Heart valve surgery in patients with the antiphospholipid syndrome: analysis of a series of nine cases

Andrea Colli, Carlos A. Mestres,*, Gerard Espinosa, Miguel A. Plasín, Jose L. Poma, Josep Font, Ricard Cervera

Department of Cardiovascular Surgery, Hospital Clinic, University of Barcelona, Villarroel 170, 08036, Barcelona, Spain

Department of Autoimmune Diseases, Hospital Clinic, University of Barcelona, Villarroel 170, 08036, Barcelona, Spain

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Abstract

Objective: Antiphospholipid syndrome (APS) is a rare coagulation disorder associated with recurrent arterial and venous thrombotic events. Heart valve abnormalities are commonly found in patients with APS. Methods: From March 1998 to March 2007, nine patients with APS underwent heart valve surgery using cardiopulmonary bypass. We retrospectively reviewed their clinical data, operative and postoperative courses and the long-term results. Results: The mean age was 43.6 ± 10.4 years, six were female and three male. Four patients underwent mitral valve replacement, three went through aortic valve replacement, one underwent combined mitral—aortic valve plasty. The syndrome was primary in seven patients and associated with systemic lupus erythematosus (SLE) in two. Follow-up was 8 days to 8 years (median 66 months). Two patients died in the early postoperative period: both due to an acute cerebrovascular accident. Four patients presented an uneventful late postoperative course. One patient experienced an ischaemic stroke 5 years after mitral valve replacement (MVR) and developed refractory congestive heart failure requiring heart transplantation three years postoperatively. Conclusions: Heart valve surgery in patients with antiphospholipid syndrome may carry considerable early and late mortality and morbidity. Thrombo-embolic complications are the most common complications. Mechanical prostheses have been used at our Institution in the previous years; however, today, after reviewing our historical results, we reconsider our general strategy and believe that tissue heart valve prostheses are the possible ideal substitutes, minimising the risks of morbidity and mortality due to the hypercoagulable state of APS.

Keywords: Antiphospholipid syndrome; Valvular heart disease; Systemic lupus erythematosus

1. Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and arterial thromboses, often multiple, and recurrent foetal losses, frequently accompanied by moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL) or anti-β2 glycoprotein-I (β2GPI) antibodies. The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases, mainly systemic lupus erythematosus (SLE) [1]. The aPL are found with a prevalence of 1—5% in the general apparently healthy population, in up to 30% in SLE patients [2,3], in 46% of patients with stroke or transient ischaemic attack under the age of 50 years [4] and in 21% of young survivors (younger than 45 years) of myocardial infarction [5].

Venous thrombosis, especially deep venous thrombosis (DVT) of the lower limbs, is the most common manifestation, occurring in 29—55% of patients during an average follow-up of less than 6 years [6]. Arterial thromboses are less frequent with strokes and transient ischaemic attacks, accounting for almost 50% of arterial manifestations [6].

Valvular heart disease (Libman—Sachs endocarditis), with a predilection for mitral valve involvement, is another clinical feature of the APS [7]. The prognosis of valve disease in this condition is not well documented, except for the high incidence of thrombo-embolic events [8]. The mechanisms of aPL-associated valvular dysfunction are unknown, but several hypotheses have been suggested. Immune complexes may injure the valvular endothelium, the phospholipid interaction between endothelial cells and platelets may be disrupted, or the capillaries within the valvular endothelium may be damaged. Any of these processes may lead to subsequent thrombotic and fibrotic changes of the valve. Titres of aPL may fluctuate or even become transiently negative in APS and have no direct role in the diagnosis or monitoring of aPL-associated valvular heart disease.
Considerable damage necessitating valve replacement is uncommon [9], and data regarding the outcome of valve replacement in patients with APS are limited and generally restricted to case reports or small series [10—19]. In the present study, we report our own experience with these challenging surgical heart valve procedures and review all patients with APS (primary and associated to SLE) who underwent valve replacement at our Institution during the last decade.

2. Material and methods

All the patients undergoing heart valve surgery at our Institution between 1998 and 2007 were reviewed. The Sapporo classification criteria were used for the diagnosis of APS [20]. Anaemia was defined as haemoglobin <12.5 mg dl⁻¹. Renal failure was defined as glomerular filtration rate (GFR) <60 ml min⁻¹ 1.73 m² calculated with the abbreviated Modification of Diet in Renal Disease formula [21]. Thrombocytopenia was defined as <150 000 platelets per mm³ [3]. Particular emphasis was laid on preoperative treatment with antiplatelets and corticosteroids.

