successfully performed. This case highlighted the significance of meticulous examination by Doppler echocardiography for evaluation of dynamic LVOT obstruction.

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Full Paper

Acute Vasoreactivity Testing With Nicardipine in Patients With Pulmonary Arterial Hypertension

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Abstract. Acute vasoreactivity testing for patients with pulmonary arterial hypertension (PAH) has been reported to be useful to identify patients with sustained beneficial response to oral calcium-channel blockers (CCBs), but there is a risk of exacerbation during the testing with oral CCBs. Therefore, we developed a testing method utilizing intravenous nicardipine, a short-acting CCB, and examined the safety and usefulness of acute vasoreactivity testing with nicardipine in PAH patients. Acute vasoreactivity testing with nicardipine was performed in 65 PAH patients. Nicardipine was administered by short-time continuous infusion (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min) followed by bolus injection (5 $\mu g/kg$). Hemodynamic responses were continuously measured using a right heart catheter. Acute responders were defined as patients who showed a decrease in mean pulmonary artery pressure of at least 10 mmHg to an absolute level below 40 mmHg with preserved or increased cardiac output. Two acute responders and sixty-three non-acute responders were identified. There was no hemodynamic instability requiring additional inotropic agents or death during the testing. Acute responders had good responses to long-term oral CCBs. The acute vasoreactivity testing with nicardipine might be safe and useful for identifying CCB responders in PAH patients.

Keywords: calcium-channel blocker, acute vasoreactivity testing, pulmonary arterial hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a condition characterized by elevated mean pulmonary artery pressure (PAP), and the prognosis is poor in most cases (1, 2). Although we and other investigators have reported that a small proportion of patients with PAH respond to long-term calcium-channel blockers (CCBs) and have a better prognosis (3 – 6), the empiric use of CCBs in PAH is not recommended because of the risk of exacerbation (7, 8).

Acute vasoreactivity testing is usually performed to predict a better prognosis and identify acute responders who are more likely to have a sustained beneficial response to oral CCBs and can be treated with these less-expensive drugs (6, 9). Although acute vasoreactivity testing is most commonly performed using inhaled nitric oxide (iNO) (10), intravenous epoprostenol (11), or intravenous adenosine (12), there are uncertainties regarding the choice of vasodilator (13).

In pulmonary arterial smooth muscle cells (PASMCs), the free Ca^{2+} concentration in the cytosol ($[Ca^{2+}]_{cyt}$) is an important determinant of contraction, migration, and proliferation. $[Ca^{2+}]_{cyt}$ in PASMCs can be increased by Ca^{2+} influx through voltage-dependent calcium channels (VDCC), receptor-operated Ca^{2+} channels (ROC), and

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store-operated Ca^{2+} channels (SOC) and by Ca^{2+} release from intracellular stores via inositol 1,4,5-trisphosphate receptors (IP_3Rs) and ryanodine receptors. NO, epoprostenol, and adenosine suppress elevation of $[Ca^{2+}]_{cyt}$ through inhibition of ROC and SOC, which are associated with G protein–coupled receptor (GPCR), IP_3R, and transient receptor potential cation channels (TRPCs); however, CCBs suppress the elevation through inhibition of VDCCs (14).

Acute vasoreactivity testing using CCBs appears to be a reasonable method for predicting response to long-term CCBs, but the safety and efficacy of oral and intravenous CCBs for the testing have not been established in PAH patients. Occurrence of life-threatening hemodynamic compromise has often been documented in nifedipine and verapamil testing (7, 15, 16). Therefore, it is now accepted that CCBs should not be used for acute testing (17, 18).

Since oral CCBs have a long half-life, there is a risk of exacerbation due to instability of pharmacokinetics when they are used for testing (7, 16). Therefore, the development of a testing method using a short-acting intravenous CCB is needed.

Nicardipine chloride, a hypotensor available in most countries in the world, is administered to patients with hypertensive emergency, to those with acute heart failure associated with hypertension, and to those with hypertension during an operation by continuous infusion at 0.5 – 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, at 0.5 – 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and at 0.5 – 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or bolus injection at 10 – 30 $\mu g/kg$, respectively, by reference to the Japanese package insert. The half-life of nicardipine after intravenous injection at 10 $\mu g/kg$ to a healthy adult is about 1 h, which is shorter than that of nifedipine at 10 mg per os (about 2.6 h). Therefore, we developed a testing method using short-acting intravenous nicardipine and examined the safety and usefulness of the test.

