

Clinical Outcomes of Thromboendarterectomy for Chronic Thromboembolic Pulmonary Hypertension: 12-Year Experience

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Background: We present our 12-year experience of pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. **Materials and Methods:** Between January 1999 and March 2011, 16 patients underwent pulmonary thromboendarterectomy. Eleven patients (69%) were classified as functional class III or IV based on the New York Heart Association (NYHA) classification. Seven patients had a history of inferior vena cava filter insertion, and 5 patients showed coagulation disorders. Pulmonary thromboendarterectomy was performed during total circulatory arrest with deep hypothermia in 14 patients. **Results:** In-hospital mortality and late death occurred in 2 patients (12.5%) and 1 patient (6.3%), respectively. Extracorporeal membrane oxygenation support was required in 4 patients who developed severe hypoxemia after surgery. Thirteen of the 14 survivors have been followed up for 54 months (range, 2 to 141 months). The pulmonary arterial systolic pressure and cardiothoracic ratio on chest radiography was significantly decreased after surgery (76 ± 26 mmHg vs. 41 ± 17 mmHg, $p=0.001$; $55\%\pm 8\%$ vs. $48\%\pm 3\%$, $p=0.003$). Tricuspid regurgitation was reduced from 2.1 ± 1.1 to 0.7 ± 0.6 ($p=0.007$), and the NYHA functional class was also improved to I or II in 13 patients (81%). These symptomatic and hemodynamic improvements maintained during the late follow-up period. **Conclusion:** Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension shows good clinical outcomes with acceptable early and long term mortality.

Key words: 1. Pulmonary arteries
2. Thromboembolism
3. Endarterectomy
4. Tricuspid valve

INTRODUCTION

Chronic thromboembolic pulmonary hypertension, caused by fibrotic stenosis or complete occlusion of the pulmonary arteries after single or recurrent episodes of acute pulmonary embolism, is rare, but induces right heart dilatation and dysfunction over time [1]. Pulmonary thromboendarterectomy is recognized as the standard treatment for most patients with

chronic thromboembolic pulmonary hypertension because medical therapies are only supportive, resulting in secondary right heart failure caused by gradually increased pulmonary hypertension [1-5]. In Korea, there is a lack of clinical studies on the early and long term clinical outcomes, including symptoms and changes of various hemodynamic indices as well as surgical considerations of pulmonary thromboendarterectomy for severe, complicated thromboembolic pulmonary

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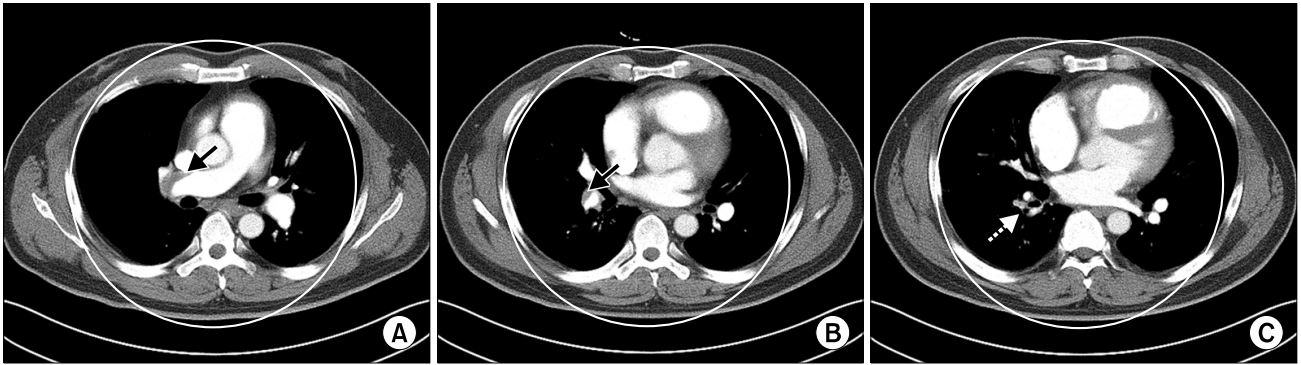


Fig. 1. Chest computed tomography (CT) angiogram shows thrombus (arrow) in the right pulmonary artery (A) and the right lower pulmonary artery (B). Irregularity of the pulmonary arterial wall or filling defect of the vessel lumen (dotted arrow) in the segmental and sub-segmental arteries was shown (C).

hypertension. In this study, we present our 12-year clinical experience of pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Seoul National University Hospital, and the requirement for informed consent was waived.

