Anti-phospholipid syndrome (APS) is an autoimmune disease characterized by the occurrence of venous and/or arterial thrombosis. Chronic thromboembolism is one of the known established pathogenesis of pulmonary hypertension, known as chronic thromboembolic pulmonary hypertension. Pulmonary endarterectomy is the treatment of choice for chronic thromboembolic pulmonary hypertension. The aim of this study is to evaluate the efficacy and risk of pulmonary endarterectomy in patients with antiphospholipid syndrome-associated chronic thromboembolic pulmonary hypertension.

Methods: Data were prospectively collected and retrospectively analyzed, for patients who underwent pulmonary endarterectomy between March 2011 and March 2020.

Results: Seventeen patients (4 male and 13 female) were identified. Thirteen patients had primary antiphospholipid syndrome and 4 had secondary antiphospholipid syndrome. The mean age was 34.82 ± 10.07 years and the mean time interval between the diagnosis and surgery was 26.94 ± 17.35 months. Dyspnea on exertion was the main symptom in all patients. Seven patients had previous deep vein thrombosis, 5 patients had a history of recurrent abortions, and 2 patients had hemoptysis. Following surgery, mean pulmonary artery pressure decreased from 47.82 ± 13.11 mm Hg to 22.24 ± 4.56 mm Hg (P < .001), and pulmonary vascular resistance improved from 756.50 ± 393.91 dyn/s/cm^-5 to 298.31 ± 132.84 dyn/s/cm^-5 (P < .001). There was no in-hospital mortality with a mean follow-up of 75.29 ± 40.21 months. The functional capacity of all patients improved from 269.46 ± 111.7 m to 490 ± 105.34 m on a 6-minute walking test.

Conclusions: Pulmonary endarterectomy is a safe and curative treatment in patients with antiphospholipid syndrome-associated chronic thromboembolic pulmonary hypertension. It has a favorable outcome by increasing the quality of life. A multidisciplinary experienced chronic thromboembolic pulmonary hypertension team is critical in the management of these unique patients.

Keywords: Antiphospholipid syndrome, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, outcome

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by arterial and venous thrombosis and/or pregnancy morbidity associated with the presence of antiphospholipid antibodies (aPL), such as anticiardiolipin (ACA), and anti-β2-glycoprotein I antibodies (anti-β2GPI) and lupus anticoagulant (LA). Antiphospholipid syndrome is classified as primary APS if there is no underlying disease and secondary if there is an associated autoimmune disease such as systemic lupus erythematosus (SLE). Venous thrombosis in APS is due to coagulation factor-related mechanisms and usually presents with deep vein thrombosis of the lower extremities and pulmonary embolism. Chronic thromboembolism is the etiology of progressive pulmonary hypertension in APS and, if left untreated, chronic thromboembolic pulmonary hypertension (CTEPH) develops and the prognosis is poor due to right heart failure and pulmonary hypertension (PH). The only curative treatment modality of CTEPH is usually pulmonary endarterectomy (PEA). To date, the literature on APS-associated CTEPH has been limited to case reports and a few case series. In this study, we report our experience with 17 APS-associated
CTEPH patients who were refractory to conventional treatment and were treated with PEA with emphasis on disease characteristics, management, and prognosis.

METHODS

Patient Population and Data Collection
Between March 2011 and March 2021, 762 consecutive patients underwent PEA at our institution. A total of 17 patients (2.23%) who met the revised Sapporo classification criteria of APS were included in the study. All patients had refractory symptoms (and/or recurrent thrombotic events) despite effective anticoagulation and/or immunosuppressive treatment. Patient data were collected from the clinical records of the institution and retrospectively retrieved from the hospital’s database, after approval of the study by the hospital’s ethical committee (number 213364230220). All patients were assessed by our multidisciplinary team of CTEPH experts, and all care was provided including detailed diagnostics and all forms of CTEPH therapy. This CTEPH expert team includes expert PEA surgeons, pulmonologists, cardiologists, radiologists, as well as rheumatologists.

All patients with the diagnosis of CTEPH were assessed with a 6-minute walking test (6-MWT), echocardiography, computerized tomographic pulmonary angiography (CTPA), lung ventilation perfusion scintigraphy (V/Q scan), and right heart catheterization (RHC). Pulmonary endarterectomy was decided for patients with perfusion defects on V/Q scan after effective conventional and at least 3 months of anticoagulant treatment with surgically accessible lesions.