Materials and Methods

Subjects

We performed acute vasoreactivity testing using intravenous nicardipine for adult patients diagnosed as having PAH without left heart disease who had been hospitalized in our hospital from April 1999 to October 2011.

Pulmonary hypertension was defined by a resting mean PAP ≥ 25 mmHg during right heart catheterization (RHC) with a mean pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg (19).

Exclusion criteria were as follows: thromboembolic pulmonary hypertension, hemodynamic instability including cardiac index (CI) less than 2.2 $L \cdot min^{-1} \cdot m^{-2}$ and systolic blood pressure (BP) less than 80 mmHg, or having symptoms associated with low cardiac output (CO) at rest.

All of the studies were approved by the Ethics Committee of Okayama University Graduate School of Medicine, Density, and Pharmaceutical Sciences, and written informed consent was obtained from all patients before the procedure. The investigation also conformed to the principles outlined in the Declaration of Helsinki.

Baseline evaluation

Baseline evaluation included medical history, WHO functional class, physical examination, 6-min walk test, and brain natriuretic peptide (BNP). Baseline hemodynamic evaluations were performed in all patients with RHC as previously described (1, 20). Baseline hemodynamic measurements included heart rate (HR), BP, right atrial pressure (RAP), mean PAP, PCWP, and CO determined by the Fick method. CI was calculated as CO / body surface area. Total pulmonary resistance (TPR) was calculated as (mean PAP/CO) × 80.

Acute vasoreactivity testing

Acute vasoreactivity testing was performed at the time of absence of hemodynamic instability. Acute pulmonary vasodilator responsiveness was assessed by administration of nicardipine (Astellas Pharma Inc., Tokyo) with short-time continuous infusion (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min) followed by a bolus injection (5 $\mu g/kg$) (Fig. 1). We used continuous infusion at a low dose for a short time before the bolus injection to ensure the PH patients' safety.

Hemodynamic responses were continuously measured before, during, and after administration of nicardipine using an RHC. S_aO_2 (saturation of arterial blood) and $S_{PA}O_2$ (saturation of pulmonary arterial blood) were measured to calculate CO every 5 min. A significant acute response to nicardipine was defined as a reduction in mean PAP of at least 10 mmHg to an absolute mean PAP of less than 40 mmHg without a decrease in CO according to the American College of Chest Physicians–developed guidelines (21). Discontinuance criteria were systemic BP less than 70 mmHg, HR elevation more than 50 bpm from baseline, and/or appearance of any other constitutional symptoms.

Chronic treatment with CCB

Chronic oral CCB therapy was initiated in patients who showed significant acute pulmonary vasoreactivity as defined above.

Statistical analysis

All values are expressed as the mean ± standard deviation.

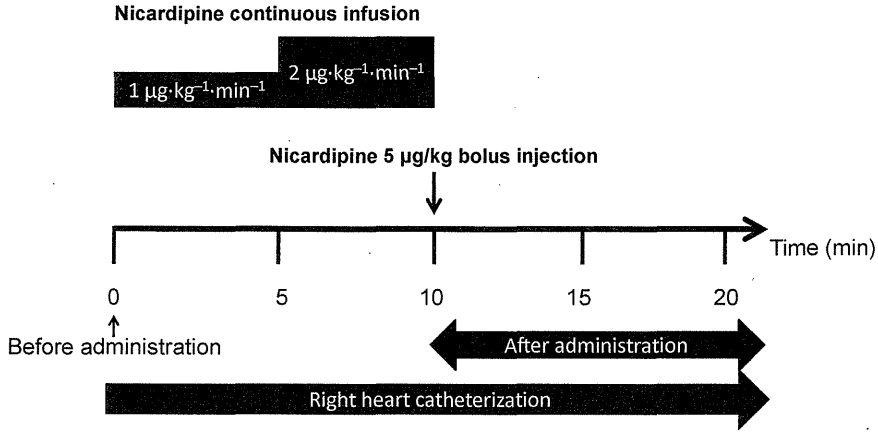

Fig. 1. Protocol of acute vasoreactivity testing with nicardipine.

Results

Study group

Sixty-five patients met the criteria of PAH and were included in the analysis. The clinical characteristics and baseline hemodynamic parameters of these 65 patients are shown in Table 1.

Responses to intravenous nicardipine and long-term CCB in acute responders

Hemodynamic changes during the testing are shown in Table 2. The values after administration shown in Table 2 were measured when maximum variation of mPAP was detected. There was no hemodynamic instability requiring additional inotropic agents or death during the testing. Two acute responders were identified.

