Mechanical heart valve prostheses and persistent lupus anticoagulant: is the thrombotic risk increased?

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The risk of thrombosis in patients with mechanical heart valve prostheses in spite of life-long adequate anticoagulation is 1–2% per year. Current recommendations for anticoagulation take into account the prosthesis itself and the co-morbid conditions that enhance the thrombotic risk. Lupus anticoagulant is diagnosed in many thrombotic recurrences. We designed an ambispective case–control study to evaluate thrombotic events in patients with mechanical heart valve prostheses and persistent lupus anticoagulant. Our objectives were to determine whether persistent lupus anticoagulant increased the risk of embolism in that population and thus, if a more intense anticoagulation would be recommended, even at the risk of increasing bleeding episodes. We included 16 patients and 16 controls with more than 80 patient-years of follow-up and with other risk factors for embolism. We observed no increased rate of thromboembolic events in patients than in controls, even during high-risk situations (i.e. bacterial endocarditis). Our population spent most of the time within the intended anticoagulation range. We conclude that adequate anticoagulation is the most important issue to prevent events, protecting against thrombosis without increasing the bleeding risk. *Blood Coagul Fibrinolysis* 16:183–185 © 2005 Lippincott Williams & Wilkins.

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Introduction

The risk of thrombosis in patients with mechanical heart valve prosthesis (MHVP) in spite of adequate anticoagulation is 1–2% per year [1]. Intensity of anticoagulation is set taking into account the prosthesis itself (generation, position) and the co-morbid conditions that may enhance the thrombotic risk [1,2] such as previous thromboembolism, atrial fibrillation and hypercoagulable states [1–4]. Valve thrombosis is caused by inadequate anticoagulation in the majority of cases [5–7] but it has also been reported during adequate anticoagulation in patients with congenital thrombophilia [8,9]. Thrombosis of a valve homograft [10] has been described in the presence of lupus anticoagulant. Few case reports addressed the issue of antiphospholipid antibodies (aPA) and MHVP thromboembolism [1,11,12]. Gencbay *et al*. [11] reported a high prevalence of aPA in a series of patients with recurrent MHVP thrombosis. Currently, no recommendations for the management of patients with aPA and prosthetic valves have been made [13].

Our objectives were to evaluate the rate of embolism in a series of patients chronically anticoagulated for MHVP with concomitant persistent lupus anticoagulant (LA), in order to determine whether LA increases the risk of embolism in that population and thus, if a more intense anticoagulation would be recommended.

Methods

The study was an ambispective case–control study of patients with MHVP anticoagulated at the Thrombosis and Hemostasis Department, National Academy of Medicine in Buenos Aires, Argentina. Follow-up included retrospective (1985–1999) and prospective data (2000–2002). Cases had at least two positive determinations of LA. Controls were patients with MHVP but without aPA (LA nor anticardiolipin antibodies). Valve type, follow-up and concomitant risk factors were the principal matching criteria for patients and controls. A difference of 2 years of age was accepted between patients and controls since no increased risk was anticipated from that difference; they were sex matched whenever possible.

The desired International Normalized Ratio (INR) was between 2.5 and 3.5 or 3.0 and 4.0 according to valve generation and embolic risk factors (i.e. previous thromboembolism, increased left atrium diameter and atrial fibrillation). Three patients in each group had a target INR of 3.5–4.5 during the retrospective phase until 1995 [14] and thereafter the target INR was 3.0–4.0. Combination with low-dose aspirin was indicated as in previous reports [14] or according to the Sixth Consensus Conference on Anticoagulation Therapy proposals [3].

Table 1 Patient characteristics

Characteristic	Lupus anticoagulant-positive	Lupus anticoagulant-negative
n	16	16
Median age ± standard deviation (range)	49.5 ± 19 (25–68 years)	51.88 ± 13.63 (23–70 years)
Sex (*n*)		
Female	8	7
Male	8	9
Valve position (*n*)		
Aortic	11	11
Mitral	4	4
Mitro-aortic	1	1
Embolic risk factors* (*n*)	9	8
Total follow-up (patient-years)	81.73	81.54
% time below INR 2.4	15.84	15.61
% time between INR 2.5–3.5	46.88	46.09
% time between INR 3.5–4.5	23.86	24.28
% time over INR 4.5	13.41	14.00
Embolic events	0	0
Bleeding episodes	1	0

INR, International Normalized Ratio. *Previous thromboembolism, atrial fibrillation, increased left atrium diameter.

