undergo LDLLT. A therapeutic option is required for patients waiting for a suitable donor or for those who are not candidates for lung transplantation.

Continuous intravenous infusion of epoprostenol has been reported to improve the prognosis of IPAH.[6,19] However, its indication for PVOD and PCH is still controversial. Some reports have cautioned against the possibility of causing massive pulmonary edema by application of epoprostenol for patients with PVOD or PCH.[9,10] Application of epoprostenol for PVOD or PCH might be unsuccessful because when the pulmonary arterioles dilate and resistance of the pulmonary veins remains fixed, transcapillary hydrostatic pressure might increase and pulmonary edema might occur.[20] In contrast, some patients with PVOD have been reported to show temporary amelioration by application of epoprostenol.[7,8] There is 1 case report that showed that long-term epoprostenol therapy improved exercise capacity and pulmonary hemodynamics in PVOD.[8] The authors concluded that in this case, the administration of epoprostenol played a role in the regulation of vascular tone in pulmonary venules rather than in the pulmonary arteries. Detailed hemodynamic measurements showed that microvascular pressures initially increased during an infusion of no more than $6\,ng \cdot kg^{-1} \cdot min^{-1}$ of epoprostenol, but at higher doses, cardiac output increased and the calculated pulmonary vascular resistance decreased.[21] To the best of our knowledge, there are no reports that have described patients with PCH being successfully treated with epoprostenol.

We administered epoprostenol to 8 patients with PVOD or PCH because they had no other therapeutic option besides lung transplantation. In our cases, we cautiously administered epoprostenol, starting with a low dose. When we increased the dose of epoprostenol too quickly, an imbalance of dilatation between pulmonary arterioles and veins occurred. However, if we slowly increased the dose in a step-wise manner and used diuretics or inotropes as necessary, the transcapillary hydrostatic pressure decreased and we could avoid severe pulmonary congestion.

For the successful treatment of PVOD and PCH with epoprostenol, early recognition and diagnosis of PVOD/PCH are essential in addition to the careful application of epoprostenol. A lung biopsy is the only method of definitively diagnosing PVOD and PCH. However, in most cases, it is difficult to perform a lung biopsy because of the severity of the patients' condition. This is why it is important to clinically diagnose PVOD/PCH with available data and results of examinations. It is vital to be aware of poor oxygenation, low DLco, and distinct radiographic findings to diagnose or suspect PVOD and PCH.[20,22] In the present study, all patients presented with marked oxygen desaturation on exertion and a severe decrease in DLco. Their chest radiographs and high-resolution CT scans revealed radiographic findings that were characteristic for PVOD and PCH, but not IPAH (**Table 4**; **Figure 3**).[14,23] Early recognition of PVOD/PCH in patients with pulmonary hypertension is possible based on these clinical and radiographic characteristics. This might lead to careful introduction and dose adjustment of epoprostenol and to successful treatment of these complicated diseases.

The present study showed that as a result of epoprostenol therapy, clinical and hemodynamic data were improved (**Table 2**; **Figure 2**), at least temporarily. All patients were critically ill before starting epoprostenol therapy. The mean 6-min walk distance, which is reported to correlate well with the prognosis in IPAH, was significantly increased after therapy. Our data showed that epoprostenol significantly improved exercise capacity and increased cardiac output of patients with PVOD or PCH, but did not decrease PAP and right atrial pressure, which are known to determine the survival of IPAH.[24] This might be one of the reasons why patients eventually showed deterioration. Most patients showed maximal improvement within half a year after starting epoprostenol therapy. In some cases, with cautious control of epoprostenol therapy, there is a possibility of longer survival than previously reported. The dose of epoprostenol given at the time when patients showed maximal improvement in clinical status was $24\,ng \cdot kg^{-1} \cdot min^{-1}$, regardless of whether they could undergo LDLLT. Although they could walk further in the 6-min walk test because of increased cardiac output with epoprostenol therapy, patients showed deterioration of interstitial infiltration in chest X-rays and CT scans and needed a higher flow of supplemental oxygen. Considering severe oxygen desaturation and limited prognosis with epoprostenol therapy, further studies are required to determine better therapeutic strategies to treat PVOD and PCH.

Conclusions

We applied epoprostenol treatment to 8 patients with atypical clinical and radiographic findings such as IPAH. Histological findings revealed that 6 patients had PVOD and the other 2 patients had PCH. Epoprostenol was applied at a higher dose and for a longer period than previously reported cases, and worked as a bridge to lung transplantation for 4 patients. It was also applied in 4 patients who had no chance to undergo lung transplantation. All patients showed temporary amelioration in WHO functional class, exercise capacity, and cardiac index with long-term epoprostenol therapy. When patients are suspected of having PVOD or PCH by characteristic clinical and radiographic findings, careful application of epoprostenol can be considered as a bridge to lung transplantation or as the only method to improve their clinical condition because they have no other therapeutic options.

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Refined Balloon Pulmonary Angioplasty for Inoperable Patients with Chronic Thromboembolic Pulmonary Hypertension

Hiroki Mizoguchi, MD; Aiko Ogawa, MD, PhD; Mitsuru Munemasa, MD, PhD; Hiroshi Mikouchi, MD, PhD; Hiroshi Ito, MD, PhD; Hiromi Matsubara, MD, PhD

Background—Although balloon pulmonary angioplasty (BPA) for inoperable patients with chronic thromboembolic pulmonary hypertension was first reported over a decade ago, its clinical application has been restricted because of limited efficacy and complications. We have refined the procedure of BPA to maximize its clinical efficacy.

Methods and Results—Sixty-eight consecutive patients with inoperable chronic thromboembolic pulmonary hypertension underwent BPA. We evaluated pulmonary artery diameters and determined the appropriate balloon size by using intravascular ultrasound. We performed BPA in a staged fashion over multiple, separate procedures to maximize efficacy and reduce the risk of reperfusion pulmonary injury. A total of 4 (2–8) sessions were performed in each patient, and the number of vessels dilated per session was 3 (1–14). The World Health Organization functional class improved from 3 to 2 ($P<0.01$), and mean pulmonary arterial pressure was decreased from 45.4±9.6 to 24.0±6.4 mm Hg ($P<0.01$). One patient died because of right heart failure 28 days after BPA. During follow-up for 2.2±1.4 years after the final BPA, another patient died of pneumonia, and the remaining 66 patients are alive. In 57 patients who underwent right heart catheterization at follow-up, improvement of mean pulmonary arterial pressure was maintained (24.0±5.8 mm Hg at 1.0±0.9 years). Forty-one patients (60%) developed reperfusion pulmonary injury after BPA, but mechanical ventilation was required in only 4 patients.

Conclusions—Our refined BPA procedure improves clinical status and hemodynamics of inoperable patients with chronic thromboembolic pulmonary hypertension, with a low mortality. A refined BPA procedure could be considered as a therapeutic approach for patients with inoperable chronic thromboembolic pulmonary hypertension. (***Circ Cardiovasc Interv.* 2012;5:748-755.**)

Key Words: peripheral vascular disease ■ pulmonary hypertension ■ reperfusion ■ revascularization

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) have a poor prognosis. Pulmonary endarterectomy can dramatically reduce pulmonary arterial pressure in selected patients with CTEPH to improve their prognosis.[1] However, not all patients can undergo pulmonary endarterectomy because of technical limitations.[2–4] Pulmonary endarterectomy for CTEPH with peripherally located organized thrombus is associated with less improvement in pulmonary hemodynamics and has a higher mortality in patients compared with those with proximal thrombi.[1] The latest guidelines for the diagnosis and treatment for pulmonary hypertension indicate that the selection of patients for pulmonary endarterectomy depends on the extent and location of the organized thrombi in relation to the degree of pulmonary hypertension and taking into consideration age and comorbidities.[5]

Editorial see p 744

Balloon pulmonary angioplasty (BPA) for a patient with CTEPH was first reported in 1988.[6] In 2001, Feinstein et al[7] reported the efficacy of BPA for a series of patients with CTEPH. Although this report showed a significant improvement in hemodynamics and exercise tolerance, these improvements were not as good as those of pulmonary endarterectomy. Moreover, 1 of 18 patients died from reperfusion pulmonary injury and right ventricular failure after BPA. The mortality rate of BPA is not superior to that of pulmonary endarterectomy. Pulmonary endarterectomy is an established treatment for CTEPH and the mortality rate was recently reported to be as low as 2.2%,[8] although it varies up to 14.3% depending on the institute.[9–11] More than 20 years after the first report of BPA, BPA is still not widely accepted as a therapeutic option for inoperable patients with CTEPH.

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From the Division of Cardiology (H.Miz., M.M., H.Mik., H.Mat.) and Department of Clinical Science (A.O., H.Mat.), National Hospital Organization Okayama Medical Center, Okayama, Japan; Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan (H.I.).

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Correspondence to Hiromi Matsubara, MD, PhD, Division of Cardiology and Department of Clinical Science, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701–1192, Japan. E-mail matsubara.hiromi@gmail.com

WHAT IS KNOWN

- The efficacy of balloon pulmonary angioplasty (BPA) was previously reported in a small series of inoperable patients with chronic thromboembolic pulmonary hypertension, who have a poor prognosis.
- However, BPA has not been widely adopted owing to relatively less improvement and higher mortality compared with surgical pulmonary endarterectomy.