Responder 1

A 26-year-old woman with idiopathic PAH was admitted to our hospital 4 years after diagnosis at another hospital. Beraprost sodium at a daily dose of 60 μg had been prescribed for 2 years, but shortness of breath became exacerbated and recurrent episodes of syncope during activity occurred. She was therefore referred to our hospital for treatment. Pretherapeutic hemodynamic data were as follows: HR, 65 bpm; systemic BP, 108/66/85 mmHg; PCWP, 7 mmHg; PAP, 84/35/55 mmHg; RAP, 5 mmHg; CO, 3.3 L/min; CI, 2.2 $L \cdot min^{-1} \cdot m^{-2}$; systemic vascular resistance (SVR), 1939 $dynes \cdot s \cdot cm^{-5}$; pulmonary vascular resistance (PVR), 1163 $dynes \cdot s \cdot cm^{-5}$; and TPR, 1333 $dynes \cdot s \cdot cm^{-5}$.

Unfortunately, her hemodynamic data were incomplete because the right heart catheter tip had moved down to the right ventricle from the pulmonary artery and could not be recovered. Systolic right ventricular pressure (sRVP) and saturation of right atrial blood ($S_{RA}O_2$) were therefore assessed as alternatives to systolic PAP and $S_{PA}O_2$, respectively. Her sRVP decreased to 41 mmHg from 69 mmHg and CO increased to 3.0 L/min from 2.0 L/min after administration of nicardipine, and she was therefore considered to be an acute responder.

Treatment with oral nifedipine at a daily dose of 10 mg was started, and then the daily dose was titrated up to 90 mg. Two years after starting the drug treatment, her data were as follows: HR, 64 bpm; systemic BP, 135/85/102 mmHg; PCWP, 5 mmHg; PAP, 35/10/22 mmHg; RAP, 0 mmHg; CO, 4.1 L/min; CI, 2.8 $L \cdot min^{-1} \cdot m^{-2}$; SVR, 1990 $dynes \cdot s \cdot cm^{-5}$; PVR, 331 $dynes \cdot s \cdot cm^{-5}$; and TPR, 429 $dynes \cdot s \cdot cm^{-5}$. Figure 2 shows improvement of right ventricular overload on an electrocardiogram and improvement in enlargement of cardiothoracic ratio and main pulmonary trunk on a chest X-ray. She has now achieved remission without PAH.

Responder 2

A 37-year-old woman with IPAH was admitted to our hospital with the chief complaint of shortness of breath.

Pretherapeutic hemodynamic data were as follows: HR, 65 bpm; systemic BP, 117/67/89 mmHg; PAP, 62/25/37 mmHg; RAP, 2 mmHg; CO, 6.1 L/min; CI, 3.6 $L \cdot min^{-1} \cdot m^{-2}$; SVR, 1135 $dynes \cdot s \cdot cm^{-5}$; and TPR, 482 $dynes \cdot s \cdot cm^{-5}$.

Hemodynamic changes in this acute responder were as follows: HR, 65 bpm; systemic BP, 111/60/79 mmHg; PAP, 39/15/24 mmHg; RAP, 2 mmHg; CO, 6.7 L/min; CI, 4.0 $L \cdot min^{-1} \cdot m^{-2}$; SVR, 923 $dynes \cdot s \cdot cm^{-5}$; TPR, 288 $dynes \cdot s \cdot cm^{-5}$; variation in mPAP, −13 mmHg; and variation in CO: +0.6 L/min.

Treatment with oral amlodipine at a daily dose of 2.5 mg was started. Four days after starting the drug treatment, the tricuspid regurgitation pressure gradient (TRPG) had decreased to 41 mmHg from 70 mmHg as

Table 1. Baseline characteristics

Variable	All (n = 65)
Sex: No. (%)	
Female	43 (66.2)
Male	22 (33.8)
Age: years	37 ± 17
Disease duration: month	48 ± 73
Cause of PAH: No. (%)	
Idiopathic	45 (69.2)
Congenital heart disease	9 (13.8) ASD,8; VSD,1
Connective tissue disease	5 (7.7) SLE,3; SSc,1; MCTD,1
Others	6 (9.2)
Medications: No. (%)	
CCB	8 (12.3)
Oral drug other than CCB	33 (50.8)
Epoprostenol	8 (12.3)
Clinical characteristics	
Height (cm)	161 ± 9.0
Weight (kg)	56 ± 13
Body mass index (kg/m^2)	22 ± 4.4
WHO functional class	2.4 ± 0.6
BNP (pg/mL)	130 ± 177
Hemodynamics	
Heart rate (/min)	78 ± 15
BP (s/d/m) (mmHg)	113 ± 17 / 62 ± 12 / 79 ± 13
PAP (s/d/m) (mmHg)	84 ± 26 / 36 ± 15 / 54 ± 18
Right atrial pressure (mmHg)	3.9 ± 3.6
CO (L/min) / CI (L·min^{-1}·m^{-2})	4.0 ± 1.7 / 2.5 ± 0.9
TPR (dyne·s·cm^{-5})	1223 ± 648