The initial investigation of LA was made due to a significant prolongation of the activated partial thromboplastin time or to the presence of embolic complications during follow-up. Patients were followed during the time LA persisted positive and, if it turned negative, follow-up continued for at least 6 months after the negative result. Concomitancy with systemic lupus erythematosus (SLE) was recorded.

LA was detected by the dilute Russell viper venom test (Sigma Diagnostics, St Louis, Missouri, USA) and activated partial thromboplastin time (PTT-LA; Diagnostica Stago, Asnières, France) on patient's plasma, in addition with mixing studies and neutralization procedures, according to SSC-ISTH recommendations [15]. The prothrombin time reagent used for INR calculation was Thromboplastin-s (Biopool; Trinity Biotech Plc, Bray, Co. Wicklow, Ireland).

Total follow-up and the aggregated person-time by step method were calculated [16].

Results

Population characteristics are presented in Table 1. None of the patients or controls had an embolic event prior to LA diagnosis. There was only one patient with SLE in the LA-positive group. The number of first-generation and second-generation valves and concomitant aspirin use was equal in both groups (30% of first generation valves in each group).

Patients and controls spent most of the time (46%) within an INR of 2.5–3.5.

No embolic events were observed during follow-up, irrespective of the presence of LA or other embolic risk factors and regardless of the use of aspirin.

A 61-year-old woman with an aortic Omniscience valve (desired INR, 3.0) placed in 2000 developed a LA in January 2001. In May 2001, she had bacterial endocarditis while LA was positive but presented no complications during 15 months of follow-up. She did not have other embolic risk factors.

In 1995 LA was diagnosed in a 50-year-old man with an aortic Sorin valve (desired INR, 3.0) placed in 1991. He remained asymptomatic and without complications until August 2001 when he suffered an upper gastrointestinal bleeding from a peptic ulcer (previous INR, 2.7). Anticoagulation was stopped and he was put on heparin (prophylactic dose). While on heparin, he developed a deep venous thrombosis; LA was still positive. He presented no further embolic complications during 76 months of follow-up. He was the only patient with major bleeding in the LA group and it occurred within the intended INR. There were no hemorrhagic events in the control group.

Discussion

Thrombotic complications of MHVP are dependent on a variety of factors [1–3]. Hypercoagulable states have been advocated but very few data are available.

A retrospective study [11] of 15 patients with more than one episode of MHVP thrombosis observed a high prevalence of aPA but the overall measurement of INR showed that 29% were below the therapeutic range, while in our series both patients and controls were below the therapeutic range only 15% of the time.

A recent study found that patients with severe valvular heart disease and aPA were at increased risk to develop thrombosis [17]. Even though the study included 33 patients with MHVP (desired INR, 3.0–4.0), no specific data are given about embolic complications in that subgroup, nor was it known whether aPA were present at the time of the thromboembolic event. We observed no thromboembolic complications of MHVP in our series; the only thrombotic complication was a venous thrombosis while anticoagulation was withheld but no valve thrombosis developed during long-term follow-up.

The only patient with SLE in our series did not behave differently to non-SLE patients.

To the best of our knowledge, there is no prospective evaluation of thromboembolic complications in patients with persistent LA and MHVP. Our study included long follow-up, with both retrospective and prospective data, and showed that LA did not increase the risk of thromboembolic complications in patients with MHVP anticoagulated at an INR of 3.0, even during bacterial endocarditis or in patients with first-generation prostheses.

One limitation of the present study is that it may have lacked sufficient power to detect a difference in thrombosis. If larger studies confirm our findings, the observations would have clinical impact. The findings would conclude that oral anticoagulation therapy at the standard desired INR for MHVP is safe and efficacious to avoid embolic complications in patients with coexistence of LA and prosthetic valves, provided they spend most of the time within the therapeutic range.

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