1) Patients and diagnostic workup

Between January 1999 and March 2011, 16 patients who underwent pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension were identified in Seoul National University Hospital, and the medical records of these patients were reviewed. The clinical symptoms included dyspnea, nonspecific chest pain, syncope, and exercise intolerance. Chest radiography was routinely performed to find several radiographic abnormalities including cardiomegaly with right heart dilatation, peripheral lung opacities, and dilation of the central pulmonary arteries, and to measure the cardiothoracic ratio. Transthoracic echocardiography, lung perfusion scans, and computed tomography (CT) angiograms were used for the preoperative diagnosis. Severity of tricuspid regurgitation (TR) on echocardiography was graded on a 5-point scale (0 indicating no TR; 1, trivial TR; 2, mild TR; 3, moderate TR; and 4, severe TR). The CT angiography findings compatible with chronic thromboembolism

were thrombus and/or irregularity of the vessel wall in the main and lobar pulmonary artery and filling defects of the vessel lumen in the segmental arteries (Fig. 1). Right heart catheterization for measuring several hemodynamic data, including pulmonary arterial pressure and pulmonary vascular resistance, was selectively performed in patients with extremely severe pulmonary hypertension on echocardiography. Pulmonary angiography was combined with right heart catheterization. Pulmonary thromboendarterectomy was indicated for the symptomatic patients with characteristic findings of chronic thromboembolic pulmonary hypertension based on the diagnostic work-up. The patients with mild symptoms, the presence of hemodynamic compromise, CT angiography findings, or a history of deep vein thrombosis and/or coagulation disorders were important for determining the need for surgery.

The predisposing factors of pulmonary thromboembolism were a history of inferior vena cava (IVC) filter insertion due to deep vein thrombosis in 7 patients and coagulation disorders in 5 patients, including protein C, S deficiency, or antithrombin III deficiency.

2) Surgical procedure

The surgical procedures used were median sternotomy with cardiopulmonary bypass (CPB) in all of the patients. In the early period, before 2002, the operation was performed under CPB and aortic cross-clamp (ACC) with deep hypothermia, without total circulatory arrest (TCA), in all of the patients

(n=2). Since 2002, however, intermittent TCA under deep systemic hypothermia had been performed for complete thromboendarterectomy. After the patient was cooled to less than 20°C and TCA was initiated, pulmonary arteriotomy was extended from the pulmonary artery bifurcation site to the right lateral portion of the superior vena cava, and thromboendarterectomy in the right pulmonary artery was then performed. The intimal peel was dissected carefully using a Jamieson sucker, which was a long miniature sucker with a rounded tip [6], and removed using gentle traction with DeBakey forceps. Thromboendarterectomy was performed up to the segmental and subsegmental pulmonary arteries. The same procedures were repeated for the left pulmonary artery. Left-sided pulmonary arteriotomy was extended laterally to the pericardial reflection. After the completion of bilateral pulmonary thromboendarterectomy, CPB was resumed and re-warming was commenced.

3) Statistical analysis

Statistical analysis was performed with SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean±standard deviation, median and ranges, or proportions. Changes in the hemodynamic variables including mean TR grade and mean pulmonary artery systolic pressure after surgery were analyzed using the repeated measured analysis of variance with Greenhouse Geisser correction. Postoperative changes in the other continuous variables were compared using paired t-test. The survival rates were estimated using the Kaplan-Meier method. All of the statistical tests were two-tailed, and all p-values less than 0.05 were considered statistically significant.