PAH = pulmonary arterial hypertension, CCB = calcium channel blocker, s/d/m = systolic/diastolic/mean, BNP = plasma concentration of brain natriuretic peptide, CO = cardiac output, CI = cardiac index, TPR = total pulmonary resistance, ASD = atrial septal defect, VSD = ventricular septal defect, SLE = systemic lupus erythematosus, SSc = systemic scleroderma, MCTD = mixed connective tissue disease.

shown by ultrasonography. Now she takes amlodipine at a daily dose of 5 mg and TRPG is 53 mmHg. Figure 3 shows improvement of septal flattening during systole and TRPG by an echocardiogram.

Non-responders

Data for the 63 non-responders were as follows: baseline mPAP, 54 ± 18 mmHg; variation in mPAP, 0.9 ± 4.4 mmHg; and variation in CO, 0.4 ± 0.9 L/min.

Table 2. Hemodynamics during nicardipine-challenging test

	Pre	Post
Non-responder		
sBP (mmHg)	113 ± 17	106 ± 16
mPAP (mmHg)	54 ± 18	54 ± 19
CO (L/min)	4.0 ± 1.7	4.5 ± 1.8
TPR (dynes·s·cm^{-5})	1236 ± 646	1090 ± 527
Responder 1		
sBP (mmHg)	105	99
sRVP (mmHg)	69	41
CO (L/min)	2.0*	3.0*
TPR (dynes·s·cm^{-5})	-	-
Responder 2		
sBP (mmHg)	117	92
mPAP (mmHg)	37	27
CO (L/min)	6.1	7.3
TPR (dynes·s·cm^{-5})	483	297

*$S_{RA}O_2$ was substituted for $S_{PA}O_2$, and cardiac output was calculated by the Fick oxygen method. sBP = systolic blood pressure, mPAP = mean pulmonary artery pressure, sRVP = systolic right ventricular pressure, CO = cardiac output, TPR = total pulmonary resistance.

Discussion

We performed acute vasoreactivity testing using intravenous nicardipine. The test was safe and two responders were identified in the 65 patients.

It has been demonstrated that long-term CCB responders have better prognosis than that of CCB non-responders, and CCBs are less expensive than other vasodilators (6, 22). Therefore, vasoreactivity testing to find responders is important and is required in clinical settings.

According to the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2009), vasodilator challenge should only be performed with short-acting, safe, and easy-to-administer drugs with no or limited systemic effects (18). Acute vasoreactivity testing is most commonly performed using inhaled iNO (10), intravenous epoprostenol (11), or intravenous adenosine (12). However, several investigators have also pointed out a problem with these agents: it is important to consider that these agents have different mechanisms of action and diverse hemodynamic effects, and their use may therefore not be interchangeable (13, 23). Since iNO vasodilates the pulmonary artery selectively and its half-life is very short (3 min), it has minimal systemic side