WHAT THE STUDY ADDS

- We have refined the procedure of BPA by using intravascular ultrasound to provide more accurate estimates of the diameters of target pulmonary arteries.
- We performed BPA in a staged fashion over multiple procedures to reduce the risk of pulmonary reperfusion injury while still achieving an effective therapeutic result.
- Although there is a learning curve in performing this procedure, our refined approach to BPA may be a treatment option for patients with inoperable chronic thromboembolic pulmonary hypertension.

We have recognized 2 major problems that need to be resolved for improving the clinical efficacy of BPA. One problem is insufficient improvement in hemodynamics after the BPA procedure, and the other is the high incidence of potentially fatal complications, including reperfusion pulmonary injury and rupture of the pulmonary artery. We have refined the BPA procedure to improve its clinical efficacy. The major difference of our refined BPA procedure is the introduction of intravascular ultrasound (IVUS) to determine the optimal balloon size. IVUS has enabled us to determine the actual size of the target lesions, which leads to improved hemodynamic outcome and reduced risk of reperfusion pulmonary injury and rupture of the pulmonary artery. We studied the clinical efficacy of this refined BPA procedure with advanced care for inoperable patients with CTEPH.

Methods

Patient Selection

Sixty-eight consecutive patients with inoperable CTEPH who underwent BPA between November 2004 and September 2011 were enrolled in this study. BPA was performed after approval of the Institutional Review Board, and written informed consent was obtained from each patient before the procedure. A diagnosis of CTEPH was based on detailed medical history, a physical examination, chest radiography, a chest computed tomography (CT) scan, transthoracic echocardiography, lung ventilation-perfusion scintigraphy, right heart catheterization, and angiographic demonstration of multiple stenoses and obstruction of bilateral pulmonary arteries. Pulmonary angiography showed at least 1 of the following features: pouching defects; webs or bands, intimal irregularities, abrupt vascular narrowing, and complete vascular obstruction.[12] All patients were diagnosed as inoperable by experienced surgeons because of the location of thrombi and surgical accessibility, age, and comorbidities. All patients were in World Health Organization (WHO) functional class III or IV despite medical treatment. None of the patients were excluded from undergoing BPA based on age restrictions or severity of hemodynamics.

Management Before BPA

All patients were administered epoprostenol to decrease pulmonary arterial pressure as much as possible. Epoprostenol was started at 1 ng/kg/min ≈5 days before the procedure and increased by 1 ng/kg/min each day to a maximum of 5 ng/kg/min by the day of BPA. If a patient was already on long-term epoprostenol therapy before BPA, the dosage was unchanged. All medications, including warfarin, were maintained, except for beraprost sodium, which was discontinued when the dosage of epoprostenol reached 2 ng/kg/min. If the cardiac index was <2.2 L/min/m^2, dobutamine at a dose of 2 to 3 μg/kg/min was administered before the procedure.

BPA Procedure

On the basis of the results of pulmonary angiography and perfusion scintigraphy, we selected in advance which branches of the pulmonary arteries to dilate. We targeted webs (Figure 1) or bands, abrupt vascular narrowing, or complete vascular obstruction (Figure 2). The lower lobe was targeted for the initial BPA in most cases. Targeted vessels were limited within 2 vessels in a single lobe of the lung in the initial BPA session to avoid the occurrence of severe reperfusion pulmonary injury. We placed a 9F indwelling sheath (ArrowFlex; Teleflex, Durham, NC) into a vein (mainly into the internal jugular vein [n=65] and occasionally into the subclavian [n=1] or femoral vein [n=2]) and brought a 6F long sheath (Bright Tip Sheath Introducer; Cordis/Johnson & Johnson, New Brunswick, NJ) to the main pulmonary artery via the 9F sheath, using 0.035-inch wire (Radifocus Guide Wire M; Terumo, Tokyo, Japan). Heparin (5000 U) was administered when the sheath was inserted, and 1000 U of heparin was added every hour during the procedure. We selected a branch of the pulmonary artery by a 6F guiding catheter (Mach 1 peripheral MP; Boston Scientific, Natick, MA) and performed angiography (Figure 1A and 1B). We crossed a 0.014-inch wire (Cruise; Asahi Intecc, Tokyo, Japan) to the targeted lesion and evaluated the lumen size of the vessel with IVUS (Eagle Eye Platinum; Volcano, San Diego, CA) (Figure 1C). Because organized thrombi are isoechoic, we used ChromaFlo (Volcano, San Diego, CA) computer software to clearly visualize and distinguish lumen and thrombi. We measured the vessel diameter at the site where thrombi occupied the lumen and the vessel was most severely stenosed. After determination of the vessel diameter with IVUS, we usually used a 2-mm balloon for the initial dilatation to avoid rupture and dissection of the pulmonary artery. We dilated the vessel by balloon catheters of appropriate size (2 to 4 mm, IKAZUCHI PAD, Kaneka, Osaka, Japan; 5 to 7 mm, Bandicoot RX, St. Jude Medical, St. Paul, MN and Aviator Plus, Cordis/Johnson & Johnson, New Brunswick, NJ; 8 mm, Sterling Monorail, Boston Scientific, Natick, MA). The appropriate size was determined according to the vessel diameter measured by IVUS. The maximal size was set not to >90% of the original size of the vessel diameter, considering tapering and shrinkage of pulmonary arteries owing to reduced flow before BPA. The balloon was inflated by hand until the indentation disappeared or until the balloon was fully expanded. After inflation, angiography and IVUS were performed to ascertain that the vessel was dilated sufficiently and did not rupture (Figure 1D, 1E, and 1F). Dilatation was repeated if it was not sufficient by evaluation with IVUS, pulmonary arterial flow did not improve angiographically, or the pressure gradient across the dilated site >10 mm Hg. The procedure was discontinued when oxygen desaturation was >4% or hemo sputum occurred.

In the following sessions, targeted vessels were also limited within a unilateral lung, until the mean pulmonary arterial pressure was decreased to <35 mm Hg. When mean pulmonary arterial pressure was <35 mm Hg, BPA could be performed in both lungs in 1 session. BPA was repeated at an interval of 5 to 14 days after the initial procedure. Additional BPA at an interval of 12 to 16 weeks after the procedure was recommended until mean pulmonary arterial pressure at the end of hemodynamic monitoring became <30 mm Hg.

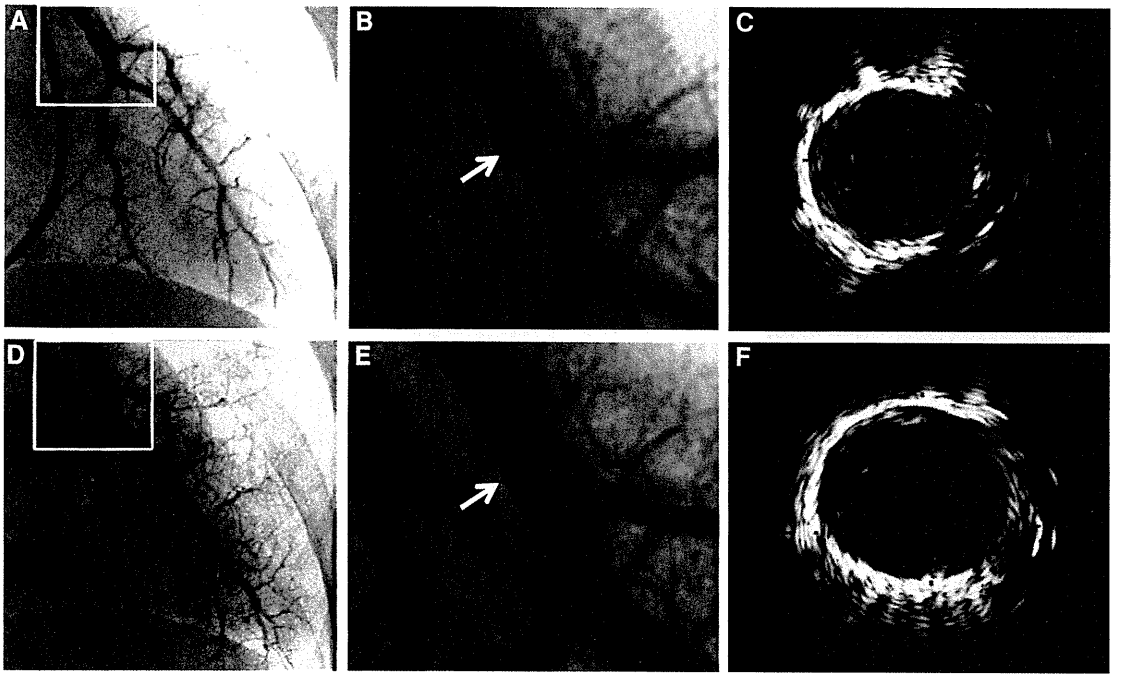

Figure 1. Representative angiographic and intravascular ultrasound (IVUS) images of balloon pulmonary angioplasty (BPA). **A**, Site of an intravascular web of the left pulmonary artery is indicated with a **square** on the angiogram. Peripheral arteries have shrunk because of a reduction in blood flow. **B**, A magnified image of a square in Figure 1A. An intravascular web is indicated with **arrows**. **C**, IVUS image (at the arrow in Figure 1B) shows organized thrombi, which occupy the lumen, and blood flow is limited in small channels. **D**, After a 5-mm balloon is dilated at 8 atm, an angiogram shows a dilated vessel and increased flow in the distal arteries after BPA. **E**, A magnified image of an intravascular web shown in Figure 1D. An intravascular web indicated with **arrows** is compressed and a vessel diameter of the distal artery is increased. **F**, IVUS image (at the arrow in Figure 1E). Thrombi are forced to 1 side and the lumen size is enlarged.

