Table 2. Comparison of extracorporeal membrane oxygenation (ECMO) decannulation and hospital discharge ratio

	Aggressive ECMO (n=45)	Delayed ECMO (n=31)	P-value
Survived off ECMO	34 (75.5%)	8 (25.8%)	$P < 0.01$
Survived to Discharge	26 (57.7%)	2 (6.5%)	$P < 0.01$

Table 3. Comparison of patients with biventricular and single ventricle physiology

		Aggressive ECMO (n=45)	Delayed ECMO (n=31)	P-Value
Biventricle	Non-Survivors	5	13	$P<0.01$
	Survived to discharge	11	2	$P<0.01$
Singleventricle	Non-Survivors	14	16	$P<0.01$
	Survived to discharge	15	0	$P<0.01$

Table 4. Comparison of ECMO duration (mean ± s)

	Aggressive ECMO	Delayed ECMO	P-Value
Non-Survivors	105.8 ± 80.8 hours	292.1 ± 249.1 hours	$P=0.034$
Survived to Discharge	96.5 ± 62.9 hours	184.5 ± 166.1 hours	$P=0.032$

Table 5. Patient profiles

	Aggressive ECMO (n = 45)	Delayed ECMO (n = 31)	P-Value
Timing of introduction			
In OR	19 (42%)	11 (35%)	$P=0.341$
In ICU, average days after operation	3.64 days	7.88 days	$p<0.01$
Reason for indication			
LCOS	19 (42%)	8 (26%)	$P=0.032$
Cardiac Arrest	12 (26%)	10 (32%)	$P=0.159$
Hypoxia	7 (16%)	4 (13%)	$P=0.052$
Hypercapnia	2 (4%)	0	$P=0.116$
Failure to wean from CPB	5 (12%)	10 (32%)	$P=0.236$

This table shows the comparison between groups A and B in terms of time to introduction of ECMO and indication criteria for ECMO.
OR: operating room; ICU: intensive care unit; LCOS: low cardiac output syndrome; n.s.: non-significant difference. Numbers inside ( ) indicate the number of patients.

Table 6. Lactate level of before and after ECMO

	Aggressive ECMO	Delayed ECMO	P-value
Before ECMO	5.5 ± 2.2 (mmol/L)	6.8 ± 3.1 (mmol/L)	$P=0.234$
After introduced ECMO	2.5 ± 1.2 (mmol/L)	2.9 ± 1.8 (mmol/L)	$P=0.435$

under stable hemodynamic conditions. We weaned the patient off ECMO within 12 h.

Descriptive statistics are expressed as mean ± standard deviation (s). The χ^2 test for a (2 × N) table, Kruskal-Wallis test and Student's t-test were used to evaluate differences between the groups for statistical significance. A p-value of <0.05 was considered to have statistical significance.

Results

The mean age of all patients was 10.8 months (range, 0 days–86 months) and the mean weight was 5.16 kg (1.16–16.5 kg). The demographic data of both aggressive ECMO and delayed ECMO are shown in Table 1. Cardiopulmonary bypass time (aggressive: 187.20 ± 117.48 min, delayed: 194.90 ± 115.33; p=0.400) and aortic cross-clamp time (aggressive: 79.93 ± 44.01 min, delayed: 64.62 ± 44.78 min; p=0.105) during surgery were not significantly different. Thirty-four patients (75.5%) from the aggressive ECMO group (n = 45) survived off ECMO and 26 patients (57.7%) survived to hospital discharge (Table 2). Eight patients (25.8%) from the delayed ECMO group (n = 31) survived off ECMO and 2 patients (6.5%) survived to hospital discharge (Table 2). Thirty-one patients (31/76, 40.8%) had biventricular physiology and 45 patients (45/76, 59.2%) single ventricle physiology. All the patients with single ventricle physiology treated with delayed ECMO died in the hospital (Table 3). The patients with biventricular physiology treated with the aggressive ECMO had significantly better results than the other groups. The patients who survived off ECMO and hospital discharge following the aggressive ECMO had significantly shorter ECMO duration than those following delayed ECMO (Table 4).

The timing of the introduction of ECMO is shown in Table 5. When ECMO was indicated for patients in the intensive care unit (ICU), the aggressive ECMO group had a significantly shorter duration of ECMO days after operation than the delayed ECMO group.

Our indication criteria for ECMO are shown in Table 5. In the aggressive ECMO group, low cardiac output syndrome was the significant reason for ECMO. In the delayed ECMO group, cardiac arrest and hypoxia were the two major reasons for ECMO.

The lactate levels before and after the introduction of ECMO are shown in Table 6. The lactate levels of both groups showed no significant difference.

Discussion

ECMO support following pediatric cardiac surgery provides effective support for postoperative cardiac and pulmonary dysfunction refractory to conventional medical management[4]. ECMO is an advanced therapy for acute cardiac and/or respiratory failure associated with congenital heart disease and pulmonary disease[5]. Indications for ECMO are affected by many factors, including ventricular function, magnitude of conventional inotropic support, and pulmonary function. No standard indication criteria or management guidelines have been established for ECMO in congenital heart disease because of its complex nature and specificity of use[6].

At our institution, in April 2005, the approach for ECMO was changed from a delayed ECMO approach, where patients were managed without ECMO for as long as possible, to an aggressive ECMO approach, where patients were indicated for ECMO as early as possible before a catastrophic event such as cardiac arrest occurred. In our results, the aggressive ECMO approach revealed a significantly better result in terms of ECMO survival and survival to hospital discharge than the delayed ECMO approach.