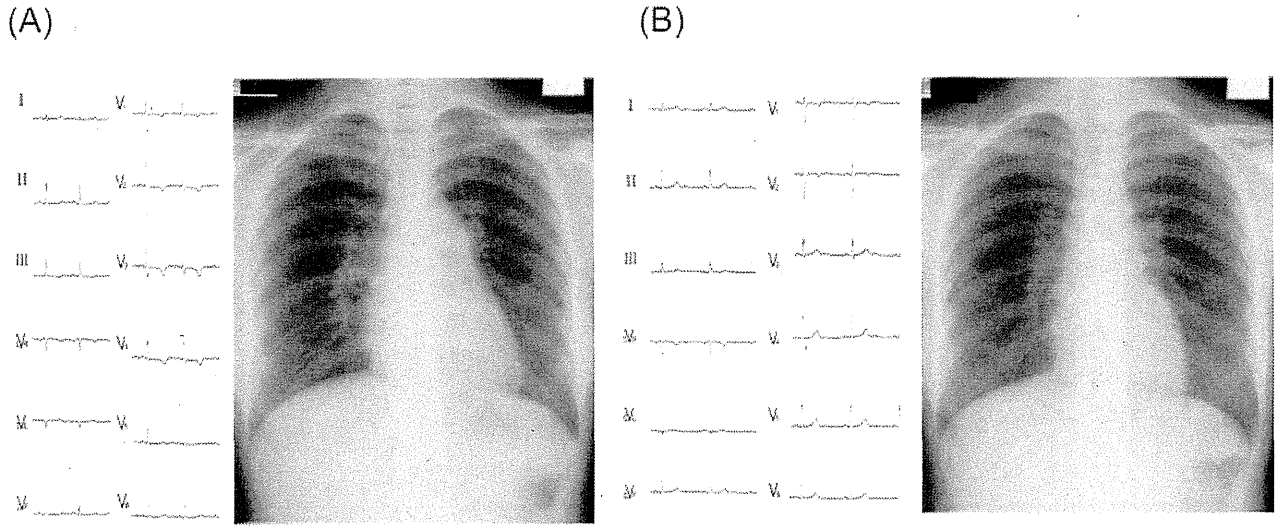

Fig. 2. Improvements in electrocardiogram and chest X-ray of responder 1. A) Before administration of nifedipine in April 1999. B) At three years after starting administration, March 2003.