Management After BPA

We used noninvasive positive airway pressure ventilation at least 24 hours after BPA. Hemodynamics were continuously monitored with a Swan-Ganz catheter (Swan-Ganz CCOmbo V; Edwards Lifesciences, Irvine, CA) after the BPA procedure until noninvasive positive airway pressure ventilation could be weaned off. We performed a chest X-ray immediately after patients returned to the Cardiac Care Unit and performed a CT scan within 4 hours after BPA to check for increased density of the dilated segments. Epoprostenol and dobutamine were discontinued 3 days after a series of BPAs. Methylprednisolone (500 mg/day) was administered for 3 days to reduce reperfusion pulmonary injury after BPA.

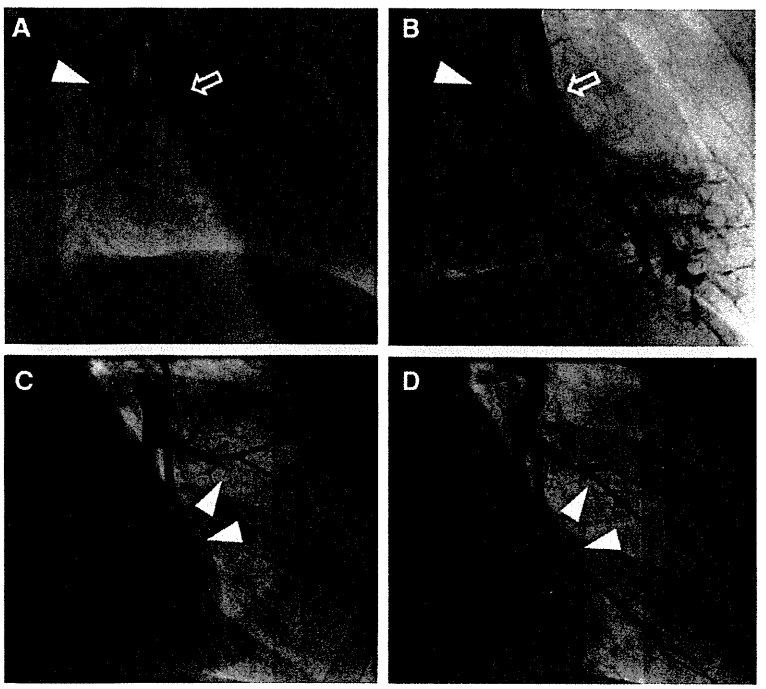

Figure 2. Representative pulmonary angiograms before and after balloon pulmonary angioplasty (BPA). **A**, Pulmonary angiogram shows abrupt vascular narrowing (**arrow**) and complete vascular obstruction (**arrowhead**) in the left lower arteries before BPA. **B**, After dilatation of target arteries with a 6-mm balloon at 6 atm, the lesions are successfully opened. **C**, Pulmonary angiogram shows complete vascular obstruction (**arrowhead**) in the left lower arteries before BPA. **D**, After dilatation of target arteries with a 2-mm balloon at 8 atm, the lesions are successfully opened.

Clinical Outcomes

Patients were followed up at least every 6 months after the final BPA. The effectiveness of BPA was evaluated by improvement of WHO functional class, hemodynamic parameters (systolic, diastolic and mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance), plasma levels of brain natriuretic peptide, and 6-minute walk distance before the first session of BPA, immediately after the final session of BPA, and at follow-up.

Statistical Analysis

Results are expressed as the mean±SD. Integers, including the number of sessions and balloons, are expressed as the median and range. Differences between variables measured at baseline and after BPA were tested by the paired *t* test. WHO functional class is expressed as the median and number of patients in each class, and changes in WHO functional class were evaluated using the Wilcoxon signed rank test. For assessing the difference among before, immediately after, and follow-up data, variables were analyzed by linear mixed modeling. Generalized linear mixed modeling was used to determine the learning curve for BPA, the incidence of complications between the initial 128 sessions (performed between November 2004 and October 2010), and the recent 127 sessions (performed between November 2010 and September 2011). All analyses were performed with IBM SPSS Statistics 20 (IBM, Armonk, NY). Statistical significance was defined as $P<0.05$.

Results

Baseline Characteristics

Our study included 53 females (78%) and 15 males (22%) with inoperable CTEPH. The mean age was 62.2±11.9 years old, with a range of 38 to 82-years old at the time of first admission. Disease duration (the time between diagnosis and the first admission to our hospital) was 3.2±3.2 years. Baseline patient characteristics are shown in Table 1. All patients were in WHO functional class III or IV with a high pulmonary arterial pressure. All patients were treated with warfarin, supplemental oxygen therapy, and >1 pulmonary hypertension-targeted drug. In addition, 5 patients were transferred to our hospital with intravenous infusion of dobutamine because of severe right heart failure.

Table 1. Clinical and Hemodynamic Data Before and After BPA

	Before BPA (n=68)	After BPA (n=67)	*P* Value
WHO functional class (I/II/III/IV)	3 (0/0/49/19)	2 (11/53/3/0)	<0.01
Oxygen inhalation (L/min)	3.0±1.4	1.3±1.0	<0.01
6MWD, m	296±108	368±83	<0.01
BNP, pg/mL	330±444	35±55	<0.01
sPAP, mm Hg	81.3±16.9	42.3±11.9	<0.01
dPAP, mm Hg	24.3±7.1	13.4±4.8	<0.01
mPAP, mm Hg	45.4±9.6	24.0±6.4	<0.01
RAP, mm Hg	8.1±4.4	1.9±1.5	<0.01
CI, L/min/m^2	2.2±0.7	3.2±0.6	<0.01
PVR, dyne sec/cm^5	942±367	327±151	<0.01

Values other than WHO functional class are expressed as mean±SD. WHO functional class is presented as the median and number of patients in each class.

6MWD indicates 6-minute walk distance; BPA, balloon pulmonary angioplasty; BNP, brain natriuretic peptide; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; and WHO, world health organization.

BPA Procedure

The 68 patients underwent a total of 255 BPA sessions. A total of 4 (2–8) sessions were performed in each patient, and the number of vessels dilated per session was 3 (1–14). Preoperative application of epoprostenol only resulted in a slight decrease in mean pulmonary arterial pressure (to 42.3±8.1 mm Hg, $P<0.05$). After observation using IVUS and Chroma-Flo, balloons matched to the vessel diameters were selected. As a result, we used 3 (1–6) balloons in 1 session, and the number of different balloon sizes per vessel was 2 (1–3). Contrast medium of 160.2±57.2 mL/session was required. Patients underwent 2 (1–6) sessions during 1 admission. The percentages of targeted arteries in 150 arteries at the initial session and in 558 arteries in the total sessions are shown in Table 2. At the initial BPA, the lower lobe of a unilateral lung was the target in most cases and none of the arteries in the left upper lobe were targeted. Ultimately, BPA was performed in all segments and there were no inaccessible lesions. The relative reductions in mean pulmonary arterial pressure and absolute change in mean pulmonary arterial pressure were correlated with the number of segments of pulmonary arteries treated by BPA (Figure 3).

Outcomes of BPA

The changes in clinical parameters before and after BPA (within 1 week after the final session of BPA) are summarized in Table 1 and Figure 4. One patient died 28 days after the third session of BPA because of right-sided heart failure, who had been transferred from another hospital after 3 months of hospitalization because of dobutamine-dependent severe right heart failure. After BPA, severe reperfusion pulmonary injury developed and subsequent worsening of right-sided heart failure required percutaneous cardiopulmonary support, which could not be recovered. Among the other 67 patients, 64 patients (96%) were in WHO functional class I or II after BPA, while there were no patients in classes I

Table 2. Distribution of Dilated Pulmonary Arteries at the Initial and Total Sessions

Right Lung Segment	Initial n (%)	Total n (%)	Left Lung Segment	Initial n (%)	Total n (%)
A1	1 (0.7)	44 (7.9)	A1+2	0 (0.0)	32 (5.7)
A2	2 (1.3)	40 (7.2)			
A3	1 (0.7)	32 (5.7)	A3	0 (0.0)	14 (2.5)
A4	3 (2.0)	27 (4.8)	A4	0 (0.0)	2 (0.4)
A5	8 (5.3)	30 (5.4)	A5	0 (0.0)	3 (0.5)
A6	2 (1.3)	6 (1.1)	A6	0 (0.0)	17 (3.0)
A7	13 (8.7)	30 (5.4)			
A8	32 (21.3)	48 (8.6)	A8	3 (2.0)	36 (6.5)
A9	33 (22.0)	48 (8.6)	A9	8 (5.3)	54 (9.7)
A10	40 (26.7)	54 (9.7)	A10	4 (2.7)	41 (7.3)

Initial indicates absolute number and percentage of targeted arteries in 150 arteries at the initial session; and total, absolute number and percentage of targeted arteries in 558 arteries in the total sessions.