RESULTS

1) Patient characteristics

The patients' mean age was 44±14 years (range, 23 to 74 years), and there were 6 female patients (37.5%). Eleven patients (69%) were classified as the New York Heart Association (NYHA) functional class III or IV, and the other 5 patients (31%) had no or mild dyspnea on effort (NYHA functional class I or II). The cardiothoracic ratio on chest radiography was 56.1±8.4. In the preoperative echocardiog-

raphy, the mean left ventricle ejection fraction and pulmonary artery systolic pressure were 60.9%±8.5% and 76.6±26.6 mmHg (range, 35 to 110 mmHg), respectively. One patient with mild pulmonary hypertension had a history of deep vein thrombosis and complained of a sudden onset of dyspnea. An IVC filter was inserted preoperatively, and pulmonary thromboendarterectomy was performed for a large amount of pulmonary thromboembolism in both pulmonary arteries that was not resolved by anticoagulation therapy. Six patients had an extremely high pulmonary artery systolic pressure, more than 100 mmHg, before surgery. A total of 8 patients (50%) showed more than a moderate degree of TR, and the mean TR grade was 2.1±1.1 degrees. Moreover, right ventricular dysfunction was identified on echocardiography in 13 patients, and severely depressed contractility of the right ventricle, regardless of the presence of TR, was found in 3 patients. The baseline patient characteristics are presented in Table 1.

2) Surgery

Most of the patients had type I (n=4, 25%) or II (n=10, 62.5%) pulmonary thromboembolism, and 2 patients (12.5%) had type III (Fig. 2). The mean CPB and ACC time were 242.1±78.2 and 80.8±51.7 minutes, respectively. In 14 patients who underwent TCA, the mean TCA time was 37.0±20.3 minutes (range, 11 to 77 minutes) and the lowest body temperature was 16.2°C. Four patients underwent a concomitant procedure including the Cox Maze IV procedure for paroxysmal atrial fibrillation, ligation of coronary arteriovenous fistula, tricuspid annuloplasty with valve repair, or patent foramen ovale (PFO) closure. Only 1 patient underwent tricuspid valve surgery for more than a moderate degree of TR. Only one patient underwent a combined surgery of tricuspid annuloplasty with MC3 ring (Edwards LifeScience, Irvine, CA, USA) and tricuspid valve repair, which was obliteration of the posteroseptal commissure, for severe TR caused by chordae rupture. Detailed information of the operative procedures performed is described in Table 2.

3) Postoperative management

Mechanical ventilation with a positive end expiratory pressure level of 5 to 8 mmHg was routinely administered during

Table 1. Patient characteristics (n=16)

Variable	Value
Mean age (yr)	44±14
Female gender	6 (37.5)
Diabetes mellitus	1 (6.3)
Hypertension	3 (18.7)
Coronary artery disease	0 (0)
NYHA functional class	
I	1 (6.3)
II	4 (25.0)
III	8 (50.0)
IV	3 (18.8)
Atrial fibrillation	4 (25.0)
History of IVC filter insertion	7 (43.8)
Coagulation disorder	5 (31.3)
CT ratio on chest radiography	56.1±8.4
Echocardiography	
Ejection fraction (%)	60.9±8.5
Mean LVEDD (mm)	44.0±4.4
Mean LVESD (mm)	28.2±6.6
PASP (mmHg)	76.6±26.6
Tricuspid regurgitation grade	
No/trivial	5 (31.2)
Mild	3 (18.8)
Moderate	5 (31.2)
Severe	3 (18.8)

Values are presented as mean±standard deviation or number (%). NYHA, New York Heart Association; IVC, inferior vena cava; CT ratio, cardiothoracic ratio; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; PASP, pulmonary artery systolic pressure.

the early postoperative period. Aggressive diuresis was required in all of the patients to decrease the incidence of pulmonary and cerebral edema that resulted from the prolonged bypass and circulatory arrest with deep hypothermia. Inhalation of a 10 to 40 ppm dose of nitric oxide was required in 11 patients with residual or persistent pulmonary hypertension. In addition, inhalation of iloprost [7,8] was selectively used in patients with severe, persistent pulmonary hypertension that was unsolved by a high-dose of inhaled nitric oxide or other agents. Inotropic support, such as dobutamine and epinephrine, and pulmonary vasodilating agents, such as milrinone, were usually necessary for the majority of the patients.