All operations were performed using standard cardiopulmonary bypass with full heparinisation (activated clotting time >450 s) and cardioplegic arrest with intermittent cold blood cardioplegia. Early outcomes included events and complications that occurred within the first 30 postoperative days or during hospital stay, if longer. All patients received postoperative oral anticoagulation with Vitamin K antagonist (VKA) drug. Anticoagulants were started after 48 h postoperatively and low-molecular-weight heparin was continued until the international normalised ratio (INR) achieved a value ranging between 2.5 and 3.5. Complications were defined according to the guidelines for reporting mobility and mortality after cardiac valvular operations [22].

3. Results

Nine patients were identified as fulfilling the Sapporo criteria for APS [20]. The preoperative characteristics are presented in Table 1. All patients were admitted with well-established diagnosis. There were seven female and two male patients. Mean age was 43.6 ± 10.4 years (range 32—56) at the time of surgery. Four patients had severe mitral valve disease, four had aortic valve disease and one patient had combined mitral—aortic valve disease. Preoperatively, six patients were classified as New York Heart Association (NYHA) functional class III, one patient class IV and two patients class II. The syndrome was primary in seven patients and associated with SLE in two. The mean interval between the first manifestation of the APS and the first cardiac operation was 8.3 years (range 3—21 years). Three patients presented with previous episodes of arterial thrombosis and two had recurrent episodes of deep vein thrombosis. Seven patients received preoperative antiplatelet treatment with low-dose aspirin. All patients, except one, were preoperatively treated with corticosteroids (Table 2).

Operative procedures included three MVRs with mechanical prostheses, two AVRs with mechanical prostheses, one double valve replacement (DVR) with mechanical prostheses, one MVR with tissue valve and one AVR with tissue valve and one aortic valve plasty with thrombectomy. Patients were followed in our outpatient clinic. Recent clinical evaluation was performed on all surviving patients. The follow-up was 8 days to 8 years (median 66 months).

3.1. Early mortality

There were no intra-operative deaths. Two patients died in the early postoperative period due to an acute cerebrovascular accident. Patient 1 presented a massive ischaemic stroke at day 5 and died on day 8. Patient 4 presented with an acute subdural haematoma on day 5; VKA oral treatment was suspended and was treated only with intravenous heparin from day 7. Unfortunately, on day 9, the patient developed an acute occlusion of the right common carotid artery and a subtotal occlusion of the left internal carotid artery. The patient was medically treated but died the day after. Patient 3 presented with recurrent episodes of arterial peripheral thrombembolism and underwent successful percutaneous intervention. Patient 7 presented recurrent episodes of methorrhagia in the first three postoperative months that required gynaecologic surgical intervention. Both patients were correctly treated with oral VKA.

3.2. Follow-up

In terms of late outcomes, patient 6 developed refractory congestive heart failure requiring heart transplantation after three postoperative years. Patient 7 experienced an
The aPL could account for platelets and fibrin being deposited on defective valves and contribute to the development of sterile Libman–Sacks vegetations, initially described in SLE [11]. The first step could be the interaction of circulating aPL with valvular endothelial cells, leading to local inflammation and superficial thrombosis and resulting in valve deformities [11]. The significance of the presence of aPL in patients with valvular heart disease not fulfilling the APS criteria is not clear yet, although recent information suggests that the link between APS, aPL, valvular heart lesions and thrombo-embolic events is not fully elucidated. Various valvular lesions have been demonstrated by echocardiography in 35—82% of patients [8]. Irregular thickening of the mitral valve, followed by the aortic valve, is the most common finding. Mitral regurgitation is the predominant haemodynamic dysfunction, followed by aortic regurgitation. In many cases, more than one valve is involved [9].

The risks of thrombosis and bleeding are both present in patients with APS. The presence of thrombocytopenia and thrombophilia may also complicate the operative management of patients with APS [16,17]. Perioperative thrombosis may be due to antiphospholipid antibodies, warfarin withdrawal before the operation and catastrophic exacerbation of APS. If bleeding diathesis is not observed in the immediate postoperative period, the diagnosis of APS had already been established at the time of surgery.

In our retrospective study, we observed high morbidity (50%) and mortality (22%) in patients with APS who underwent valve replacement. These results are clearly very poor if compared to operative mortality presented in the Third Adult Cardiac Surgical Database Report 2006 (http://www.sectcv.es/component/option,com_docman/task,cat_view/gid,156/Itemid,46/ accessed 8 January 2008), in which the value for AVR is 2% and is 3% for MVR for the average age of 66—70 years. Cardiac surgical experience with APS patients relies on case reports describing one or two patients. Berkun et al. [19] recently presented an increased morbidity and mortality in a group of 10 patients with APS undergoing valve replacement. In all 10 patients, the diagnosis of APS was not confirmed preoperatively.