Surgical Procedure
Our surgical technique was described previously. In brief, median sternotomy and cardiopulmonary bypass (CPB) institutions were standard. Bilateral pulmonary endarterectomy was performed in all patients under deep hypothermia (20 °C) and total circulatory arrest with intermittent cross-clamping of the aorta. Concomitant surgical procedures were performed during the re-warming period. Early postoperative hemodynamic measurements were completed in the operating room before patients were transferred to the intensive care unit.

Patient Follow-Up
Patients were followed up during their third and sixth postoperative months. To describe the functional class of the patients the World Health Organization (WHO) class system was used. Postoperative data on WHO classes, 6-MWT results, and echocardiographic data were collected. Preoperative and post-operative clinical findings and all available data were analyzed in the study.

Statistical Analysis
Statistical analysis was performed using Statistical Package for the Social Sciences Software. Continuous variables following normal distribution were expressed as mean and standard deviation, variables following non-normal distribution were expressed as median (interquartile, IQR) and categorical variables were reported as numbers and percentages. For dependent group comparisons, the Wilcoxon sign rank test and paired samples t-test were used, and for categorical variable comparisons, the marginal homogeneity test was used. For all statistical analyses, a P value less than .05 was defined as a statistical significance.

RESULTS
Thirteen patients had primary APS and 4 patients had secondary APS. Dyspnea on exertion was the main symptom in all patients and 2 patients also had hemoptysis. Seven patients had previous deep vein thrombosis and 5 patients had a history of recurrent abortion. Four patients had ACA and LA, 3 patients had a j2GPI and 10 patients had only ACA in the study group. In addition to anticoagulation treatment, 5 patients in the primary APS group received anti-PH treatment preoperatively. On the other hand, 2 patients received azathioprine and the other 2 received azathioprine along with anticoagulation and corticosteroid treatment in the secondary APS group.

Preoperative clinical data of the patients were documented in Table 1. Preoperative laboratory data were summarized in Table 2. Two patients with WHO class symptoms IV, who required oxygen treatment and had a preoperative pulmonary vascular resistance (PVR) greater than 1000 dyn/s/cm⁻⁵, did not have 6-MWT. One patient had no RHC due to a mobile mass on the tricuspid valve on echocardiography, which was diagnosed as thrombus after surgery. Concomitant surgical procedures, including the closure of the patent foramen ovale in 3 patients and extirpation of a mass on the tricuspid valve, were performed during the rewarming phase of surgery. Operative data were summarized in Table 3.

Intubation was prolonged for 3 days in only 1 patient with postoperative reperfusion injury. One patient required early revision for cardiac tamponade due to warfarin overdose. One patient who had postoperative atrial fibrillation on the first postoperative day was restored to sinus rhythm with drug treatment. There was no in-hospital mortality. Postoperative clinical and hemodynamic data were summarized in Table 4. Systolic and mean pulmonary artery pressures (PAP) and PVR were decreased significantly after PEA. The changes in these hemodynamic measurements correlated with the clinical status of the patients and described WHO class I (88.2%) and II (11.8%) symptoms (Figure 1) and increased 6-MWT by >54% (Figure 2). Platelet counts decreased significantly in all patients in the early postoperative period, and 1 patient with severe thrombocytopenia (<30000) received...
Patients were followed up for a mean of 75.2 months (2-130 months) with only 1 patient lost to follow-up. There was 1 late death in the ninth year after PEA due to COVID-19 pneumonia and the remaining 15 patients are still being followed up. One patient who discontinued anticoagulation treatment without medical consultation had recurrent pulmonary emboli and required reoperation 1 year after primary PEA. The surgical PEA specimen taken from this patient is shown in Figure 3.

**DISCUSSION**

We describe 17 patients diagnosed with APS-associated CTEPH who underwent pulmonary endarterectomy. This report is the first largest single-center experience of pulmonary endarterectomy of patients diagnosed with APS-associated CTEPH. All patients received optimal conventional medical treatment with anticoagulation and immunosuppression before surgery. The mPAP and PVR values after PEA surgery were significantly reduced. There was no in-hospital mortality, and only 1 patient required reoperation due to noncompliance with anticoagulation treatment. All patients improved to WHO functional class I and II. Unfortunately, 1 patient died due to COVID-19 pneumonia in the ninth year after surgery.