4) Early postoperative morbidity and mortality

In-hospital mortality was 12.5% (2 of 16 patients). One pa-

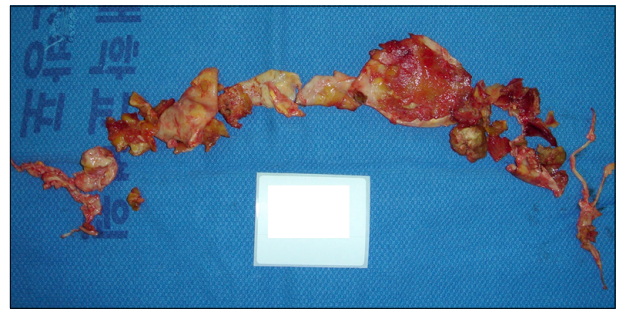


Fig. 2. A specimen of bilateral type II pulmonary thromboendarterectomy. Intimal thickening and fibrosis with thrombus extending to the segmental arteries.

Table 2. Operative information (n=16)

Variable	Value
Mean CPB time (min)	242.1±78.2
Mean ACC time (min)	80.8±51.7
Mean TCA time (min)	37.0±20.3
Use of TCA	14 (87.5)
ECMO use	4 (25)
IABP use	1 (6.3)
Type of pulmonary thromboembolism	
I	4 (25)
II	10 (62.5)
III	2 (12.5)
Combined operation	4 (25)
TVP/TAP	1 (6.3)
Maze procedure	1 (6.3)
PFO closure	1 (6.3)
Ligation of coronary AVF	1 (6.3)

Values are presented as mean±standard deviation or number (%). CPB, cardiopulmonary bypass; ACC, aortic cross clamp; TCA, total circulatory arrest; ECMO, extracorporeal membrane oxygenator; IABP, intraaortic balloon pump; TVP, tricuspid valvuloplasty; TAP, tricuspid annuloplasty; PFO, patent foramen ovale; AVF, arteriovenous fistula.

tient had extremely high pulmonary hypertension before surgery. The patient's pulmonary artery systolic pressure was 110 mmHg on echocardiography, and the pulmonary vascular resistance was 1,600 dynes on right heart catheterization. Moreover, incomplete thromboendarterectomy was performed because of a poor operative view. After the weaning of CPB, the patient did not recover from persistent severe pulmonary hypertension. The patient died on postoperative day 5 due to biventricular failure with intractable ventricular arrhythmias,

despite the use of an extracorporeal membrane oxygenator (ECMO). Another patient also had a high level of residual pulmonary hypertension with right ventricular dysfunction after surgery, and showed reperfusion pulmonary edema with a persistent pulmonary hemorrhage. The patient died of septic shock with multi-organ failure on postoperative day 41, despite the long term use of ECMO. The mean length of stay in the intensive care unit was 15.6 ± 16.4 days (range, 2 to 47 days), and the mean length of hospital stay was 29.1 ± 22.2 days (range, 5 to 66 days). Postoperative complications included prolonged ventilation (n=9), reperfusion pulmonary edema (n=5), persistent pulmonary hypertension (n=5), new onset of atrial fibrillation (n=3), bleeding requiring reoperation (n=2), pulmonary hemorrhage (n=2), acute renal failure (n=2), prolonged pleural effusion (n=1), and heart failure requiring an intra-aortic balloon pump (IABP) (n=1). ECMO support was required in 4 patients who developed severe hypoxemia caused by tracheal bleeding, acute respiratory distress syndrome (ARDS), or heart failure.