Ungeleider et al. have suggested that mechanical assistance should be routine after a Norwood stage 1 procedure and described an aggressive approach of mechanical assistance improving hospital survival rate[7]. Cooper et al. have suggested that the initiation of ECMO support should be based on "urgent" rather than "emergency" criteria, i.e., before the occurrence of end-organ dysfunction or circulatory collapse[8]. The risk factors for mortality due to ECMO are as follows: age below 1 month, male gender, long duration of mechanical ventilation support prior to introducing ECMO, and the development of renal or hepatic dysfunction during ECMO[6,9]. Following pediatric cardiac surgery, it is critical to maintain both systemic and pulmonary blood flow. The advantage of aggressive ECMO is the prevention of ventilator-induced lung injury caused by respiratory care injuries resulting from setting up mechanical ventilation.

Booth et al. demonstrated that the survival of cardiac patients supported by ECMO is associated with indication and cardiac diagnosis[2]. The ELSO Registry reported that rates of survival to weaning from ECMO and survival to hospital discharge were 59% and 39% in neonatal patients, and 62% and 46% in pediatric patients, respectively[3]. In our study, rates of survival to weaning from ECMO and survival to hospital discharge were 75.5% and 57.7%, respectively. Our aggressive ECMO approach was shown to be superior to that of the ELSO Registry average. Hence, the aggressive ECMO approach may result in better ECMO outcomes for patients with congenital heart disease than the delayed ECMO approach.

Patients with single ventricle physiology, especially those with hypoplastic left heart syndrome, had a significantly higher mortality rate than those with biventricular physiology[6,10]. In our review, the aggressive ECMO approach brings better outcomes, at least in patients with single ventricle physiology, than the delayed ECMO approach.

It is well known that long ECMO duration increases the risk of complications, such as bleeding, hemolysis, and systemic inflammatory syndrome. Long ECMO duration also increases the mortality rate associated with ECMO and may affect the progression of multiple organ dysfunction and have a negative influence on immunological systems[6,11-13]. A previous study of ours, as well as one by Baslaim et al., clearly indicated that patients with long ECMO duration (more than 3 days) may benefit less from ECMO support and may have an increased risk of mortality.[6,10]

In general, the purpose of pediatric ECMO as a mechanical circulatory support following cardiac surgery is recovery of cardiac function by unloading the right and left ventricle preloads and increasing the ECMO flow rate, as well as resting the lungs from the high demand for oxygen-saturated blood by the body. On the other hand, increasing the ECMO flow rate increases the left ventricular afterload and wall stress. These ECMO mismatches have a negative impact and outcome during pediatric ECMO following cardiac surgery. Hence, not only early introduction of ECMO, but also weaning as early as possible from ECMO might help to get better outcomes.

Several groups have reported improved survival in patients placed on ECMO in the operating room compared with those cannulated in the ICU[12,13]. Chaturvedi reported the avoidance of severe end-organ damage before restoration of adequate perfusion to pursue an aggressive approach for early indication of ECMO with the aim of reducing the morbidity and mortality associated with prolonged periods of hypoperfusion and cardiac arrest[13]. Our review also showed that it might be better to choose an aggressive ECMO approach of an early introduction of ECMO before progress to multiple organ dysfunctions could possibly prevent cardiac arrest, which results in a poor outcome. The ELSO Registry Report in 2009 showed a poor outcome for extracorporeal cardiopulmonary resuscitation after cardiac arrest, with survival rates of 26% in neonates, 47% in infants, and 39% in pediatric patients[3].

In conclusion, we recommend an aggressive ECMO approach following pediatric cardiac surgery, which requires early introduction and early discontinuation of ECMO support before end-organ dysfunction and circulatory collapse, rather than the conventional approach of delaying ECMO introduction. The aggressive ECMO

approach improved outcomes of ECMO therapy in our institution.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Conflict of Interest Statement

I declare, on behalf of myself and all authors, the following: We have no material, financial, or other relationship with any healthcare-related business or other entity whose products or services may be discussed in, or directly affected in the marketplace, by this manuscript.