Chronic thromboembolic pulmonary hypertension is the result of massive, recurrent pulmonary thrombotic events and remodeling process, obstructing the pulmonary vasculature. Antiphospholipid syndrome is an autoimmune syndrome associated with a hypercoagulable state. Colorio et al. reported the presence of thrombophilic risk factors in 75% of patients with CTEPH and 50% were aPL. Antiphospholipid syndrome is a multisystemic, autoimmune disease complex associated with recurrent arterial and venous thrombotic events, abortion, and thrombocytopenia due to antibody-induced thrombosis. The presence of aPL is necessary for diagnosis, and they are associated with the hypercoagulable state leading to thrombosis. Definite APS is present when at least 1 clinical criterion and 1 laboratory criterion.9 Anti-phospholipid antibodies are auto-antibodies responsible for the pathogenesis of the disease. They are a group of heterogeneous antibodies that can be idiopathic or secondary to some autoimmune diseases such as SLE, infections, some malignancies (hairy cell leukemia, epithelial tumors, and lymphoproliferative disorders), and some drugs (diphenylhydantoin, procainamide, and chlorpromazine).

### Table 1. Preoperative Clinical Data

| Variables                  | n (%) | Mean ± SD |
|----------------------------|-------|-----------|
| Age (day), mean ± SD       | 34.82 ± 10.07 |
| Gender, n (%)              |       |
| Male,                      | 4 (23.5) |
| Female                     | 13 (76.5) |
| BMI (kg/m²) mean ± SD      | 26.10 ± 5.22 |
| BSA (m²) mean ± SD         | 1.8 ± 0.2 |
| Hemoptysis, n (%)          | 2 (11.8) |
| Dyspnea, n (%)             | 17 (100.0) |
| Abortus, n (%)             | 5 (29.4) |
| Recurrent emboli, n (%)    | 1 (5.8) |
| NYHA Class, n (%)          |       |
| Class III                  | 10 (58.8) |
| Class IV                   | 7 (41.17) |
| APS, n (%)                 | 13 (76.5) |
| SLE and APS, n (%)         | 4 (23.5) |
| Concomitant Pathologies    |       |
| DVT, n (%)                 | 7 (41.2) |
| PFO, n (%)                 | 3 (17.6) |
| Tricuspid mass             | 1 (5.8) |
| Disease duration (month)   | 26.94 ± 17.35 |
| Follow-up duration (month) | 75.29 ± 40.21 |

BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; APS, antiphospholipid Syndrome; SLE, systemic lupus erythematosus; DVT, deep vein thrombosis; PFO, patent foramen ovale.

### Table 2. Preoperative Laboratory Data

| Variables                          | Mean ± SD/Median (IQR) |
|------------------------------------|------------------------|
| 6MWD (m)                           | 269.47 ± 111.70        |
| Echocardiographic PAP systolic (mm Hg) | 80 (65.5-101)         |
| Echocardiographic PAP mean (mm Hg)  | 50 (41.5-58)           |
| Cardiac catheter PAP systolic (mm Hg) | 76.44 ± 21.60         |
| Cardiac catheter PAP mean (mm Hg)   | 40.94 ± 12.74          |
| Cardiac index (L/min/m²)            | 2.65 ± 0.66            |
| Cardiac output (L/min/m²)           | 4.50 ± 0.73            |
| Preoperative PVR (dyn/s/cm²)        | 756.50 ± 393.91        |
| TAPSE                               | 15.76 ± 3.47           |
| LVEF (%)                            | 63.88 ± 2.23           |

6MWD, 6-minute walking distance; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction.

### Table 3. Operative Data

| Variable                             | n(%)/Mean ± SD |
|--------------------------------------|----------------|
| CPB (minute)                         | 198.53 ± 42.06 |
| AKK (minute)                         | 47.53 ± 37.98  |
| TCA (minute)                         | 22.12 ± 6.59   |
| PFO closure                          | 3 (17.6)       |
| Tricuspid mass resection             | 1 (5.8)        |
| Extubating time (hours)              | 17.59 ± 4.50   |
| Intensive care unit (hours)          | 2.76 ± 1.34    |
| Hospitalization (days)               | 8.35 ± 2.31    |