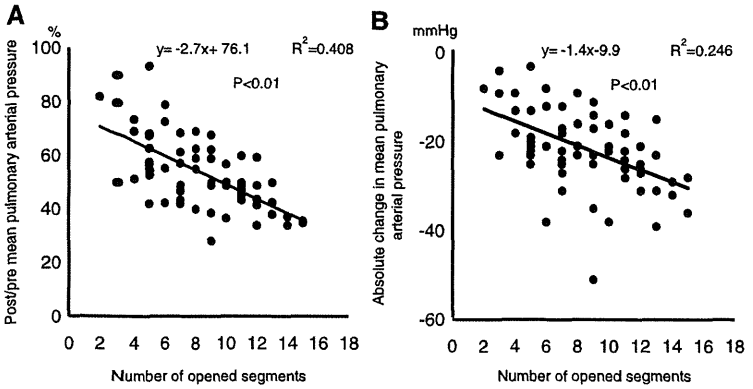

Figure 3. Correlation between the number of opened segments and the decrease in mean pulmonary arterial pressure. The relationships of reduction in mean pulmonary arterial pressure (**A**) and absolute change in mean pulmonary arterial pressure (**B**) with the number of segments of pulmonary arteries 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

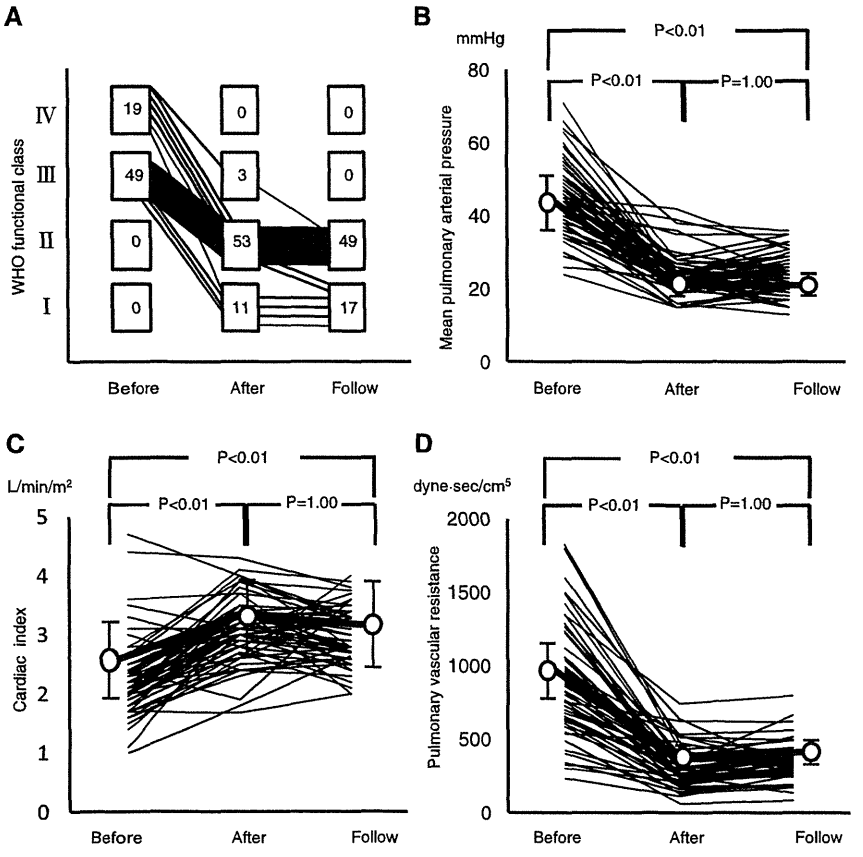

Figure 4. Change in parameters after balloon pulmonary angioplasty (BPA). Parameters before BPA (n=68), immediately after BPA (after) (n=67), and at follow-up (follow) (n=66 for **A** and 57 for **B–D**) were compared. World Health Organization (WHO) functional class (**A**), mean pulmonary arterial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

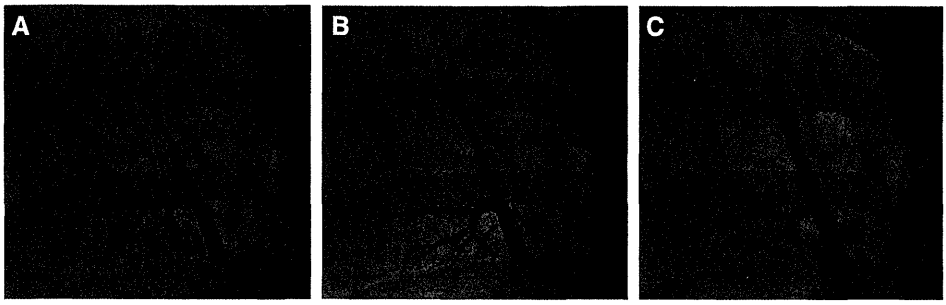

Figure 5. Representative pulmonary angiograms before balloon pulmonary angioplasty (BPA), after BPA, and at follow-up. Pulmonary angiograms before BPA (**A**), immediately after BPA (**B**), and at 1.5 years after the final BPA (**C**) are shown. The dose of epoprostenol was 5 ng/kg/min before and immediately 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 mm Hg,[13,14] and therefore, previously reported pulmonary arterial pressure after BPA >30 mm Hg 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

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（＊東京女子医科大学第四内科
〒162-8666 東京都新宿区河田町 8-1）

最近の肺高血圧治療法

小川愛子（おがわあいこ）＊・松原広己（まつばらひろみ）＊

肺高血圧症とは

肺高血圧症は，肺小細動脈の壁肥厚や狭窄により肺動脈圧が上昇し，右心不全となり労作時息切れや呼吸困難を呈する原因不明の疾患である．心臓カテーテル検査で，安静時平均肺動脈圧が 25 mmHg 以上であれば確定診断となる．ダナポイント分類では病因により五つに大別されており，原因疾患により治療方針が異なるため鑑別診断が重要である（表）[1]．

最新の肺高血圧症治療

1．肺高血圧症治療薬

肺高血圧症では，分類ごとに推奨される治療法が大きく異なる．以前は酸素療法や抗凝固療法による治療しかなかったが，①血管収縮作用をもつエンドセリンの増加，②血管拡張作用をもつ NO 産生系の障害，③プロスタグランジン I_2 の低下，の三つの要因が明らかとなり，それぞれに介入する治療薬が開発され，わが国でも現在 6 剤が使用可能である．1 群ではこれらの肺高血圧症治療薬により予後が改善してきたが[2]，他の群ではその有効性は確立されておらず，2，3 群では原疾患の治療が主体となる．図 1 に，当院で加療した特発性肺動脈性肺高血圧症の一例を示す．治療前は心エコー図で，拡大した右室による左室圧排像が認められたが，肺高血圧症治療薬投与により軽快し，心電図所見なども改善した．

表　ダナポイント分類

1．肺動脈性肺高血圧症(pulmonary arterial hypertension，PAH)
　1.1　特発性
　1.2　遺伝性
　1.3　薬剤性
　1.4　各種疾患に伴う PAH(膠原病，門脈圧亢進症，先天性シャント性心疾患など)
　1.5　新生児遷延性肺高血圧症
1′．肺静脈閉塞症/肺毛細血管腫症
2．左心疾患に伴う肺高血圧症
3．呼吸器疾患・低酸素血症に伴う肺高血圧症
4．慢性血栓塞栓性肺高血圧症
5．その他の疾患に伴う肺高血圧症(血液疾患，全身性疾患など)

2．慢性血栓塞栓性肺高血圧症に対するカテーテル治療

4 群の慢性血栓塞栓性肺高血圧症については，現在のガイドラインでは血栓内膜摘除術あるいは肺移植のみが推奨されている[1]．当院では，肺動脈末梢に器質化血栓が存在する手術適応のない症例に対してバルーン肺動脈形成術を行っている．図 2 に一例を示す．治療前は心エコー図，心臓カテーテル検査にて高度の肺高血圧を認め，肺血流シンチグラフィで亜区域性の血流欠損像を，肺動脈造影で閉塞像を認めた．バルーン肺動脈形成術により血流が改善し末梢動脈が描出され，肺動脈圧も著明に改善した．

3．新たな治療

現在の治療では改善効果が不十分な症例も存在しており，本来抗癌剤である imatinib など，新たな治療薬の臨床応用が試みられつつある．

肺高血圧症の臨床検査所見とその意義の変化

過去 10 年あまりの間に，肺高血圧症治療は大きく進歩してきた．それに伴い，臨床検査所見の変化も以前とは異なってきた．

肺高血圧症の診療における心電図の有用性はこれまであまり注目されてこなかったが，治前療後で肺高血圧症例の心電図所見を比較したところ，推定肺動脈圧の改善に伴って胸部誘導の陰性 T 波が改善し，また，