References

1. Bartlett RH, Gazzaniga AB, Jefferies MR, et al. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Trans Am Soc Artif Intern Organs* 1976; 22: 80–93.
2. Booth KL, Roth SJ, Laussen PC, et al. Extracorporeal membrane oxygenation support of the Fontan and bidirectional Glenn circulations. *Ann Thorac Surg* 2004; 77: 1341–1348,
3. ECLS Registry Report. International summary, July 2009. Extracorporeal life support organization. Ann Arbor (MI).
4. Laforte A, Walter EMD, Hetzer R, et al. Extracorporeal membrane oxygenation for intraoperative cardiac support in children with congenital heart disease. *Interact Cardio Vasc Thorac Surg* 2010; 10: 753–758.
5. Schmid C, Philipp A, Mueller T, Hilker M. Extracorporeal life support systems, indications, and limitations. *Thorac Cardiovasc Surg* 2009; 57: 449–454.
6. Itoh H, Kasahara S, Sano S, et al. Risk factor analysis of cardiac ECMO for congenital heart disease. *Membrane Oxygenator (Japanese)* 2009; 32: 43–46.
7. Ungerleider RM, Shen I, Burch G, et al. Use of routine ventricular assist following the first stage Norwood procedure. *Cardiol Young* Feb 2004; 14 Suppl 1: 61–64.
8. Cooper DS, Jacobs JP, Ravishankar, et al. Cardiac extracorporeal life support: state of the art in 2007. *Cardiol Young* 2007; 17: 104–115.
9. Morris M, Ittenback R, Godinez R, et al. Risk factors for mortality in 137 pediatric cardiac intensive care unit patients managed with extracorporeal membrane oxygenation. *Crit Care Med* 2004; 32: 1061–1069.
10. Baslaim G, Basshore J, Jamjoom A, et al. Can the outcome of pediatric extracorporeal membrane oxygenation after cardiac surgery be predicted? *Ann Thorac Surg* 2006; 12: 21–27.
11. Kumer S, Zurakowski D, Moulick A, et al. Extracorporeal membrane oxygenation in postcardiotomy patients: factors influencing outcome. *J Thorac Cardiovasc Surg* 2010; 140: 330–336.
12. Kolovos NS, Bratton SL, Moler FW, et al. Outcome of pediatric patients treated with extracorporeal life support after cardiac surgery. *Ann Thorac Surg* 2003; 76: 1435–1441.
13. Chaturvedi RR, Marcrae D, Brown KL, et al. Cardiac ECMO for biventricular hearts after pediatric open heart surgery. *Heart* 2004; 90: 545–551.

Circulation
Cardiovascular Interventions
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

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

Hiroki Mizoguchi, Aiko Ogawa, Mitsuru Munemasa, Hiroshi Mikouchi, Hiroshi Ito and Hiromi Matsubara

Circ Cardiovasc Interv 2012;5;748-755; originally published online November 27, 2012;
DOI: 10.1161/CIRCINTERVENTIONS.112.971077
Circulation: Cardiovascular Interventions is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-7640. Online ISSN: 1941-7632

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.

Received March 30, 2012; accepted October 30, 2012.

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.).

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.112.971077/-/DC1.

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

Circ Cardiovasc Interv **is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.112.971077**

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.

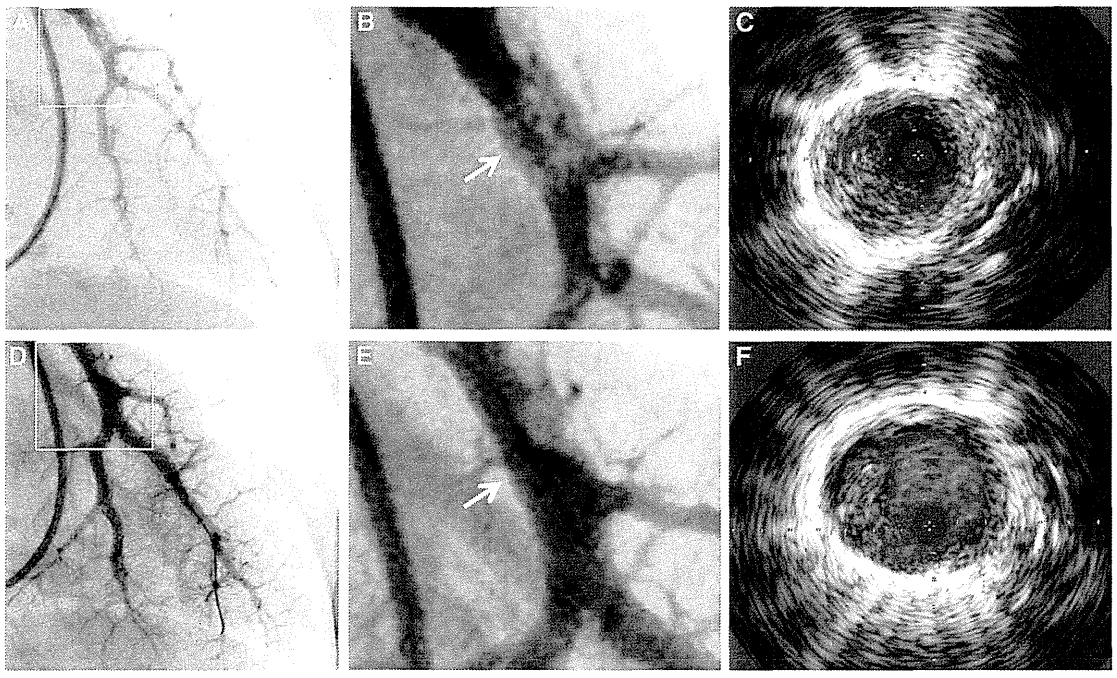


Figure 1. Representative angiographic and intravascular ultrasound (IVUS) images of balloon pulmonary angioplasty (BPA). **A,** Site of an intravascular web of the left pulmonary artery is indicated with a **square** on the angiogram. Peripheral arteries have shrunk because of a reduction in blood flow. **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.

