Outcomes of patients with antiphospholipid syndrome after pulmonary endarterectomy

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Abstract

OBJECTIVES: Antiphospholipid syndrome (APS) is a risk factor for chronic thromboembolic pulmonary hypertension, for which the treatment of choice is pulmonary endarterectomy. The increased risk of postoperative thrombotic complications in patients with APS may complicate the perioperative management. The primary objective of this study was to investigate the impact of APS on mortality and morbidity rates after pulmonary endarterectomy. The secondary objective was to describe platelet count changes after pulmonary endarterectomy in patients with APS.

METHODS: Data were collected prospectively for consecutive patients with APS who underwent pulmonary endarterectomy over a 5-year period [2007–2011] and for consecutive patients without APS who underwent pulmonary endarterectomy at the same centre during 2008–2011 [controls]. Major complications and daily platelet counts were collected. Haemodynamic parameters obtained by right heart catheterisation were recorded preoperatively and on the day after surgery.

RESULTS: We identified 17 patients with APS [3.6% of all pulmonary endarterectomies] and 190 controls. Early haemodynamic results after pulmonary endarterectomy were similar in the two groups, with a greater than 35% decrease in pulmonary vascular resistance. Significantly higher proportions of patients with APS than of controls experienced stroke [11.8 vs 1.0%, P = 0.03] and delirium [47 vs 20%; P = 0.02]. Compared with the controls, the patients with APS had significantly lower platelet counts and had a higher occurrence rate of platelet counts of ≤50 g/l [71 vs 4%; P < 0.0001]. Intensive care unit (ICU) mortality was not significantly different between the two groups [0/17 vs 7/190 (3.7%), P = 0.49].

CONCLUSIONS: Neurological complications and severe thrombocytopenia were more common after pulmonary endarterectomy in patients with than without APS. Haemodynamic results and ICU mortality rate were similar in the two groups.

Keywords: Antiphospholipid syndrome · Pulmonary endarterectomy · Mortality · Stroke · Thrombocytopenia

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by recurrent vascular thromboses and the production of antiphospholipid antibodies such as anticardiolipin antibody (aCL) and lupus anticoagulant (LA) [1]. APS increases the risk of chronic thromboembolic pulmonary hypertension (CTEPH) [2], for which pulmonary endarterectomy (PEA) is the treatment of choice [3, 4]. PEA is associated with many of the complications seen with other cardiothoracic surgical procedures, as well as with a number of specific complications [4]. In addition, APS is associated with an increased risk of postoperative thrombotic complications after vascular procedures [5]. Features of APS that complicate the perioperative management include thrombocytopenia, specific anticoagulation needs and high risks of thrombosis and bleeding [5, 6].

The risks associated with APS mandate a careful assessment of the risk/benefit ratio of PEA. Few data are available to guide clinicians in this task. Outcomes of patients with APS after PEA have been described in anecdotal case-reports. Among the 181 patients with CTEPH included in a cohort study, 105 underwent PEA, including 12 with APS [7]. Survival after PEA was not significantly different between patients with and those without APS. However, the study report does not detail the postoperative complications [7]. Here, our primary objective was to investigate the potential impact of APS on mortality and complication rates in patients admitted to the intensive care unit (ICU) after PEA. The secondary objective was to describe platelet count changes in patients with APS during the postoperative period.

PATIENTS AND METHODS

Study population

We conducted an observational prospective study at the Centre Chirurgical Marie-Lannelongue, Le Plessis-Robinson, France.

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The study was approved by our institutional review board [Comité d’Ethique du Centre Chirurgical Marie Lannelongue; no. 2007-4]. From January 2007 to December 2011, consecutive patients with APS who underwent PEA were included prospectively. Consecutive patients without APS who underwent PEA at our centre between January 2008 and March 2011 and who had been included prospectively in another study served as controls.

All patients in both groups underwent PEA as described by Dartevelle et al. [8]. No changes in technique or medical management occurred during the study period. More specifically, anticoagulant therapy protocols for patients with APS were not modified. Heparin [anti-Xa activity, 0.4–0.6 IU/ml] was begun 4–6 h after ICU admission if bleeding was controlled. Vitamin K antagonist therapy was started on the third postoperative day.

**Data collection**

For each patient, we recorded the following data: age, sex, weight, body mass index [BMI], preoperative treatment of pulmonary arterial hypertension, preoperative PaO2, durations of cardiopulmonary bypass [CPB] and cardiac arrest, whether PEA was done as an emergent procedure, the Simplified Acute Physiology Score II [SAPS II], whether the patient had systemic lupus erythematosus [SLE], duration of mechanical ventilation, ICU length of stay and ICU mortality.