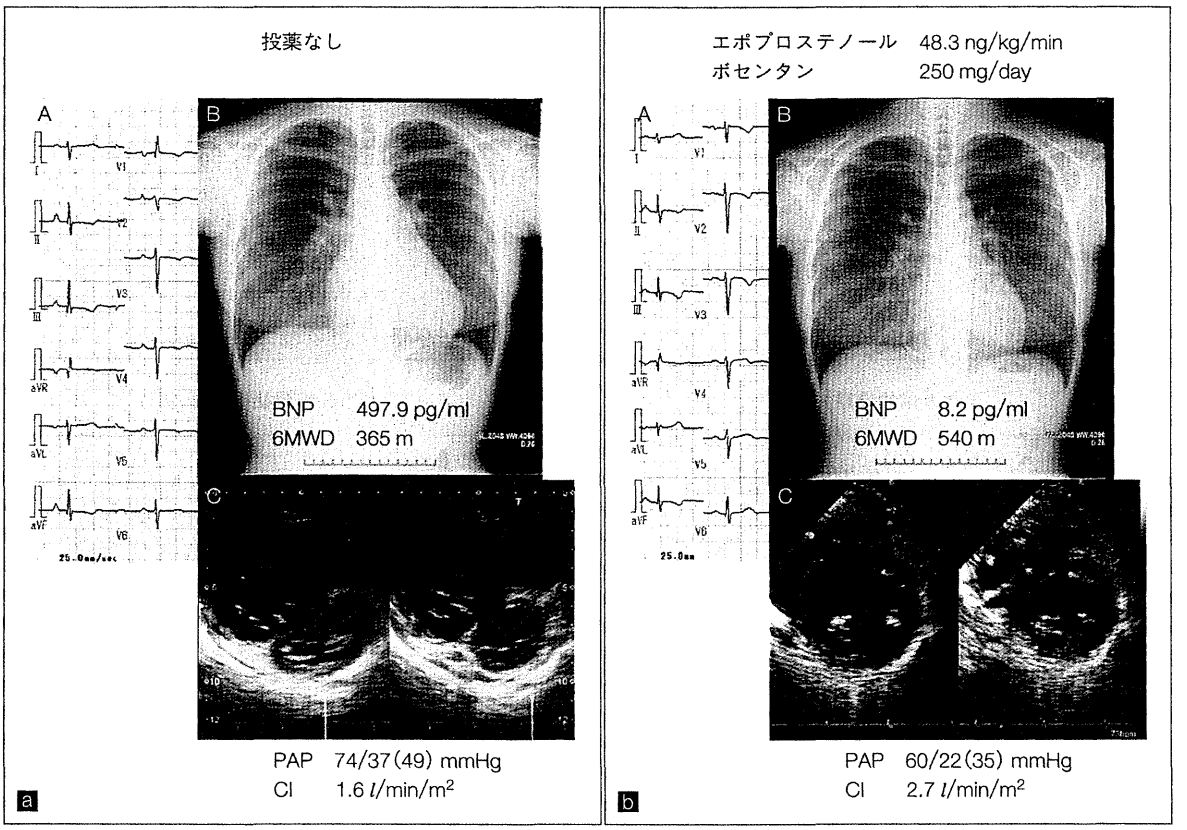

図1 特発性肺動脈性肺高血圧症の一例
a：初診時，b：9か月後(A：心電図，B：胸部X線写真，C：心エコー図)．
PAP：pulmonary arterial pressure(肺動脈圧)，CI：cardiac index(心係数)．
心電図では，右軸偏位，V1誘導の高いR波が減高し，心エコー図では左室圧排所見が消失した．

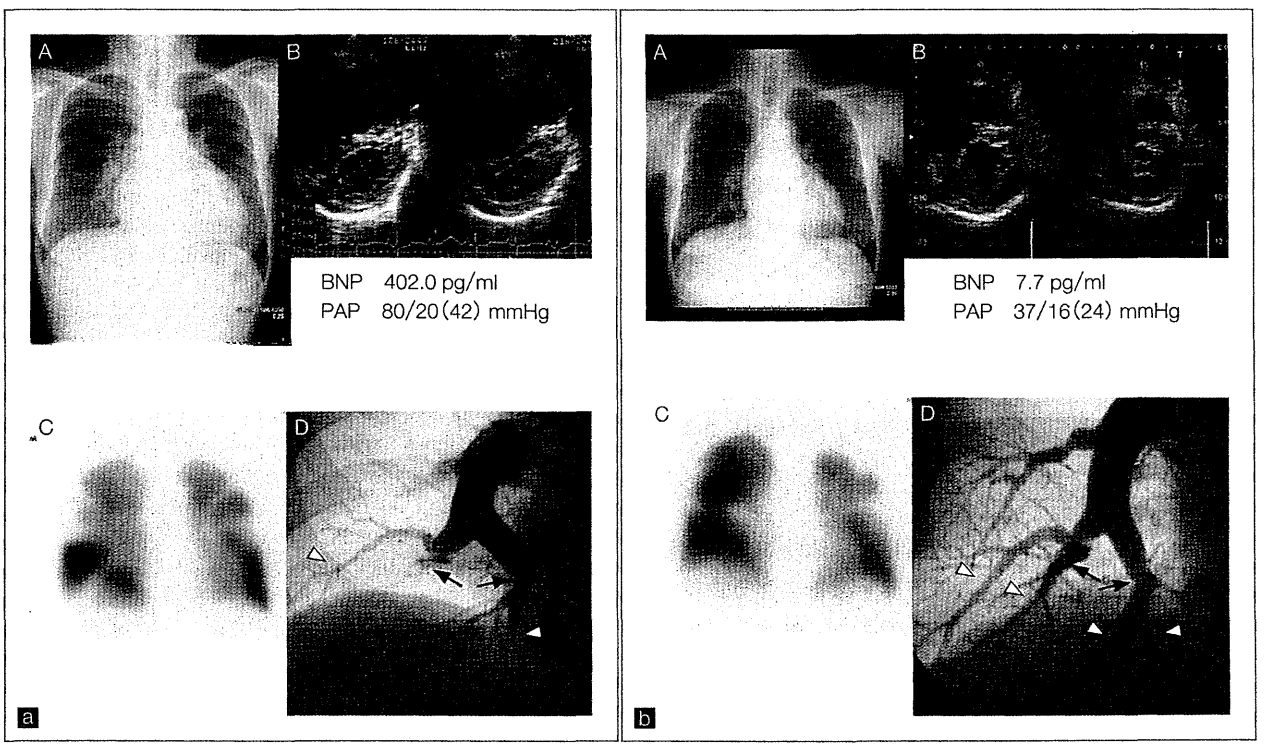

図2 バルーン肺動脈形成術により著明に改善した慢性血栓塞栓性肺高血圧症の一例
a：初診時，b：治療後(A：胸部X線写真，B：心エコー図，C：肺血流シンチグラフィ，D：肺動脈造影)．治療前の肺動脈造影では閉塞像(矢印)を認めたが，バルーン肺動脈形成術により血流が改善し末梢動脈(矢頭)が描出された．