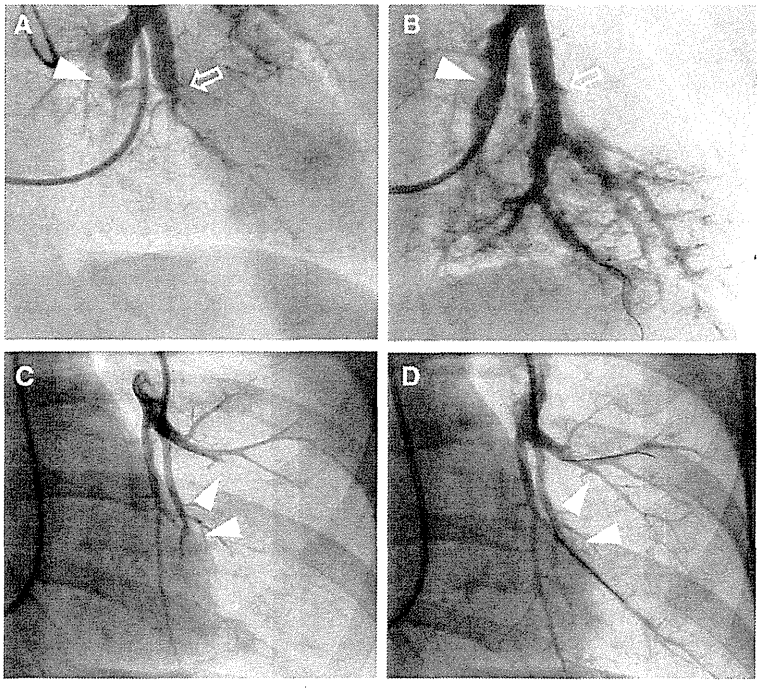


Figure 2. Representative pulmonary angiograms before and after balloon pulmonary angioplasty (BPA). **A**, Pulmonary angiogram shows abrupt vascular narrowing (**arrow**) and complete vascular obstruction (**arrowhead**) in the left lower arteries before BPA. **B**, After dilatation of target arteries 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.

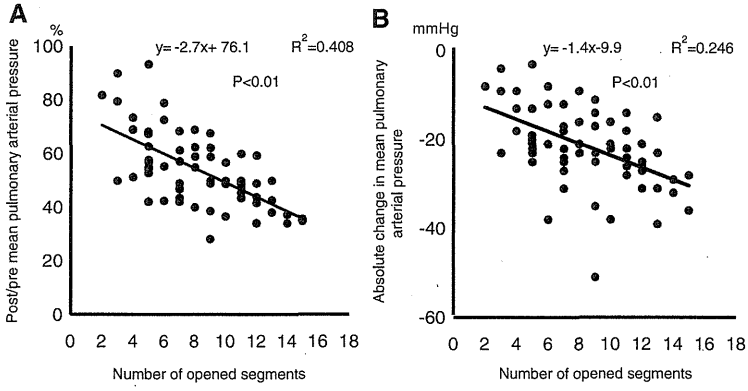


Figure 3. Correlation between the number of opened segments and the decrease in mean pulmonary arterial pressure. The relationships of reduction in mean pulmonary arterial pressure (**A**) and absolute change in mean pulmonary arterial pressure (**B**) with the number of segments of pulmonary arteries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

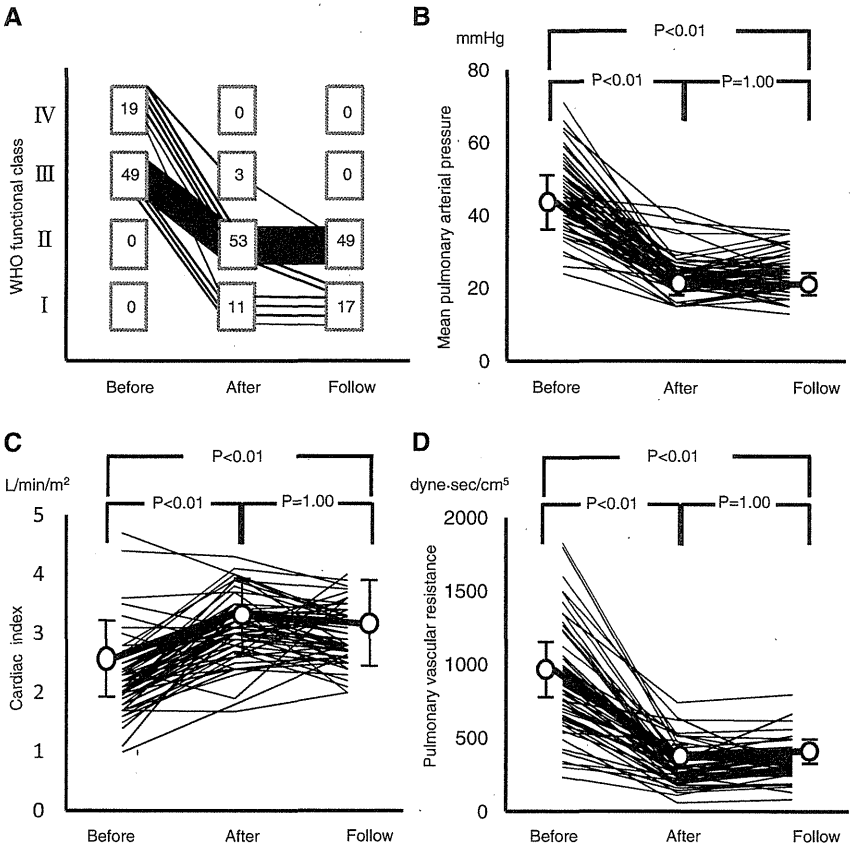
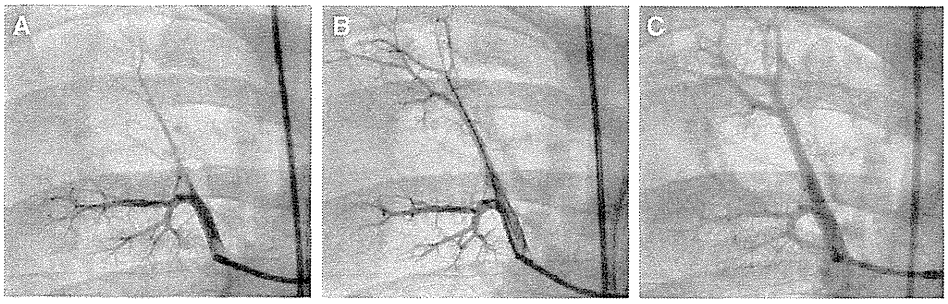