### 4. Discussion

The link between APS, aPL, valvular heart lesions and thrombo-embolic events is not fully elucidated. Various valvular lesions have been demonstrated by echocardiography in 35—82% of patients [8]. Irregular thickening of the mitral valve, followed by the aortic valve, is the most common finding. Mitral regurgitation is the predominant haemodynamic dysfunction, followed by aortic regurgitation. In many cases, more than one valve is involved [9].

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The high mortality observed in our study population may be accounted for by several factors, such as co-morbidities (poor NYHA class, renal insufficiency, anaemia and history of thrombo-embolism), the advanced nature of the heart valve disease at time of surgery and the use of steroids. Progressive heart failure was present in seven patients of our study population. Four patients (44%) presented at least with mild renal failure and of this, one patient already required dialysis. As already well described, renal failure is associated with both increased early mortality and late complications after heart valve surgery [19]. The presence of a preoperative anaemia is an important risk factor for perioperative red blood cell transfusion, which is associated with increased postoperative morbidity and mortality and is independently associated with adverse outcomes after cardiac surgery [23]. All the patients of our study presented preoperative anaemia.

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postoperative period, it should be realised that the patients are at increased risk of thrombo-embolism with significant central nervous system complications. Two of our patients experienced a serious haemorrhagic event. One was methotrexatillation and the other was an acute subdural haematoma. The patient that presented the subdural haematoma experienced, soon after this episode, an acute episode of thrombosis of the left carotid artery and subtotal occlusion of the right carotid artery, which eventually led to death.

Cerebral ischaemia is the most common arterial thrombotic manifestation of APS and is known to be an important cause of morbidity and mortality. Therefore, early institution of antiplatelet therapy, in addition to anticoagulant treatment, should be considered as perioperative antithrombotic treatment.

The chronic use of steroids and other immunosuppressive drugs are well-recognised treatments associated with a double-operative mortality [24]. All the patients of our study population were taking steroids.

In our retrospective study, the majority of patients received a mechanical prosthesis (six patients). Intra-operative valve inspection revealed virulent tissue destruction with significant thickening and verrucous vegetations in many cases. Therefore, valve repair was not feasible or inappropriate, rendering replacement as the only option. The decision to use this type of valvular substitute was made upon the consideration that patients should be treated with anticoagulation due to their hypercoagulopathy state.

With recently improved survival of patients with APS and SLE due to better medical treatment, including prevention of thrombosis and other complications, more patients can be expected to survive long enough to develop progressive valvular disease. As there is no effective medical treatment available neither to prevent the development of heart valve disease nor to slow its progression, it is likely that more patients will require valve replacement. In this regard, considering the younger age of these patients at the time of surgical intervention (median age 43.6 ± 10.4 years) and the better prognosis with intensive medical treatment, a mechanical valve may be theoretically advantageous over a tissue valve. However, the use of tissue heart valves has progressively increased in the last years in the international cardiac surgery community as well as at our Institution for the general population and also for patients presenting coagulopathy. For this reason and for the high number of thrombo-embolic events observed in our retrospective study due to the hypercoagulability state associated with APS, we consider that our previous policy should be reviewed and that tissue heart valves should be considered as the ideal valve heart substitute in this specific subgroup of patients. We are aware that future studies are needed also to deeply study the possible immunological deterioration of tissue heart valves. Our departmental policy is not class I, level of evidence A; however, we believe that our clinical data and the review of the literature suggest that the current generation of tissue heart valves can be safely used in patients with APS. The use of a tissue heart valve allows for an easier management of routine oral anticoagulation therapy and also a safer management of thrombus-embolic and bleeding complications typical of APS patients.

In conclusion, our retrospective analysis suggests that heart valve surgery in patients with APS is associated with considerable morbidity and mortality. The reasons are multiple, including advanced valvular disease, renal failure, previous thrombo-embolic accidents, the chronic use of steroids and immunosuppressive drugs. Thus, to decrease the operative risks in this specific subgroup of patients an early intervention should be considered. The use of mechanical prostheses has been preferred at our Institution in previous years but, today, after reviewing our historical results, we are reconsidering our general strategy and believe that tissue heart valve prostheses are the possible ideal substitute, minimising the risks of morbidity and mortality due to the hypercoagulability state of the APS. Future prospective studies are required to shed more light on a challenging topic.

References