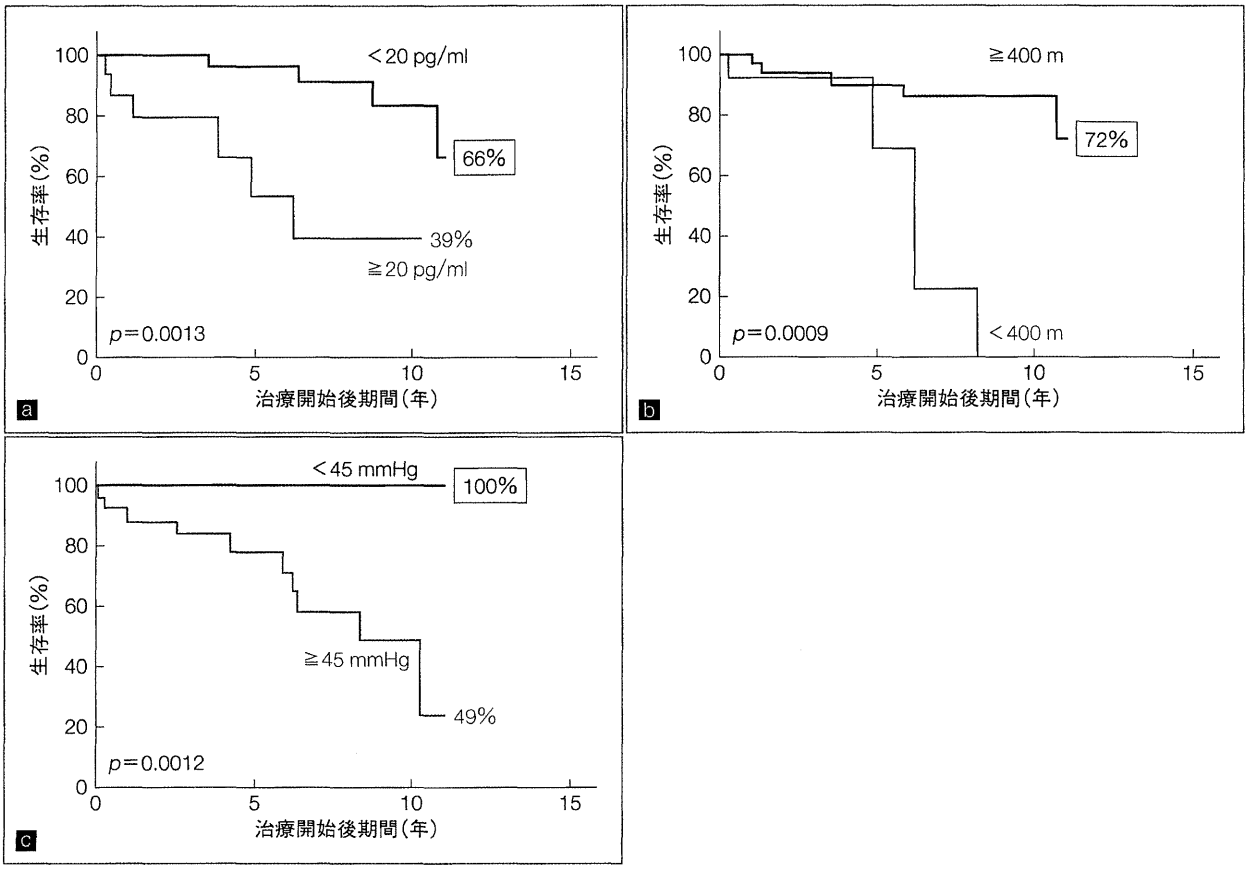

図3　治療後検査データからみた10年生存率　〔第75回日本循環器学会学術集会にて発表(一部改変)〕
a：血中BNP濃度，b：6分間歩行距離，c：平均肺動脈圧．当院で加療を行った特発性肺動脈性肺高血圧症47症例において，治療後に達成できた各種検査データの値により生存率を比較検討した．

V1誘導の高いR波が減高してくるなど，心電図所見が治療経過の評価に役立つ可能性が示唆された[3]．

また従来，血中BNP(brain natriuretic peptide)濃度や6分間歩行距離は，血行動態の悪化・改善に伴って変動するためフォローに有用であるとされてきたが，これらがいったん正常値となっても良好な長期予後には直結しない(図3)．当院においては，平均肺動脈圧が45 mmHg未満に達した症例では10年生存率100%を達成しており，BNP濃度や6分間歩行距離ではなく肺動脈圧の低下こそが長期予後改善につながると考えられる．

おわりに

肺高血圧症症例の各種検査所見は，原疾患や重症度により異なる．また，病態の進展・改善に伴う血行動態の変化を反映し，検査所見も大きく変動する．早期に正確な診断を行い，原疾患の違いにより適切な治療法を選択し，検査所見により経過を判断しながら治療を進めていくことが重要である．

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(* 独立行政法人国立病院機構岡山医療センター臨床研究部
〒701-1192 岡山市北区田益1711-1)

日本成人先天性心疾患学会雑誌 第1巻 第2号 17～23 (2012年)

【特 集】成人先天性心疾患の診療体制を問う

成人先天性心疾患の診療体制－ 循環器内科医の立場から

八尾 厚史
東京大学 保健・健康推進本部 講師

要 旨

近年の外科治療の進歩により，95%の先天性心疾患 (CHD) 患者が成人化を迎えることとなった．本邦ではすでに40万人を超えているとされる成人先天性心疾患 (ACHD) 患者は，その多くが小児科医師により管理をされているのが現状で，小児のみならず成人化した多数のCHD患者までも小児科医師が診るという極めて非合理的な危機的状況下にあり，ACHD患者の循環器内科医師への転科 (transfer) が求められている．しかしながら，循環器内科医師は (A) CHDに関する経験・知識に薄く，その自覚はあるもののACHD診療に積極的に参加するという意識は低い．東京大学医学部附属病院では，2008年4月から循環器内科医師によるACHD専門外来を小児科医師との連携のもと開設し，種々の重症例に対しても問題なく対応できることを示すに至った．その結果をもとに，2011年から2012年にかけて全国の22主要施設の循環器内科に呼びかけACHD循環器内科ネットワークを設立し，小児科医師との連携のもとACHD専門外来開設を含むACHD診療への積極的参加を提案したところ，合意を得るに至った．今後，これらの施設を中心にACHD診療体制の構築が推進されることに期待したい．

キーワード：成人先天性心疾患 (ACHD)，成人先天性心疾患の診療体制，循環器内科，チーム医療

はじめに

現在，すべての分野で小児慢性疾患患者に対する移行期医療が問題視されるようになってきた．今後診療科ごとで移行期医療の在り方に関する議論が行われ，新たな分野として移行期医療体制の確立に向かうものと思われる．こういった中，2007年の時点ですでに40万人以上に達したとされる成人先天性心疾患 (ACHD) [1]分野においては，その患者実数のみならず30%が中等症以上という重篤性を考えても早急な現実的対処の施行と将来的な診療体制の確立へ向けての事業を並行して行っていくことが急務である．先天性心疾患 (CHD) 児出生率は総出生数の約1%とされ，そのほとんどが手術的に修復を受け，95%が成人化するとされている．そして，成人化したCHD (ACHD) 患者は無症状の心房中隔欠損術後といった軽症例から肺高血圧最重症のEisenmenger症候群や単心室循環 (Fontan循環) といった循環器内科医師に馴染みの薄い重症複雑例までさまざまである．また，Down症を筆頭に染色体異常を持った患者も少なくなく，やはり現状の経験および専門知識の少ない循環器内科医師のみでの対応は難しいと言わざるを得ない．さらに，各国のガイドラインでも見られるように各疾患の治療に関するエビデンスレベルは低い[2,3]．このような経験や専門知識が薄い循環器内科医師がエビデンスの乏しい状況下でACHD患者を受け入れ診療を行うに際し，現在どのような対策が行われているのかに関して，そして今後どのような診療体制を構築すべきかに関して論じてみたい．

欧米諸国の事情と日本の状況

欧米諸国ではACHD集約施設による管理が推奨されている．2008年のACC/AHAガイドラインに示されたACHD集約施設に求められる要件[4]を表1に示す．ここでのトレーニングを受けた循環器医とは，小児科出身であれ循環器内科出身であれACHD専門医である必要があるが，欧米では通常循環器内科出身の医師である．日本ではACHD専門医師は存在せず，各施設で小児科医師が引き続き成人化したCHD患者を管理していることが普通である．欧米では，ACHD専門医の資格は段階的にレベルが設けられており，非常に専門性が高いものとなっている[5,6]．そういった専門医制度もまだなく，そしてすでに40万人を超えるとされるACHD患者が存在する本邦[1]で，どうやってACHD患者を診療していくのかは，極めて難解な問題といえる．さらに，ACHD患者を仮に専門の医師が診るとしても，表1にもあるようにさまざまな人員や医療技術そして医療体制が必要であり，循環器内科や小児科が単科で対応できうるものではない．ACHD患者を中心に総合診療体制を構築する必要がある．表1のガイドラインの要件をもとに独自の基準を作成し我々が行った調査では，2009年の時点で日本には14の施設のみがACHD集約施設としての稼働の可能性があるとい

う結果となった[7]. 表1の要件に比べ我々の基準は甘い基準であり，ACC/AHAガイドラインをそのまま適用した場合，ACHD専門医を度外視したとしても，循環器内科/小児循環の医師以外に関する基準を踏まえると日本には集約施設はその時点で1つも存在しえなかった可能性が高い.

さて，ここでACHD集約施設を有する欧米諸国で果たしてACHD患者の移行(transition)医療が適切に行われているのであろうか？ACHD患者がスムーズに小児科から集約施設に移ること(transfer)ができているかといえば必ずしもそうではなく，紹介された患者の約半数しか集約施設で管理されなかったというカナダからの報告がある[8]. この調査における患者の受け渡し(transfer)成功の可否に大きく関わる要因として，ACHD患者自身の自律性と病気の理解度が挙げられている．この部分に対する対策としては，患者の精神的発達により異なるが自律性および病気の理解度を上げていく教育を12歳から20歳代において小児科医師は行う必要があるとしている[2]. 将来的にはこの部分に対する小児科医師によるサポートが必要であるが，日本の現状を打破するためには患者教育が不十分な現状を踏まえ，循環器内科医師による未熟なACHD患者に対する対応も必要になると考えるほうが実際的であろう．ACHD診療に必須な要件(表1)を踏まえた上で日本の現状を加味して，循環器内科医師としてどういう対応ができるかに関して以下に論じてみたい.

循環器内科医師の問題点と現状から見た対策

表2にACHD診療に対する循環器内科医師の問題点を示す．この要因を鑑みるにつけて循環器内科医師がいきなりすべてのACHD患者の診療をするのはやはり困難といわざるを得ない．しかも，ACHD患者の手術記録を含め過去の診療記録は不明瞭であることもしばしばであり，基本的なもしくは歴史的なACHD診療・治療法に関する知識が薄いことは障害となることがある．この点に関しては，我々の行った調査から図1に示されるように循環器内科医師の多くが循環器内科医師のこういった実情を理解しており，セミナーなどの教育セッションやコンサルト機構充実の必要性を自覚している．そして，ACHD患者の特殊性からACHD患者は集約施設で診るべき心臓疾患との認識もある[7]. しかしながら，その一方で循環器内科においてACHD専門外来開設の意向は9%と低く，こういった循環器内科のACHD診療意欲の低さが規定因子となって日本での集約施設候補が先の14施設にとどまっていた[7]. ここで言えることは，ACHDに関するトレーニングや教育は必要としながらも，学会や循環器内科学におけるACHD分野の位置づけそしてACHD診療の重要性の比重に関しては認識が薄いということである．こういった意識から，主要施設での専門外来の必要性が軽視された可能性があるわけであるが，当時の本邦での虚血性心疾患患者数は約80万人くらいであるということを考慮すれば，ACHD40万人以上(約30%が中等症以上)[1]という数字は非常に大きい数字であることは想像に難くないはずである．したがって，こういったACHD分野の軽視という背景には，実際のACHD患者数がどれくらいなのかそしてその重症度はどの程度なのかに関する認識が一般の循環器内科医師に欠けていることが考えられるのである.