Figure 4. Change in parameters after balloon pulmonary angioplasty (BPA). Parameters before BPA (n=68), immediately after BPA (after) (n=67), and at follow-up (follow) (n=66 for **A** and 57 for **B–D**) were compared. World Health Organization (WHO) functional class (**A**), mean pulmonary arterial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



Before (epoprostenol 5 ng/kg/min) | After (epoprostenol 5 ng/kg/min) | Follow (epoprostenol free)

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

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

References

1. Thistlethwaite PA, Madani M, Jamieson SW. Outcomes of pulmonary endarterectomy surgery. *Semin Thorac Cardiovasc Surg*. 2006;18:257–264.
2. Thistlethwaite PA, Kaneko K, Madani MM, Jamieson SW. Technique and outcomes of pulmonary endarterectomy surgery. *Ann Thorac Cardiovasc Surg*. 2008;14:274–282.
3. Madani MM, Jamieson SW. Technical advances of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Semin Thorac Cardiovasc Surg*. 2006;18:243–249.
4. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation*. 2011;124:1973–1981.
5. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, et al; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009;30:2493–2537.
6. Voorburg JA, Cats VM, Buis B, Bruschke AV. Balloon angioplasty in the treatment of pulmonary hypertension caused by pulmonary embolism. *Chest*. 1988;94:1249–1253.
7. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation*. 2001;103:10–13.
8. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, Fedullo PF, Jamieson SW. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg*. 2012;94:97–103; discussion 103.
9. Corsico AG, D'Armini AM, Cerveri I, Klersy C, Ansaldo E, Niniano R, Gatto E, Monterosso C, Morsolini M, Nicolardi S, Tramontin C, Pozzi E, Viganò M. Long-term outcome after pulmonary endarterectomy. *Am J Respir Crit Care Med*. 2008;178:419–424.
10. Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, Ilkjaer LB, Klepetko W, Delcroix M, Lang I, Pepke-Zaba J, Simonneau G, Dartevelle P. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg*. 2011;141:702–710.
11. Ishida K, Masuda M, Tanabe N, Matsumiya G, Tatsumi K, Nakajima N. Long-term outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *J Thorac Cardiovasc Surg*. 2012;144:321–326.
12. Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. *Radiology*. 1992;182:393–398.
13. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest*. 1982;81:151–158.
14. Lewczuk J, Piszko P, Jagas J, Porada A, Wójciak S, Sobkowicz B, Wrabec K. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818–823.
15. Ricou F, Nicod PH, Moser KM, Peterson KL. Catheter-based intravascular ultrasound imaging of chronic thromboembolic pulmonary disease. *Am J Cardiol*. 1991;67:749–752.
16. Adams A, Fedullo PF. Postoperative management of the patient undergoing pulmonary endarterectomy. *Semin Thorac Cardiovasc Surg*. 2006;18:250–256.
17. Olman MA, Auger WR, Fedullo PF, Moser KM. Pulmonary vascular steal in chronic thromboembolic pulmonary hypertension. *Chest*. 1990;98:1430–1434.
18. Bresser P, Fedullo PF, Auger WR, Channick RN, Robbins IM, Kerr KM, Jamieson SW, Rubin LJ. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2004;23:595–600.
19. Kerr KM, Auger WR, Marsh JJ, Devendra G, Spragg RG, Kim NH, Channick RN, Jamieson SW, Madani MM, Manecke GR, Roth DM, Shragg GP, Fedullo PF. Efficacy of methylprednisolone in preventing lung injury following pulmonary thromboendarterectomy. *Chest*. 2012;141:27–35.
20. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, Guérin C, Schortgen F, Lefort Y, Antonelli M, Lepage E, Lemaire F, Brochard L. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. *JAMA*. 2000;284:2352–2360.
21. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. *Crit Care*. 2006;10:R79.
22. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, Harrington RA, Anderson JL, et al; ACCF/AHA. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation*. 2009;119:2250–2294.
23. Suntharalingam J, Treacy CM, Doughty NJ, Goldsmith K, Soon E, Toshner MR, Sheares KK, Hughes R, Morrell NW, Pepke-Zaba J. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. *Chest*. 2008;134:229–236.
24. Jaïs X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, Hoeper MM, Lang IM, Mayer E, Pepke-Zaba J, Perchenet L, Morganti A, Simonneau G, Rubin LJ; Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. *J Am Coll Cardiol*. 2008;52:2127–2134.
25. Jensen KW, Kerr KM, Fedullo PF, Kim NH, Test VJ, Ben-Yehuda O, Auger WR. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. *Circulation*. 2009;120:1248–1254.