5) Late follow-up and survival

Thirteen of the 14 survivors have been followed up for 54 months (range, 2 to 141 months) after discharge. During that period, late death occurred in one (6.3%) patient. The patient died suddenly of unknown cause at 44 months postoperatively. All of the patients were anticoagulated with coumadin at the international normalized ratio of 2 to 3. None of the patients showed recurrent symptoms or anticoagulation-related complications during the follow-up periods. The mean survival of all the patients was 47.6 ± 46.2 months (range, 0.2 to 141 months), and the 1-, 5-, and 10-year survival rates were 87.1%, 76.2%, and 76.2%, respectively (Fig. 3).

6) Clinical outcomes

The mean NYHA functional class improvement was from 2.7 to 1.2 ($p=0.001$), and 13 patients (81%) showed a significant improvement to functional class I or II. Moreover, the cardiothoracic ratio on chest radiography was decreased from 56.1 ± 8.4 to 48.1 ± 2.9 ($p=0.003$), during the mean 27 months after surgery. Arterial oxygen pressure on arterial blood gas analysis (ABGA) was improved from 66.1 ± 10.3 to 93.0 ± 32.2 mmHg ($p=0.016$), postoperatively.

Results of Pulmonary Thromboendarterectomy

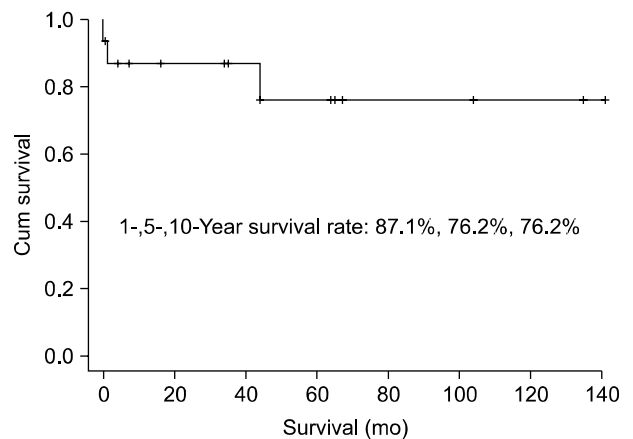


Fig. 3. Kaplan-Meier overall survival curve of all the patients who underwent pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension.

7) Postoperative echocardiography

In the early postoperative period, echocardiography was performed in 11 patients before discharge. Pulmonary arterial systolic pressure was significantly decreased from 76.6 ± 26.6 mmHg to 40.6 ± 17.2 mmHg ($p=0.001$), and the TR grade was also reduced from 2.1 ± 1.1 to 0.7 ± 0.6 degrees ($p=0.007$). On the late follow-up echocardiography during the mean 15 month period, the mean pulmonary arterial systolic pressure was slightly decreased to 38.8 ± 13.6 mmHg, and the mean TR grade was changed to 0.8 ± 0.6 degrees. However, there was no significant difference compared with the early postoperative data. The early and late postoperative symptom changes, arterial blood oxygenation, and various hemodynamic indices are presented in Table 3. In 4 patients who underwent a combined cardiac procedure, the abnormal coronary flow from the left circumflex coronary artery to the pulmonary artery via the arteriovenous fistula had disappeared, and atrial fibrillation was converted to a normal sinus rhythm, postoperatively. Severe TR was reduced to trivial regurgitation, and there was no residual shunt flow via PFO after closure.

DISCUSSION

The incidence of chronic thromboembolic pulmonary hypertension is rare, and has been known to occur in 2% to 4% of patients with acute pulmonary embolism [9,10]. Because

Table 3. Early and late postoperative changes of symptom, oxygenation, and hemodynamic indices

Variable	Preoperative data	Early postoperative data	Last follow-up data	p-value
CT ratio (%)	56.1±8.4	-	48.1±2.9	0.003
Mean NYHA Fc	2.7±0.8	-	1.2±0.4	0.001
PaO ₂ on ABGA	66.1±10.3	93.0±32.2	-	0.016
Mean TR grade	2.1±1.1	0.7±0.6	0.8±0.6 ^{a)}	0.007
PASP (mmHg)	76.6±26.6	40.6±17.2	38.8±13.6 ^{a)}	0.005

Values are presented as mean±standard deviation.