We recorded the following major complications: stroke, confusion, pneumonia, mediastinitis, acute respiratory distress syndrome [ARDS], re-thrombosis, atrial fibrillation, pulmonary haemorrhage, heparin-induced thrombocytopenia [HIT], haemodialysis and need for extracorporeal membrane oxygenation [ECMO]. Haemodynamic parameters obtained by right heart catheterization in the preoperative period and on the day after surgery were recorded, as well as treatments used for APS-related complications. Daily platelet counts were collected. Definitions and laboratory tests for immunoglobulin-G (IgG)-aCL are provided in the supplementary material.

**Statistical analysis**

Data were entered and analysed using the Statview 5.0 software (SAS Institute, Inc., Cary, NC, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were described as mean ± SD or median [25th–75th percentiles] as appropriate and compared using Student’s t-test or the Mann–Whitney U-test as appropriate. The χ² test or Fisher exact test were chosen to compare categorical variables. To evaluate changes over time in platelet counts, we used repeated-measures analysis of variance [ANOVA] followed by the Scheffe F test when appropriate. Values of P < 0.05 were considered significant.

**RESULTS**

During the study period, 476 patients underwent PEA, including 17 [3.6%] with APS. Table 1 lists the main features of the patients with APS and controls. Compared with the controls, the patients with APS were younger and less severely ill at ICU admission; they less often had pulmonary vascular resistance [PVR] values of >900 dyne s/cm². The aCL titre was >100 IgG phospholipids [GPL] in 5 of the 17 patients with APS.

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**Table 1:** Characteristics of the 17 patients with APS and 190 controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>APS (n = 17)</th>
<th>Controls (n = 190)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42 ± 15</td>
<td>58 ± 15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>7 (41)</td>
<td>93 (49)</td>
<td>0.54</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 ± 5.8</td>
<td>26.7 ± 6.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Preoperative PaO2</td>
<td>4 (23)</td>
<td>41 (21)</td>
<td>0.99</td>
</tr>
<tr>
<td>PVR &gt; 900 dyne s/cm² (n, %)</td>
<td>65 ± 14</td>
<td>66 ± 11</td>
<td>0.94</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>1 (6)</td>
<td>5 (3)</td>
<td>0.40</td>
</tr>
<tr>
<td>Bosentan</td>
<td>5 (29)</td>
<td>42 (22)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>3 (18)</td>
<td>29 (15)</td>
<td>0.79</td>
</tr>
<tr>
<td>SAPS II score, point</td>
<td>3 (18)</td>
<td>78 (43)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Table 2:** Perioperative haemodynamic data

<table>
<thead>
<tr>
<th>Variables</th>
<th>APS (n = 17)</th>
<th>Controls (n = 181)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative mean PAP (mmHg)</td>
<td>45 ± 14</td>
<td>46 ± 12</td>
<td>0.80</td>
</tr>
<tr>
<td>Preoperative cardiac output (l/min)</td>
<td>5.6 ± 1.6</td>
<td>4.6 ± 1.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Preoperative PVR (dyne s/cm²)</td>
<td>727 ± 419</td>
<td>880 ± 370</td>
<td>0.11</td>
</tr>
<tr>
<td>Postoperative mean PAP (mmHg)</td>
<td>27 ± 6</td>
<td>26 ± 8</td>
<td>0.69</td>
</tr>
<tr>
<td>Postoperative cardiac output (l/min)</td>
<td>5.1 ± 1.2</td>
<td>4.8 ± 1.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Postoperative PVR (dyne s/cm²)</td>
<td>465 ± 231</td>
<td>485 ± 210</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean variation of PVR (%)</td>
<td>−36 ± 25</td>
<td>−39 ± 30</td>
<td>0.72</td>
</tr>
</tbody>
</table>

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**Early haemodynamic results**

Early haemodynamic results after PEA were similar in patients with APS and controls (Table 2). In both groups, PVR decreased by >35%.
Early outcomes

ICU complications and death rates are reported in Table 3. The 30-day mortality was not significantly different between the two groups [1/17 (5.9%) vs 7/190 (3.7%), \( P = 0.50 \)]. The preoperative aCL titre was not associated with an increased frequency of any of the complications. Only stroke and delirium occurred in significantly different proportions of patients in the two groups; both were more common in the APS group. Two patients with APS experienced severe stroke; ischaemic stroke occurred 15 days after PEA (international normalized ratio = 2.7) in 1 patient, whose condition improved with corticosteroid therapy; and subdural haematoma developed in a setting of catastrophic APS 10 days after PEA in another patient, who was given danaparoid for suspected HIT (anti-Xa activity, 0.65 IU/ml).