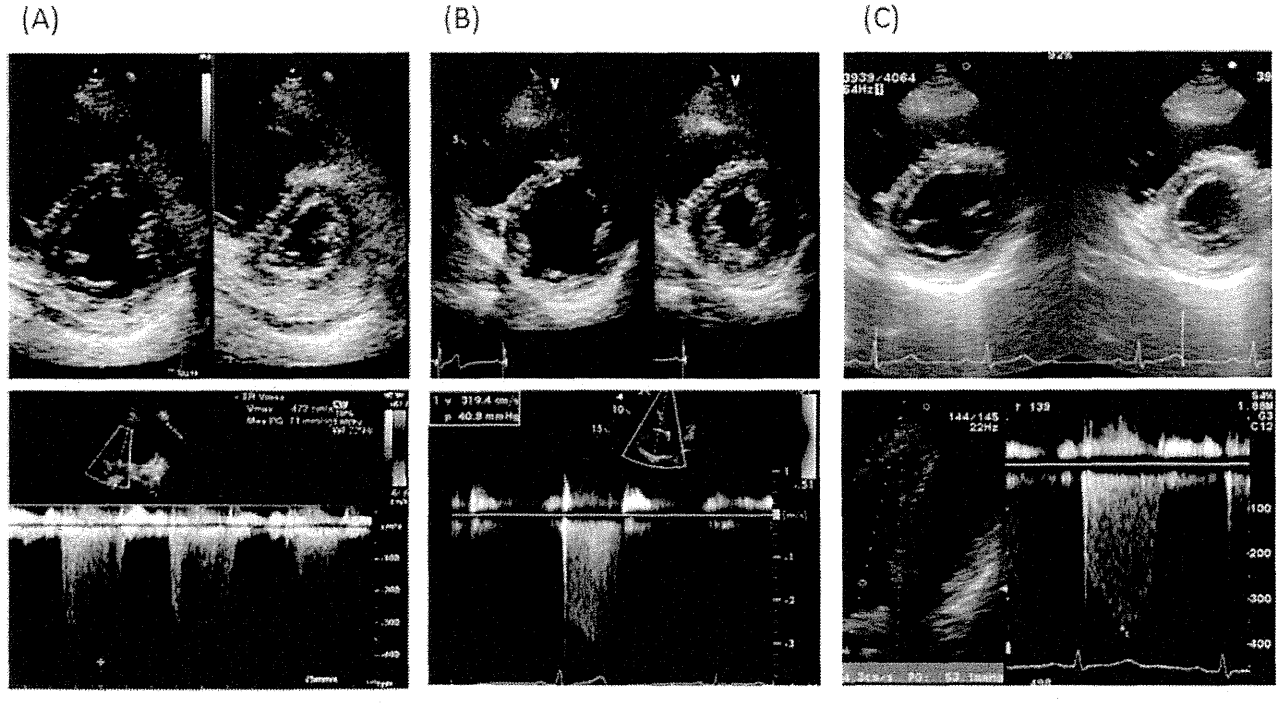

Fig. 3. Improvement in transthoracic echocardiogram of responder 2. Upper panels are parasternal short-axis view images in diastole and end-systole, and lower panels are tricuspid regurgitation (TR) velocity images. A) Before administration of amlodipine in October 2009, septal flattening at end-systole was observed (upper panel). TR velocity was 422 cm/s (lower panel) and TR pressure gradient (TRPG), which is used for estimation of systolic PAP, was 71 mmHg. B) At six days after starting administration of amlodipine at 2.5 mg in November 2009, septal flattening at end-systole was improved (upper panel). TR velocity was 319.4 cm/s (lower panel) and TRPG was 41 mmHg. C) With administration of amlodipine at 5 mg in January 2011, septal flattening at end-systole was improved (upper panel). TR velocity was 364.3 cm/s (lower panel) and TRPG was 53 mmHg.

effects (24). However, the duration of inhalation and the concentration for testing have not been standardized. Although adverse effects of iNO are very rare, to prevent leakage of NO, a delivery system, a gas cylinder, and respiratory therapy are required.

Intravenous epoprostenol revealed the patients most likely to benefit from CCB therapy; however, a favorable response to epoprostenol does not indicate that all patients will have a long-term response to CCBs (22). Epoprostenol causes frequent adverse reactions such as flushing, headache, and hypotension (24). In addition, this drug is ten-times more expensive in Japan than in America.

Adenosine is an easily available, stable, and inexpensive medication that has pulmonary vasodilatory properties. Its half-life is 5 – 10 s. When given intravenously, the short half-life allows a relatively higher plasma concentration of the agent in the pulmonary circulation rather than the systemic circulation, thus reducing systemic side effects (25). Adverse effects are palpitation, bronchospasm, hypotension, bradycardia, and atrioventricular block (26).

Acute vasoreactivity testing with the above-described drugs still fails to identify all of the patients who will have a long-term CCB response (6, 9), and it is unclear why some patients have an initial positive vasoreactivity testing but do not respond to CCBs after some time.

Furthermore, according to the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (2009), the use of CCBs given orally or i.v. as an acute test is discouraged due to the risk of potentially life-threatening complications; however, the statement was based on the reports in which oral nifedipine, intravenous/oral verapamil, or intravenous diltiazem was used for acute vasoreactivity testing (18, 27 – 30). We performed acute vasoreactivity testing using intravenous nicardipine. The test was safe in the 65 patients.

Nicardipine is an intravenous CCB, available not only in Japan but also in other countries, and is administrated as a hypotensor. This drug inhibits uptake of Ca^{2+} to vascular smooth muscle cells to dilate blood vessels (31). It has been reported that nicardipine has more powerful antagonism in vascular smooth muscle cells than in cardiomyocytes and is more vasoselective than other CCBs (nifedipine, verapamil, diltiazem) (32). Nicardipine, an intravenous CCB, is short-acting compared to oral CCBs. Therefore, it appeared that acute vasoreactivity testing using nicardipine could be carried out safely and might be useful for identifying long-term CCB responders more specifically than other vasodilators. Since our study was carried out in a small population, further controlled studies in larger populations are needed to confirm our results of testing including safety.

Since nicardipine was reported to induce reflex tachycardia and palpitation, we used low dosage by reference to that for patients with acute heart failure (33 – 35), and marked elevation in HR during testing was not observed in our study (Table 2). Fortunately, there were no critical hypotensive effects, and the testing could be carried out safely. However, it is often difficult to restore a patient's condition when the condition has deteriorated. Therefore, PAH patients should be closely monitored in the intensive care unit during acute vasoreactivity testing.

We did not compare this testing with other conventional vasodilator approaches and an active control group. Therefore, appropriate dosage for testing and usefulness were not adequately established. However, the mechanisms by which elevation of $[Ca^{2+}]_{cyt}$ are suppressed by nicardipine and by other drugs (NO, epoprostenol, and adenosine) are different, and addition of nicardipine testing with other vasodilator approaches might therefore raise the precision of acute vasoreactivity testing.

A positive test is observed in about 10% – 15% of patients with IPAH. Approximately half of these patients will experience long-term benefits of CCBs (23). As stated above, only a small number of patients benefit from CCBs. However, survival rate of long-term CCB responders was 97% in an average follow-up period of 7 years in a large retrospective study (n = 557) in which IPAH patients were treated with CCBs after demonstrating acute pulmonary vasoreactivity (6). Therefore, treatment with a CCB is one of the favorable and possible treatment options.

In conclusion, acute vasoreactivity testing with nicardipine might be safe for PAH patients and might be useful for identifying long-term CCB responders in PAH patients.

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