以上の循環器内科医師の現状を踏まえるならば，セミナーなどから徐々にACHDに関する知識や医療の教育から始めて循環器内科医師の養成を行っていくべきであろうか？いや，現状の緊急性から循環器内科医師に実地で参加していけるような医療体制を至急に構成し，並行してACHDに関する教育を進めていく必要がある.

循環器内科医師によるACHD診療の試み

以上述べてきたような循環器内科医師の不足要素(表2)を補いACHD患者を循環器内科医師で管理していく手立てがすぐにでもあれば，40万人以上のACHD患者の循環器内科への引き渡し(transfer)が進むものと思われる．確かに，ACHD分野に関する教育から始めACHD専門のトレーニング施設において十分な経験を積み，ACHD専門医として承認を得た医師にACHD患者管理を任せていくという正当な手順を踏むのが理想かもしれない．しかしながら，そのような手順では現実的にはACHD患者の引き渡しに何年かかるかはわからないし，そのような手順を受け入れる余裕や意識の高い循環器内科医師が十分数存在するのかは疑問である．しかも現時点での根本的な問題として，トレーニング施設としての施設基準すらない本邦では現実性に乏しい手順と言わざるを得ない．実践性の高い方法の模索が必要なのである.

そこで，東京大学医学部附属病院循環器内科(東大循環器内科)は2008年4月成人先天性心疾患専門外来を開設し実践を優先するとともに，その実践において具体的問題点の探索と解決を図ることを開始した．東大循環器内科が考案した“循環器内科医師によるACHD専門外来”は当時知る限り日本初の試みであり，患者利益を損なわない観点から以下の特長を持ったものであった．まず，外来担当の医師は循環器専門医を取得し，十分に一般循環器内科診療の経験のある医師であることとした．また，外来

日を小児循環器専門の医師および小児心臓外科医師と同一の曜日に合わせ，紹介患者を循環器内科担当医師に紹介しやすくした点，また同時に循環器内科医師からの小児循環器医師や小児心臓外科医師への相談や連携を行いやすくした点である．これにより**表2**に示されるような循環器内科医師のACHD診療における経験・知識不足やそれによる不安を現場でカバーできうるのではないかと考えられ，患者利益の尊重を貫けるものと考えられた．また，循環器内科医師のACHD診療におけるトラブルを予防するという意味から複雑な病態を有する患者は紹介元小児科医師や同院小児科医師外来と併診することで対応した．**図2**に2008年4月外来開設から2012年2月までの紹介患者数の推移を示す．また，紹介患者の病名一覧を**表3**に示す．これらの結果を見ても複雑心奇形や定期的投薬治療もしくは侵襲的治療を必要とする中等度以上の患者が60－70%を占めていることがわかる．また，循環器内科医師に馴染みの少ないFontan循環術前/術後患者や複雑心奇形未修復や姑息的シャント術後のみの重症例なども相当数見られた．こういった厳しい状況下ではありながら，手術適応の決定やインターベンション施行などの判断においては循環器内科主導のもと小児科医師との連携により十分対応が可能であり，重大なインシデントを生じることなく医療を提供することができた．つまり，小児(循環器)医師や小児心臓外科医師との緊密な連携により，一般的循環器内科診療に十分な経験を有する循環器専門医が即戦力としてACHD診療に参加できうるものと考えられた．

この予備調査途中経過をもとに，全国の主要施設の循環器内科医師にACHD診療への積極的参加を促すべく，2011年から全国の主要施設の循環器内科医師によるACHD診療対策委員会・循環器内科ネットワーク作成に乗り出すに至った．この第一義的目的は，各主要施設循環器内科にACHD患者の実態およびACHD診療の現状を訴え，東大循環器内科の手法を紹介し，ACHD診療を事実上開始していただくことであった．2011年12月に東京大学内で開かれた第一回会議および2012年6月に聖路加国際病院内で開かれた第二回会議において，各施設代表者に本件の説明と理解を要請したところ，現在22施設の循環器内科がACHD診療への準備を行うことで合意している(**図3**)．本活動は，厚生労働省科学研究費事業「成人に達した先天性心疾患の診療体制の確立に向けた総合的研究」(国立循環器病センター白石公班長)の一環として，そして日本成人先天性心疾患学会承認事業として現在も展開している．今後，これらの施設にてACHD専門外来の設置を含め循環器内科医師主導によるACHD診療が進むものと期待している．しかしながら，ACHD集約施設認定基準の作成に向けては，ACHD専門医制度確立や種々の診療チームの形成(**表1**)などまだまだ課題が多い．循環器内科医師によるACHD診療体制の確立を全国規模で推する必要がある．

表1． ACHD集約施設に求められるスタッフおよびサービス
－2008年ACC/AHAガイドライン（文献2）から抜粋改変－

ACHD専門の循環器内科医	1名以上数名
先天性心疾患心臓外科医	2名以上数名
専門のナース・ナースプラクティショナー	1名以上数名
心臓麻酔医	数名
CHD専門のトレーニングを積んだエコー専門医	2名以上数名
(術中経食エコーなど)	
CHD専門の診断心臓カテーテルのできること	
CHDに対する冠動脈以外のカテーテルインターベンションができること	
電気生理専門医	1名以上数名
(ペースメーカーや植え込み型除細動器手技ができる)	
運動負荷試験ができる(負荷エコー，核医学的，心肺機能検査，代謝的)	
心臓画像検査ができる(心臓MRI，CT，核医学的)	
さまざまな事象に対応できる多科にまたがる医療チームがある．	
(ハイリスク女性科的疾患/妊娠，肺高血圧，心不全・心移植，遺伝疾患，神経科，腎臓科，心臓病理，リハビリテーション部，社会福祉課)	
情報部(データの収集，データベースの供給など)	

表2　循環器内科医師によるACHD患者診療においての主な障害

1. すでに十分多忙である.
2. 先天心に対する知識や医療技術の不足
   a) 病態自体とくに(シャント，肺循環を含む)血行動態の理解
   b) 略号や呼び名
   c) 外科的治療に関する知識
   d) カテーテル検査や治療の進め方/行ない方に関する知識と技術
   e) 遺伝異常と心疾患/付随する異常に関する基本的知識
3. 小児科/小児心臓外科医師とのコミュニケーション不足
4. 小児科管理から成人医療への移行時に生じる患者教育など患者とのコミュニケーションに対する不安
5. ACHD患者が他の疾患および妊娠などの合併時における対応への不安
6. エビデンス不足による不十分なガイドライン

表3　ACHD患者の紹介・初診時の病態の詳細

診断名	患者数(%) (総数105名)	手術治療		
		未治療	修復術後 完全/不完全	姑息術後
AS (no bicuspid)	2 (1.9)	0	2/0	0
ASD	9 (8.6)	4	3/1	1 (縫縮術)
AVSD/ECD	8 (7.6)	1	6/1	0
Bicuspid AV	3 (2.9)	2	1/0	0
CoA/IAA	1 (1.0)	0	0/1	0
ccTGA	3 (2.9)	3	0/0	0
Epstein	4 (3.8)	1	2/1	0
PDA	2 (1.9)	1	1/0	0
PTA	1 (1.0)	0	1/0	0
PA-VSD/TOF-PA	5 (4.8)	0	4/0	1
TOF	22 (21.0)	1	17/4	0
TGA	8 (7.6)	1	5/2	0
TA/SV	9 (8.6)	3	3/1	2 (シャント術)
VSD	18 (17.1)	11	7/0	0
Others	10 (9.5)	9	1/0	0

AS (no bicuspid)：大動脈狭窄(2尖弁を除く)，ASD：心房中隔欠損，AVSD/ECD：房室中隔欠損/心内膜床欠損，Bicuspid AV：大動脈2尖弁，CoA/IAA：大動脈縮窄/大動脈離断，ccTGA：先天性修正大血管転位，PDA：動脈管開存，PTA：総動脈管遺残，PA-VSD/TOF-PA：肺動脈閉鎖-心室中隔欠損/ファロ-4徴症-肺動脈閉鎖，TOF：ファロー4徴症，TGA：大血管転位，TA/SV：三尖弁閉鎖/単心室，VSD：心室中隔欠損