CT ratio, cardiothoracic ratio; NYHA Fc, New York Heart Association functional class; PaO₂, arterial oxygen pressure; ABGA, arterial blood gas analysis; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure.

^{a)}No significant difference in p-value between early postoperative data and last follow-up data.

the history of pulmonary embolism has been difficult to determine and many patients show a slowly progressive deterioration in clinical status, the diagnosis of chronic thromboembolic pulmonary hypertension is often overlooked and delayed until pulmonary hypertension worsens and causes dyspnea, hypoxemia, or right ventricular dysfunction [11]. Nearly all of the patients that only receive medical therapy die of secondary right heart failure caused by pulmonary hypertension, because medical therapies using anticoagulants, thrombolytic agents, or vasodilators are generally unsatisfactory and are only palliative. However, pulmonary thromboendarterectomy has been recognized as the standard treatment for most patients because it has been highly successful and curative [1-5].

Considering the pathophysiology of chronic thromboembolic pulmonary hypertension, persistent macrovascular obstruction and vasoconstriction trigger small vessel arteriopathy, which result in further abnormal vascular remodeling and an increase of pulmonary vascular resistance. A combination of these vasculopathic changes results in pulmonary hypertension and right ventricular pressure overload. On the other hand, some previous studies have reported that ineffective fibrinolysis caused by abnormal fragmentation of fibrinogen [12] and chronic staphylococcal infection [13], and neurohumoral factors, such as a potent vasoconstrictor including endothelin-1 [14], play a role in the progression of chronic thromboembolic pulmonary hypertension. Jamieson and Kapelanski [6] suggested a classification of pulmonary thromboembolic disease based on their previous reports [15]. According to the Jamieson classification, type I is a fresh or organized clot in the main or lobar pulmonary arteries, type II is intimal thickening and fibrosis without visible thrombus,

type III is fibrosis, intimal webbing, and thickening within the distal segmental arteries only, and type IV is microscopic distal arteriolar vasculopathy. In the present study, based on the operative findings, most of the cases were type I or II pulmonary thromboembolism, and only 2 cases were type III.

Diagnostic evaluation of chronic thromboembolic pulmonary hypertension included transthoracic echocardiography, lung perfusion scans, cardiac catheterization, pulmonary angiography, and CT angiograms. Transthoracic echocardiography provides the basic information on the chamber enlargement, ventricular functional status, pulmonary artery systolic pressure in case of the presence of TR, and other structural abnormalities including PFO [15]. The common echocardiographic findings of chronic thromboembolic pulmonary hypertension are right atrial and ventricular dilatation, interventricular septal deviation toward the left ventricle due to pressure overload of the right ventricle, TR, and pulmonary hypertension. However, echocardiography cannot be used for a definite diagnosis and differentiation between acute and chronic pulmonary embolism [11]. A lung perfusion scan is useful to differentiate chronic thromboembolic pulmonary hypertension from other causes of pulmonary hypertension, by using it for identifying the ventilation-perfusion mismatched segmental defect caused by thromboembolic obstruction. In addition, right heart catheterization has been used to assess the cardiac function and the severity of pulmonary hypertension by measuring the pulmonary artery pressure and resistance. Although pulmonary angiography has been the essential test for diagnosing chronic thromboembolism and for determining its location and surgical resectability, the procedure is often restricted in patients with severe pulmonary hy-

pertension because of the invasiveness of the procedure and the possibility of hemodynamic compromise. Therefore, more recently, CT angiogram has been used as an alternative to the pulmonary angiography because of the safety of the procedure and its high resolution. CT angiogram shows the eccentric thromboembolic materials in the main and lobar pulmonary arteries, the subpleural densities, right heart chamber enlargement, and the mosaic patterns of lung parenchyma [11]. In our cases, the initial diagnosis of chronic thromboembolism was based on the results of transthoracic echocardiography, lung perfusion scans, and CT angiograms. Right heart catheterization was indicated in selected patients to further define the physiological characteristics. Pulmonary angiography was not performed as the initial test of choice because the CT angiogram provided enough information to perform pulmonary endarterectomy and to rule out alternative diagnoses in our patients.