No significant differences were found between the two groups for the median duration of mechanical ventilation [1 (1–2) vs 2 (1–6) days, respectively; \( P = 0.09 \)] or mean ICU stay length [10.5 ± 7.9 vs 10.6 ± 9.8 days, respectively; \( P = 0.96 \)].

Postoperative platelet count changes

Platelet counts differed significantly between the two groups (Fig. 1). Compared with the controls, the patients with APS had significantly lower platelet counts and had a higher occurrence rate of platelet counts of ≤50 g/l (71 vs 4%; \( P < 0.0001 \)). The platelet count nadir did not correlate significantly with the preoperative aCL titre \( [r = 0.18; \ P = 0.48] \). Serological testing for platelet factor-4-heparin (PF4-H) was performed in 13 (76%) patients with APS and was positive in 3, of whom only 1 had a positive functional assay leading to a diagnosis of HIT.

Treatment of APS

Eight [47%] patients received specific treatments for APS. Preoperatively, high aCL titres prompted plasma exchange in 2 patients and dropped sharply after the procedure. Postoperatively, corticosteroid therapy (1 mg/kg for 8 days) was used in 2 patients to treat neurological complications and in 4 to treat thrombocytopenia; of these 4 patients, 2 also received intravenous IgG therapy (1 g/kg for 2 days) starting on the third postoperative day. Platelet counts started to rise after 3 days of treatment.

DISCUSSION

In our study, haemodynamic results and mortality after PEA were similar in patients with and in those without APS. Neurological complications were significantly more common among patients with APS. Significant differences in postoperative platelet counts were found between the two groups.

Table 3: Postoperative complications

<table>
<thead>
<tr>
<th>Complications (n, %)</th>
<th>APS (n = 17)</th>
<th>Controls (n = 190)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>2 (12)</td>
<td>2 (1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Delirium</td>
<td>8 (47)</td>
<td>38 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (18)</td>
<td>50 (26)</td>
<td>0.41</td>
</tr>
<tr>
<td>Mediastinitis</td>
<td>3 (18)</td>
<td>10 (5)</td>
<td>0.08</td>
</tr>
<tr>
<td>ARDS</td>
<td>2 (12)</td>
<td>20 (10)</td>
<td>0.13</td>
</tr>
<tr>
<td>Rethrombosis</td>
<td>2 (12)</td>
<td>6 (3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (12)</td>
<td>40 (21)</td>
<td>0.36</td>
</tr>
<tr>
<td>Pulmonary haemorrhage</td>
<td>1 (6)</td>
<td>6 (3)</td>
<td>0.36</td>
</tr>
<tr>
<td>HIT</td>
<td>1 (6)</td>
<td>5 (3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>0</td>
<td>2 (1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Postoperative ECMO</td>
<td>1 (6)</td>
<td>7 (4)</td>
<td>0.49</td>
</tr>
<tr>
<td>ICU deaths</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

APS: antiphospholipid syndrome; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit.

Figure 1: Changes in absolute platelet count after PEA in patients with APS and controls. Blue bars: controls. White bars: patients with APS. D0, day of ICU admission after surgery. Significant differences were shown between patients with APS and controls \([F = 23.2; \ P < 0.0001]\). Mean values at all time points differed significantly \((\ P < 0.0001)\) between the two groups. Controls: \(*P < 0.0001\) between days 1 and 2; \(**P < 0.0001\) between days 3 and 4; \(\overset{\ddagger}{P} < 0.0001\) between days 4–6. Patients with APS: \(*\overset{\ddagger}{P} < 0.0001\) between days 1 and 2.
APS is among the conditions associated with the development of CTEPH [2] and, similar to other disorders linked to CTEPH [7]. may increase the risk of complications after surgery. Among these complications, several are potentially life threatening, such as recurrent thrombosis, catastrophic APS and bleeding [5, 9]. A study of valve replacement surgery in patients with APS showed high mortality and morbidity rates that were chiefly ascribable to the multiple associated comorbidities [5].

A decrease in PVR is the key criterion for successful PEA [3, 4, 10]. However, in patients with APS, the challenges raised by perioperative haemostatic management [6, 11] and the increased risk of thrombosis may jeopardize the immediate postoperative haemodynamic results. The haemodynamic results in our study are consistent with previous data [7, 8, 10]. The PVR decrease was of similar magnitude in patients with and in those without APS, and neither did the mortality rate differ between the two groups, in keeping with earlier results [7].