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

1. Thistlethwaite PA, Kemp A, Du L, Madani MM, Jamieson SW. Outcomes of pulmonary endarterectomy for treatment of extreme thromboembolic pulmonary hypertension. J Thorac Cardiovasc Surg. 2006;131:307-313.

Circulation
Arrhythmia and Electrophysiology
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Cardiac Dysfunction and Prolonged Hemodynamic Deterioration After Implantable Cardioverter-Defibrillator Shock in Patients With Systolic Heart Failure

Norihisa Toh, Nobuhiro Nishii, Kazufumi Nakamura, Takeshi Tada, Hiroki Oe, Satoshi Nagase, Kunihisa Kohno, Hiroshi Morita, Kengo F. Kusano and Hiroshi Ito

Circ Arrhythm Electrophysiol 2012;5;898-905; originally published online July 26, 2012;
DOI: 10.1161/CIRCEP.111.970285
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3149. Online ISSN: 1941-3084

Cardiac Dysfunction and Prolonged Hemodynamic Deterioration After Implantable Cardioverter-Defibrillator Shock in Patients With Systolic Heart Failure

Norihisa Toh, MD; Nobuhiro Nishii, MD; Kazufumi Nakamura, MD; Takeshi Tada, MD; Hiroki Oe, MD; Satoshi Nagase, MD; Kunihisa Kohno, MD; Hiroshi Morita, MD; Kengo F. Kusano, MD; Hiroshi Ito, MD

Background—We investigated the acute effects of implantable cardioverter-defibrillator shock on myocardium, cardiac function, and hemodynamics in relation to left ventricular systolic function.

Methods and Results—We studied 50 patients who underwent implantable cardioverter-defibrillator implantation and defibrillation threshold (DFT) testing: 25 patients with left ventricular ejection fraction (LVEF) ≥45% and 25 patients with LVEF <45%. We measured cardiac biomarkers (creatine kinase, creatine kinase-MB, myoglobin, cardiac troponin T and I, and N-terminal probrain natriuretic peptide). Left ventricular relaxation was assessed by global longitudinal strain rate during the isovolumetric relaxation period using speckle-tracking echocardiography. Blood sampling and echocardiography were performed before, immediately after, and 5 minutes and 4 hours after DFT testing. Mean arterial pressure was measured directly during DFT testing. Cardiac biomarkers showed no significant changes in either group. LVEF was decreased until 5 minutes after DFT testing and had recovered to the baseline at 4 hours in the group with reduced LVEF (P<0.001), whereas LVEF reduction was not observed in the group with preserved LVEF (P=0.637). Global isovolumetric relaxation period was decreased until 5 minutes after DFT testing and had recovered to the baseline at 4 hours in both groups (preserved LVEF: 0.39±0.14 versus 0.23±0.13* versus 0.23±0.13* versus 0.40±0.13 s^{-1}, *P<0.001 versus baseline; reduced LVEF: 0.15±0.05 versus 0.08±0.04† versus 0.09±0.04† versus 0.15±0.05 s^{-1}, †P<0.001 versus baseline, repeated-measures ANOVA). Time to recovery of mean arterial pressure to the baseline was prolonged in the group with reduced LVEF (P<0.001).

Conclusions—Implantable cardioverter-defibrillator shock transiently impairs cardiac function and hemodynamics especially in patients with systolic dysfunction, although significant tissue injury is not observed. (***Circ Arrhythm Electrophysiol.* 2012;5:898-905.**)

Key Words: echocardiography ■ hemodynamics ■ implanted cardioverter defibrillators ■ ventricular fibrillation ■ cardiac function

Both primary and secondary preventional trials have demonstrated that implantable cardioverter-defibrillators (ICDs) reduced mortality from sudden cardiac death because of malignant ventricular arrhythmia.[1,2] Despite this survival advantage, several studies have demonstrated that ICD shock, whether it is appropriate, is associated with increased risk of mortality among patients with reduced left ventricular (LV) systolic function.[3–6] Furthermore, defibrillation threshold (DFT) testing at the time of ICD implantation sometimes invokes several critical complications, especially in patients with reduced LV contractility.[7–9] These complications include transient ischemic attack or stroke, cardiopulmonary arrest because of refractory ventricular fibrillation (VF) or pulseless electric activity, cardiogenic shock, embolic events, and death. Although ICD shock is related to short- and long-term critical complications in patients with LV systolic dysfunction, the association between electric defibrillation and cardiac function has been investigated in only a few animal experimental studies,[10–12] and there are few clinical data regarding the effect of ICD shock on cardiac function and its association with tissue damage and subsequent hemodynamic change in patients with systolic heart failure.

Clinical Perspective on p 905

Recently, strain and strain rate (SR) derived from 2-dimensional speckle-tracking echocardiography have

Received November 27, 2011; accepted June 15, 2012.

From the Department of Cardiovascular Medicine (N.T., N.N., K.N., T.T., H.O., S.N., K.K., H.M., K.F.K., H.I.), and Department of Cardiovascular Therapeutics (H.M.), Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan; and Center of Ultrasonic Diagnostics (H.O.), Okayama University Hospital, Okayama, Japan.