CPB, cardiopulmonary bypass; AKK, aortic cross clamp; TCA, total circulatory arrest; PFO, patent foramen ovale.
The most important antibodies are ACA, LA, and α2GPI.10 All LA are aPL, but only 25% of all aPL are LA positive.11 The most common ACAs in clinical practice are raised against cardiolipin. A definitive diagnosis requires the detection of at least 1 of the isotypes Ig G, Ig M, on at least 2 or more occasions at least 12 weeks apart by standardized tests. Although the association of these isotypes with various clinical presentations is not certain, high titers of IgG have been found to

| Variable                          | Preoperative       | Postoperative     | P     |
|-----------------------------------|--------------------|-------------------|-------|
| 6MWD (m)                          | 269.46 ± 111.7     | 490 ± 105.34      | .001* |
| Echocardiographic PAP systolic (mm Hg) | 80 (65.5-101)    | 30 (24-35)        | <.001*|
| Echocardiographic PAP mean (mm Hg) | 50 (41.5-58)      | 20 (20-25)        | <.001*|
| Cardiac catheter systolic (PAP) (mm Hg) | 76.44 ± 21.60    | 39.69 ± 7.91      | <.001*|
| Cardiac catheter mean (PAP) (mm Hg) | 40.94 ± 12.74     | 27.38 ± 5.83      | <.001*|
| PVR (dyn/s/cm³)                   | 756.50 ± 393.91   | 298.31 ± 132.84   | <.001*|
| Cardiac index (L/min/m²)          | 2.65 ± 0.66       | 3.02 ± 0.77       | .044  |
| Cardiac output (L/min/m²)         | 4.50 ± 0.73       | 5.13 ± 0.96       | .002* |
| Thrombocyte count                 | 210 (46-464)      | 126 (97-178)      | .001* |
| TAPSE                             | 15.76 ± 3.47      | 17.88 ± 2.69      | .003* |

6MWD, 6-minute walking distance; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic excursion.

Figure 1. Preoperative and postoperative NYHA and tricuspid regurgitation data. NYHA, New York Heart Association; TR, tricuspid regurgitation.

Figure 2. Comparison of pre- and post-operative 6-minute walking distance test. 6MWD; 6-minute walking distance.
be associated with both arterial and venous thrombosis and recurrent abortions.\textsuperscript{22} anti-β\textsubscript{2}I antibody is a plasma glycoprotein that inhibits the coagulation network. anti-β\textsubscript{2}I antibodies impair the ability of beta-2-glycoprotein to inhibit platelet aggregation and complement activation, leading to a propensity for thrombosis.\textsuperscript{2} The presence of more than 1 isotype leads to an increased risk of thrombosis.\textsuperscript{13} but in the study group only 4 patients had ACA and LA, the other patients had a single autoantibody αβ2GPI or ACA.

The factors closely associated with morbidity and mortality in APS are thromboembolic complications. The incidence of thrombotic vasculopathy in APS is reported to be 30% with 70% of venous and 30% of arterial origin. Venous thrombosis is either isolated deep vein thrombosis (DVT) or more commonly DVT with pulmonary embolism. The most common form of arterial thrombosis is either transient ischemic attack or cerebrovascular stroke. Recurrent abortions should also be asked about the presence of APS. In our study group, there were 7 patients who presented with DVT for the first time and 5 patients with recurrent abortions.

In a study by Kaya et al\textsuperscript{14} 30 patients with DVT without the presence of any major risk factors were compared with 20 healthy subjects and they found ACA IgG antibodies in 37% of DVT cases compared to none in the control group and they suggested looking for APS in cases with DVT without any risk factor. In the literature, there are also APS patients diagnosed after pulmonary embolism without DVT.\textsuperscript{15} We also had 10 patients diagnosed with APS after pulmonary thromboembolism without DVT.

Respiratory involvement in APS patients has a wide spectrum. Pulmonary hypertension can occur in APS patients in the form of primary PH, non-thromboembolic secondary PH, or CTEPH.\textsuperscript{16} Since all APS patients with PH and pulmonary vasculopathy have APA, it is suggested that it should be used routinely as a screening test.\textsuperscript{17} There are conflicting results on the incidence of pulmonary thromboembolism in primary and secondary APS. Love and Santoro\textsuperscript{18} reported the incidence of pulmonary thrombosis in primary and secondary APS as 13% and 42%, respectively. In contrast, Weber et al\textsuperscript{19} found that the incidence of pulmonary thromboembolism was higher in primary APS patients. Among our patients, 13 (76.4%) had primary APS.

Although CTEPH is reported to be rare in APS,\textsuperscript{20} it is more common than primary PH and non-thrombotic PH.\textsuperscript{21} After acute pulmonary embolism, incomplete resolution of thrombi, vascular remodeling after endothelial damage, and microthrombosis lead to CTEPH in 3% of patients. In all patients with PH after acute pulmonary embolism, CTEPH should be evaluated with RHC, computerized tomographic pulmonary angiography, and lung ventilation-perfusion scintigraphy scan, as it is the only curative subgroup of patients with PH.\textsuperscript{22} Concomitant cardiac pathologies have been described previously.\textsuperscript{23} Closure of patent foramen ovale was performed in our 3 patients.