Stroke and delirium were the only two complications that were more common in patients with APS than in controls. PEA is associated with multiple risk factors for postoperative neurological complications, including the use of CPB and circulatory arrest [12, 13]. In a recent randomized controlled trial, mild or moderate confusion or mood alteration was noted in 12% of patients after PEA [13]. Central vascular events or transient ischaemic attacks have been reported in 0.3–5.6% of patients after PEA [10, 13]. APS is also associated with neurological complications [14]. Thus, stroke and transient ischaemic attacks occurred in 20 and 11% of patients with APS, respectively [15]. Many large studies found that high aCL titres and presence of LA were associated with cerebral ischaemia/thrombosis and cognitive dysfunction [1, 16, 17]. In a study of PEA, IgG-aCL titres of >10 U/ml were found in 15% of patients [28/184] and were associated with a higher rate of transient ischaemic attacks [32 vs 10%, P = 0.023], although the rates of death and major complications were similar [18]. The pathogenic mechanisms underlying the neurological complications of APS are incompletely understood [19]. Catastrophic APS occurs in <1% of all patients with APS [15], but is fatal in about 50% of cases [9, 20]. In our study, the only patient with catastrophic APS after PEA died of cerebral complications 10 days after ICU discharge. The treatment of catastrophic APS is not standardized [21]. High-dose corticosteroids, intravenous immunoglobulins and plasma exchange constitute the first-line treatment options [20, 21].

The other important complication is the occurrence of thrombocytopenia and its related morbidity, diagnostic problem and management. Thrombocytopenia affects >20% of patients with APS overall [19] and 60% of those with catastrophic APS [9]. In addition, thrombocytopenia is a common and multifactorial manifestation in ICU patients [22]. In patients who underwent cardiothoracic surgery with CPB, thrombocytopenia usually persisted for 72 h postoperatively [22]. HIT was diagnosed in <2% of these patients [22]. Interestingly, APS and HIT are both related to autoimmunity [23]. HIT is related to the production of antibodies against PF4-H complex. Antibodies to PF4 (as opposed to PF4-H) have been found in up to 81% in patients with APS [24] and must be distinguished from HIT by functional assays [24]. No specific guidelines are available for managing thrombocytopenia in patients with APS [19, 23], who are usually given treatments similar to those used in autoimmune thrombocytopenic purpura [11, 23]. We used low-dose corticosteroid therapy (1 mg/kg for 8 days) and/or intravenous immunoglobulins (1 g/kg/day for 2 days).

Identifying patients with APS at risk of postoperative APS-related complications is challenging but important to ensure that optimal treatment is started as soon as possible. The concomitant presence of SLE substantially worsens the prognosis of APS [20]. The presence of LA and high IgG-aCL titres were major risk factors for thrombosis in all studies [1, 16–19] but one [25]. Thrombocytopenia was strongly associated with the presence of aCL in patients with SLE (odds ratio, 4.05) [25]. However, none of the laboratory variables is sufficiently predictive to warrant specific treatment [19]. Our preoperative management plan includes a single plasma exchange session followed by intravenous immunoglobulins in patients with one or more of the following risk factors: aCL titre >100 GPL, SLE, thrombocytopenia (<100 g/l) and previous arterial thrombosis. In the present study, 2 of 17 patients met these criteria. Both experienced a sharp drop in aCL titres after plasma exchange and had platelet counts >60 g/l throughout the postoperative period, which was uneventful. All patients with neurological complications received corticosteroid therapy [9, 20].

Our study has several limitations. All patients were enrolled at the same surgical centre. Thus, the general applicability of our findings to other centres requires evaluation. The number of patients with APS was small, in keeping with the low prevalence of this disease, and the statistical power of our study was therefore limited. A multicentre international study would be of interest. The control group was recruited during only part [39/60 months] of the enrolment of APS patients. However, we think that it was a representative sample. Finally, the postoperative management of APS was not standardized, although it was based on a careful analysis of the literature.

In conclusion, despite a higher risk of neurological complications and severe thrombocytopenia, patients with APS who receive careful preoperative preparation and postoperative care have haemodynamic results and mortality rates after PEA similar to those seen in patients without APS.

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**SUPPLEMENTARY MATERIAL**

Supplementary material is available at EJCTS online.

**REFERENCES**


Trehel-Tursis V, Louvain-Quintard V, Zarrouki Y, Imbert A, Dubine S, Stéphan F. Clinical and biological features of patients suspected or confirmed to have heparin-induced thrombocytopenia in a cardiothoracic surgical ICU. Chest 2012;142:837–44.