Correspondence to Norihisa Toh, MD, Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1, Shikata-Cho, Kita-ku, Okayama City, Okayama 700–8558, Japan. E-mail nori-t@fd5.so-net.ne.jp

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.111.970285**

enabled us to quantify myocardial deformation without angle dependency,[13] and global SR during the isovolumetric relaxation period (SR_{IVR}) provides more accurate assessment of LV relaxation than conventional parameters.[14] In this study, we investigated the effects and mechanisms of ICD shock on myocardial functions by echocardiography, direct central arterial pressure measurement, and measurement of cardiac biomarkers with respect to LV systolic function.

Methods

Study Sample

The study population consisted of 50 consecutive patients who were admitted to our institution to undergo transvenous ICD implantation and DFT testing between April 2008 and December 2009. The underlying heart diseases were ischemic cardiomyopathy in 13 patients, dilated cardiomyopathy in 9 patients, hypertrophic cardiomyopathy in 6 patients, cardiac sarcoidosis in 3 patients, and idiopathic ventricular fibrillation in 19 patients. The patients were divided into 2 groups according to the preoperative LV ejection fraction (LVEF): a group of patients with preserved LVEF (LVEF ≥45%) and a group of patients with reduced LVEF (LVEF <45%).[15,16] All tests that were performed were approved by the medical ethical review committees of Okayama University Hospital. Informed consent was obtained from each patient.

Study Protocol

The study protocol is summarized in Figure 1. ICD implantation was performed using local anesthesia combined with sedation only for DFT testing. At the end of ICD implantation, we induced VF by T-wave shock after monitored anesthesia care using a bolus injection of thiopental (4 mg/kg). For minimizing change in loading condition during monitored anesthesia care, saline infusion rate was set at 0.33 mL/min. Defibrillation shock was fixed to 20 J and automatically delivered from the ICD after detection of VF. We repeated the same protocol 5 minutes after the first DFT testing and did not use a step-down protocol in any of the subjects. We performed venous blood sampling and echocardiographic examination before, immediately after, and 5 minutes and 4 hours after 2 consecutive DFT testing. Vascular access was achieved through the femoral artery, and central arterial pressure was continuously monitored in the ascending aorta during DFT testing.

Analysis of Laboratory Data

To evaluate myocardial injury by DFT testing, we measured cardiac biomarkers: serum levels of creatine kinase (CK), CK-MB fraction (CK-MB), myoglobin, cardiac troponin T, cardiac troponin I, and N-terminal probrain natriuretic peptide (NT-proBNP). CK activity was measured with CicaLiquid reagents (Kanto Chemical, Tokyo, Japan) on a Bio-Majesty analyzer (Nihondenshi, Tokyo, Japan), with upper normal limits of 287 U/L for men and 163 U/L for women. The CK-MB activity was determined using a commercially available immunoinhibition assay (CicaLiquid CK-MB; Kanto Chemical, Tokyo, Japan), with an upper normal limit of 25 U/L. Myoglobin was measured using a commercially available radioimmunoassay (Daiichi III; TFB Inc, Tokyo, Japan), with an upper normal limit of 60 ng/mL. Cardiac troponin T was assessed by an electrochemiluminescence immunoassay on an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). The lower limit of detection was 0.01 ng/mL, and the discrimination level used for myocardial injury was 0.10 ng/mL. Cardiac troponin I was determined using a 2-site immunoenzymatic assay (Access AccuTnI, Beckman Coulter, Brea, CA), with an upper normal limit of 0.50 ng/mL. NT-proBNP was measured using an electrochemiluminescence immunoassay on an Elecsys 1010 analyzer (Roche Diagnostics), with an upper normal limit of 125 pg/mL.

Analysis of Echocardiographic Data

All echocardiographic studies were performed with Vivid 7 (GE Healthcare, Milwaukee, WI). We measured LV volume and ejection fraction according to the recommendations of the American Society of Echocardiography.[17] From mitral flow velocity pattern, we measured peak mitral inflow early diastolic and atrial filling velocities and the E-wave deceleration time. Peak early diastolic mitral annular velocities were measured at septal and lateral mitral annular sites by pulsed tissue Doppler imaging, and then the average values were used for analysis (e′ velocity). The ratio of peak E velocity to e′ velocity (E/e′) was calculated as a surrogate for LV filling pressure. Longitudinal SR analysis was performed using the speckle-tracking system in an EchoPAC PC (GE Healthcare) as previously described.[14] In brief, after tracing the entire LV endocardium, the displacement of speckles of the myocardium was analyzed automatically through the cardiac cycle in the speckle-tracking system. Then the SR curve of each segment was displayed and approved. LV global SR was calculated with the use of the entire length of the LV myocardium, and peak global SR during the isovolumetric relaxation period was defined as global SR_{IVR}. The global SR_{IVR} values from the 3 apical views were averaged and used for analysis. All echocardiographic measurements and analysis were performed offline by an experienced investigator (N.T.), with no clinical information about the patients.