Thistlethwaite et al. [15] suggested that the three major purposes of pulmonary thromboendarterectomy are hemodynamic, respiratory, and prophylactic goals. The hemodynamic recovery included amelioration of pulmonary hypertension and right ventricular dysfunction [16] and the reduction of severity of TR. The respiratory goal was to improve pulmonary function by removing a large ventilated but non-perfused physiologic dead space, and the prophylactic objectives were to prevent the progression of right ventricular dysfunction and secondary vasculopathy of the patent distal pulmonary vessels. In the present study, the pulmonary artery pressure and TR grade were dramatically decreased in the early postoperative period, and those improvements continued to the late follow-up period. Moreover, the NYHA functional class and systemic arterial oxygenation on ABGA were also greatly improved after surgery, from the perspective of the respiratory purpose. Although the quantitative measurement of right ventricular function, such as ejection fraction or ventricular volume index, was not estimated, the size of the right heart chambers were reduced on echocardiography, and the cardiothoracic ration on chest radiography was significantly decreased, postoperatively.

Several previous studies have demonstrated that the severity of functional TR significantly reduces after pulmonary thromboendarterectomy without additional valve repair [15,17,

18]. Pathophysiologically, as a result of right ventricular remodeling caused by the elimination of chronic pressure overload, the tricuspid annular geometry was restored, and the tricuspid valvular function was recovered to normal. Therefore, the tricuspid valve procedure for functional TR was not recommended as a combined procedure of pulmonary thromboendarterectomy. We only performed tricuspid valve surgery in one patient that had more than a moderate degree of functional TR that was identified on preoperative echocardiography. Only one patient with severe TR caused by a chordae rupture underwent tricuspid ring annuloplasty and tricuspid valve repair as concomitant procedures. The TR grade was significantly decreased to less than a mild degree after pulmonary endarterectomy in almost all the patients, and the degree was maintained without prominent worsening in the late follow-up echocardiography.

On the other hand, Thistlethwaite et al. [19] suggested that the preoperative screening for concomitant coronary and valvular disease should be considered, especially in older patients scheduled for pulmonary thromboendarterectomy, and they presented the successful outcome of combined surgery including coronary artery bypass grafting, valve surgery, and PFO closure. In the current study, a total of 4 patients underwent a concomitant cardiac operation including Cox Maze IV procedure, ligation of coronary arteriovenous fistula, PFO closure, or tricuspid ring annuloplasty with valve repair. All of the procedures were performed during the cooling or rewarming period without the additional operation time for concomitant surgery, and they showed good surgical outcomes.

Early postoperative deaths have usually been associated with respiratory failure caused by reperfusion pulmonary edema and/or pulmonary hemorrhage, and by persistent pulmonary hypertension with right heart failure in cases of incomplete thromboendarterectomy [1].

In the two mortalities of our study, one patient suffered from the ARDS caused by persistent pulmonary hemorrhage and pulmonary edema after surgery, and the patient died of septic shock related to pneumonia and the long term use of ECMO. Another patient with type II thromboembolism underwent pulmonary thromboendarterectomy without TCA, and a sufficient removal of distal thrombus was not performed due to the poor operative view. The patient died of intractable

right ventricular failure and ventricular arrhythmias with persistent severe pulmonary hypertension. After the use of deep hypothermic TCA [20] and refinements in the operative techniques, however, complete thromboendarterectomy on both sides of the pulmonary artery was possible; thus, the successful reduction of the pulmonary artery pressure was achieved, and the early clinical results markedly improved.

CONCLUSION

Pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension resulted in remarkable early and long term clinical and hemodynamic improvement with acceptable mortality and morbidity rates. TCA with deep hypothermia for complete thromboendarterectomy may be necessary, and concomitant tricuspid surgery is not required for functional TR.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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