The ASPIRE registry showed that patients who declined pulmonary endarterectomy had a 5-year survival rate of 53% compared with operated patients (83%).\textsuperscript{24} Mortality is inevitable due to right heart failure. Pulmonary endarterectomy is the curative treatment option with acceptable morbidity and mortality. To date, published data on the outcomes of PEA in APS mainly comprise case reports.\textsuperscript{25-27} Nakajima et al\textsuperscript{28} proposed PEA for patients with APS and high PVR depending on their promising early postoperative hemodynamic and functional improvement. Similarly, Elmogy et al\textsuperscript{29} recommended PEA as a curative treatment to lower PVR in patients with the diagnosis of SLE and antiphospholipid syndrome. Consistent with these findings, PVR, systolic, and mean PAP decreased significantly after PEA in our patients.

Colorio et al\textsuperscript{30} compared the results of PEA in their study of 16 APS and 22 control group patients and reported that postoperative functional capacity and survival were better in APS patients.

There are limited data in the literature regarding the postoperative complications of PEA in APS patients. The experience of the center is extremely important. Only 1 patient in the study group had reperfusion injury and recovered with conservative treatment. Two of our patients are still being followed up with anti-PH treatment for persistent PH.

Camous et al\textsuperscript{31} compared the outcomes of 17 APS patients with 190 patients in the control group after PEA, reporting a higher incidence of postoperative stroke, delirium, and thrombocytopenia in APS patients with no difference in mortality. Neurologic complications from arterial thrombosis and cerebral ischemia have also been reported.\textsuperscript{32} We did not observe any neurologic complications. Thrombocytopenia after CPB can be seen in all cardiothoracic procedures including PEA in the first 72 hours. Approximately 2% of these patients develop heparin-induced thrombocytopenia (HIT). Thrombocytopenia in APS and HIT has an autoimmune origin.\textsuperscript{33} Mild to moderate thrombocytopenia (7010^3-12010^3/ mm\textsuperscript{3}) can be seen in 20-50% of APS patients, but only 5-10% have severe thrombocytopenia without bleeding tendency. Thrombocytopenia is not one of the laboratory criteria for the diagnosis of APS.\textsuperscript{34} Preoperative replacement therapy is not recommended as it may induce an antibody response and further decrease platelet counts. If necessary, the administration of glucocorticosteroids is recommended as first-line therapy, followed by immunosuppressive treatment.\textsuperscript{35} Only
1 patient in our group developed postoperative severe thrombocytopenia and was treated with daily corticosteroid (1 mg/kg) for 7 days and immunoglobulin (1 mg/kg) for 2 days.

Catastrophic APS is a rare form of the disease with high mortality. In our series, we did not find any recurrent thrombotic events or catastrophic form of the disease. One of our patients with secondary APS who discontinued anticoagulation medication without medical consultation had recurrent pulmonary emboli and required reoperation due to clinical deterioration. The duration of anticoagulation treatment in APS patients is still controversial. Derksen et al found no recurrence in 19 patients on continuous anticoagulation therapy for 8 years but observed recurrent thrombi in 50.8% at 2 years and in 78% at 8 years in patients who discontinued treatment. Lifelong anticoagulation treatment is recommended after PEA. Immunomodulatory treatment in addition to anticoagulation to prevent recurrent thrombotic events has been suggested, but prospective large-scale clinical trials are needed. In our group, only 4 patients with coexisting SLE had immunosuppressive treatment with azathioprine or azathioprine as immunomodulators. Although the incidence of CTEPH after pulmonary embolism is reported to be only 0.57-4.7% and screening for CTEPH is not supported by current guidelines, it should be considered in APS patients.

The major limitation of the study is its retrospective design and the relatively small number of patients. However, as the number of APS patients with CTEPH is limited and ethical considerations would be present, a controlled trial of PEA in CTEPH associated with APS is unlikely.

In conclusion, although only a small series of patients were included in the study, the surgical results are promising for this rare subgroup of CTEPH patients. We believe that this study will increase the awareness of APS-associated CTEPH patients with a good therapeutic outcome with PEA. Patients with APS-associated CTEPH should be referred to experienced CTEPH centers to investigate the presence of CTEPH and assessment for PEA, which will increase their life expectancy and quality of life.

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