The following measures were taken to obtain adequate echocardiographic images for analysis promptly and maintain operative field sterility: (1) we enrolled only patients with optimal echocardiographic images, (2) the transducer position was fixed at apical impulse for minimizing loss of time and maintaining sterility because an apical

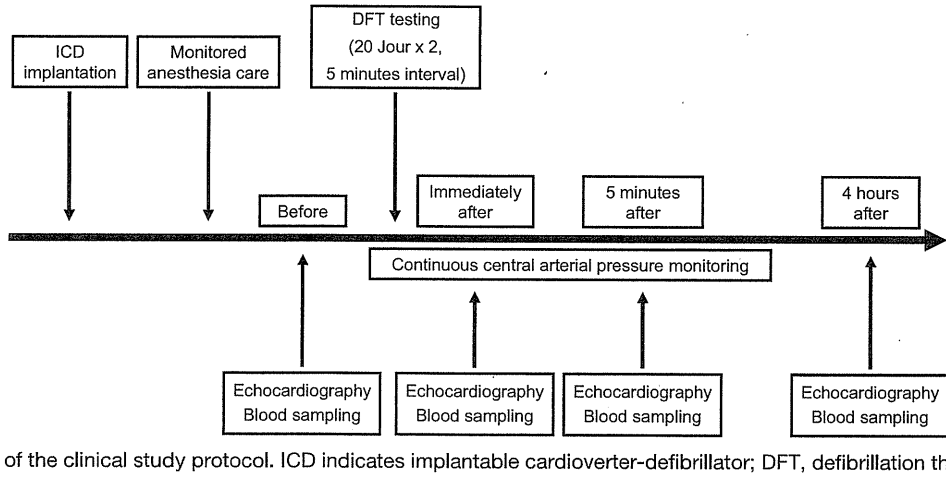


Figure 1. Outline of the clinical study protocol. ICD indicates implantable cardioverter-defibrillator; DFT, defibrillation threshold.

window was sufficient for acquiring all data as mentioned above, and (3) the operative field and catheter insertion site were carefully covered with sterile surgical drapes.

Analysis of Hemodynamic Data

Continuous measurements of systolic and diastolic arterial pressures were performed at the ascending aorta during DFT testing. Mean arterial pressure (MAP) was obtained by direct integration of the blood pressure curve. Time to reach baseline MAP was defined as the interval between the second ICD shock and the time MAP returned again.

Statistical Analysis

Data are expressed as mean±SD. Unpaired *t* test was used to detect statistical differences for continuous variables with normality of data distributions between 2 groups, and categorical data and percentage frequencies were analyzed by the Fisher exact test. Serial data (before and after the procedure) were analyzed by linear mixed-effects models, and 2-way repeated-measures ANOVA was conducted. If a significant difference between 2 groups or among 4 time points was detected by a global test, ad hoc multiple comparison was performed. Central arterial pressures before and after DFT testing were compared by paired *t* test. Ten subjects were randomly selected from each group and analyzed blindly by 2 independent investigators (N.T. and H.O.) to assess the intraclass correlation coefficient for evaluating reproducibility of longitudinal SR measurements. $P<0.05$ was considered statistically significant. All analyses were performed with JMP 9 (SAS Institute, Cary, NC).

Results

Clinical Characteristics

Table 1 shows the characteristics of the study population. There were no significant differences in age, sex, and body surface area between the 2 groups. New York Heart Association functional class was higher in the group with reduced LVEF than in the group with preserved LVEF. The group with reduced LVEF more frequently included ischemic and dilated cardiomyopathies than the group with preserved LVEF. Idiopathic ventricular fibrillation was the major cause of ICD implantation in the group with preserved LVEF. Concomitant cardiovascular drug therapy was common in the group with reduced LVEF.

Serial Changes of Serum Markers Before and After DFT Testing

Serial changes of serum markers are listed in Table 2. At baseline, there were no differences in biomarkers except for NT-proBNP between the groups before DFT testing. Baseline NT-proBNP was significantly higher in the group with reduced LVEF than in the group with preserved LVEF ($P<0.002$).

All patients received 2 consecutive 20-J shocks with a 5-minute interval. All induced VFs were successfully terminated by the first 20-J shock, and shocks neither higher nor lower than 20 J were delivered. Although the response to DFT testing in CK-MB and NT-proBNP differed between the groups using repeated-measures ANOVA, DFT testing did not cause significant changes in CK, CK-MB, myoglobin, and NT-proBNP in either group. DFT testing slightly increased cardiac troponin T in the group with preserved LVEF and cardiac troponin I in the group with reduced LVEF, but these values did not exceed the normal ranges (Table 2).

Table 1. Baseline and Clinical Characteristics of the Study Population

Variable	Preserved LVEF (n=25)	Reduced LVEF (n=25)	*P* Value
Age, y	55±13	57±14	0.661
Sex, male	20 (80)	15 (60)	0.217
Body surface area, m^2	1.72±0.20	1.66±0.19	0.254
NYHA functional class			<0.001
I	19	0	
II	6	20	
III	0	5	
Cardiac disease history			
Ischemic cardiomyopathy	1 (4)	12 (48)	0.001
Dilated cardiomyopathy	0 (0)	9 (36)	0.002
Hypertrophic cardiomyopathy	5 (20)	1 (4)	0.190
Cardiac sarcoidosis	0 (0)	3 (12)	0.235
Idiopathic ventricular fibrillation	19 (76)	0 (0)	<0.001
Concomitant cardiovascular therapies			
ACE inhibitors/ARBs	6	19	0.001
β-Blockers	9	23	<0.001
Calcium channel blockers	3	1	0.609
Diuretics	3	23	<0.001
Class III antiarrhythmic agent	9	5	0.345
Statins	3	5	0.702

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers. Values are n (%) or mean±SD.