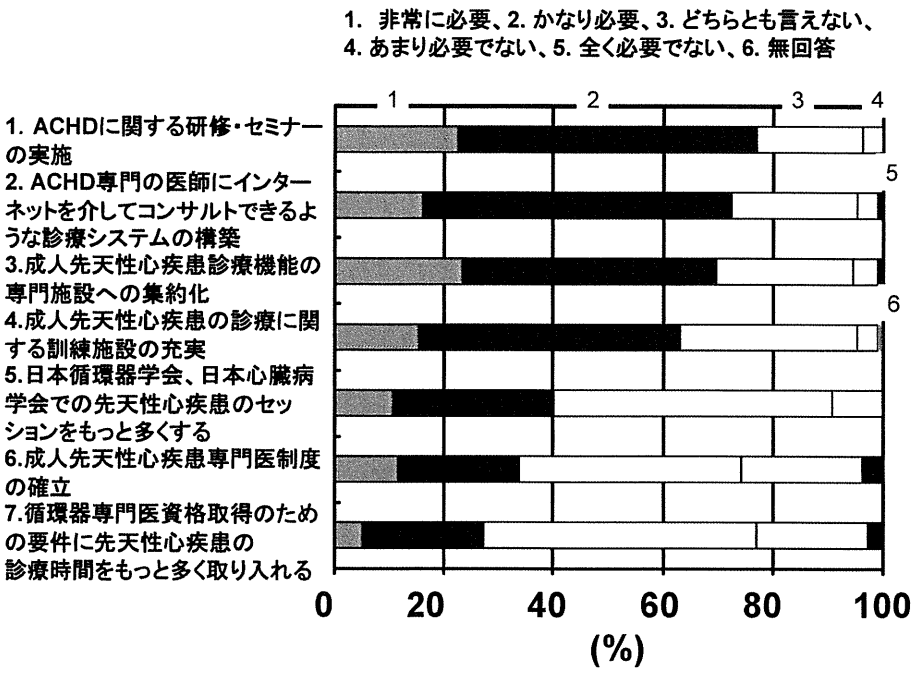

図1　循環器内科医師の意識調査結果(文献7より引用改変)

東大成人先天性心疾患外来紹介患者内訳
2012年3月1日現在
紹介総人数105人(男48名、女57名)
紹介時年齢　平均34.4±14.3歳(16-75)
紹介元　当科から　14
院内他科　46
小児病院　22
総合病院　10
その他　13

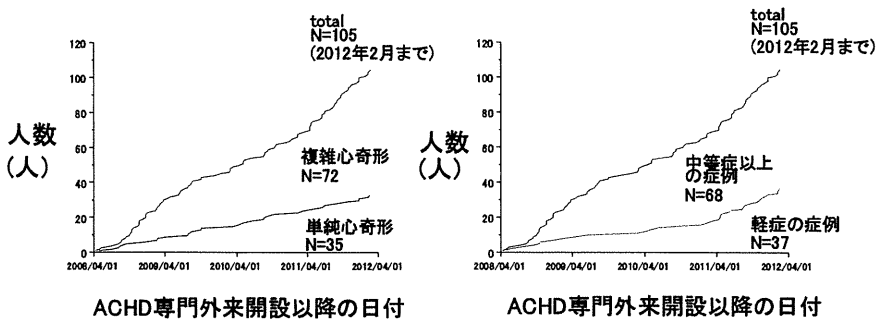

図2　東京大学医学部附属病院における新規に紹介されたACHD患者数の推移

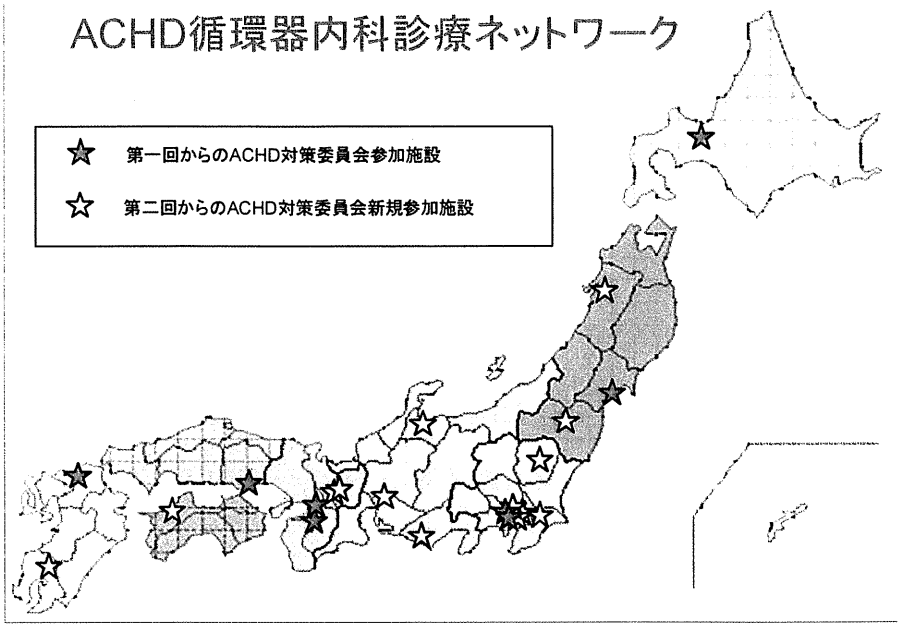

図3 ACHD循環器内科診療ネットワーク参加施設の全国分布
第一回および第二回ACHD対策員会参加施設により構築した循環器内科診療ネットワークを示す(2012年6月までの時点).

おわりに

「成人先天性心疾患の診療体制－循環器内科医の立場から」と表して述べてきたが,一言で言うならば,ACHD患者の重篤性と絶対数から小児科医師との連携の上に立った実臨床の早急なる実践とそれによるACHD診療の経験・知識の構築が循環器内科医師に求められている.それとともに,ACHD患者のすべてのニーズに答えACHD専門的診療を可能にする集約施設確立への準備も必要である.また,ACHD分野で世界的にも不足しているエビデンス構築のためには,主要施設間での連携を通じた症例の把握は必須である.そのためには,循環器内科ネットワークは全国レベルのみならず地方レベルでの病診連携といった形でも構築していく必要がある.日本成人先天性心疾患学会はもとより日本循環器学会を筆頭に循環器関係の各学会の協力や連携も必須であり,全国各地一体となった循環器内科医師の活動が求められる.

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INTERNAL MEDICINE

□ EDITORIAL □

Do Electrocardiography Scores Predict the Presence of Right Ventricular Dysfunction in Patients with Pulmonary Hypertension?

Kohtaro Abe

Key words: electrocardiography, pulmonary hypertension, right ventricular dysfunction

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Electrocardiography (ECG) is non-invasive and inexpensive. Although the diagnostic utility of ECG for ischemic heart diseases has been established, ECG has not been used as a screening tool to evaluate patients with pulmonary hypertension (PH) (1). Because ECG frequently seems to show changes consistent with right ventricular (RV) hypertrophy and right axis deviation in PH patients, its predictive value in PH has been widely studied. Ahearn et al. reported that 13% of 61 patients with PH demonstrated normal ECG findings despite having an average mean pulmonary arterial pressure (PAP) of 47 mmHg (2). The National Institutes of Health (NIH) registry has also demonstrated similar results. Of the 187 patients with PH in the NIH registry, RV hypertrophy was not noted on ECG in 13% and right axis deviation was not present in 21% (3). Therefore, ECG has been considered to be an inadequate screening tool to rule out the presence of clinically relevant PH. However, whether ECG predicts the presence of RV dysfunction in PH patients has so far not been fully investigated.

In patients with PH, it is very important to predict the presence of RV dysfunction, as the severity of RV dysfunction is a strong determinant of a poor prognosis (4). Echocardiography is commonly used as a non-invasive tool to estimate the RV function and PAP. Among many echocardiographic parameters, tricuspid annular plane systolic excursion (TAPSE) is very useful for detecting RV dysfunction and predicting poor prognoses in PH patients (5). However, in some cases, well-established sonographic techniques may be required to describe the exact apical four chamber view of an enlarged RV. Recently, cardiac magnetic resonance (CMR) has been developed to provide reliable data regarding the RV parameters, such as the mass index, wall motion, wall thickness, volume and ejection fraction (6). Although CMR is able to assess regional and global RV performance without complex geometric limitations, it is difficult to frequently perform CMR because the procedure demands significant technical support and expertise. Therefore, non-invasive and convenient approaches to predict the presence of RV dysfunction are needed.

Nagai et al. reported that two ECG variables, qR pattern and R/S >1 in lead V_1, are significantly positive in comparison to other ECG parameters in patients with RV dysfunction (7). In addition, PH patients who are positive for these two variables show significant RV dysfunction. Therefore, the authors concluded that the ECG scores (a score of 2 for the qR pattern and a score of 1 for R/S >1 in lead V_1) noted in their study might be useful for predicting the presence of RV dysfunction in PH patients. Although it is still questionable as to whether the ECG scoring system is useful as a screening tool for RV dysfunction, it can nevertheless provide very important information for physicians to help them determine whether to perform more invasive and expensive procedures in PH patients with higher ECG scores. In the future, a larger study is needed to confirm the accuracy of the ECG scoring system for predicting the presence of RV dysfunction in PH patients.

The author states that he has no Conflict of Interest (COI).

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Department of Advanced Cardiovascular Regulations and Therapeutics, Kyushu University, Japan
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Correspondence to Dr. Kohtaro Abe, koabe@cardiol.med.kyushu-u.ac.jp