Bioprosthetic Valve Thrombosis while on a Novel Oral Anticoagulant for Atrial Fibrillation

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INTRODUCTION

Valvular heart disease (VHD) affects >100 million people worldwide.[1] Surgical valve replacement is currently offered for many patients with VHD,[2] and 80% of devices are bioprosthetic valves (BPVs).[3]

Thromboembolism is a major life-threatening complication in patients with prosthetic heart valves. Anticoagulation with vitamin K antagonists (VKAs) is considered reasonable 3 to 6 months postoperatively to prevent BPV thrombosis (BPVT).[4] However, the appropriate antithrombotic therapy for preventing BPVT in the setting of comorbid atrial fibrillation (AF) is not well defined. The increasing availability and widespread use of direct oral anticoagulants (DOACs) raises questions of safety in patients with BPVs and AF.

There are currently no randomized controlled trials using DOACs in patients with BPVs and AF. We present the case of a patient with mitral and aortic BPVs with comorbid AF who was treated with a DOAC and ultimately developed thrombosis of both valves.

CASE DESCRIPTION

A 63-year-old Caucasian man presented with a 1-month history of progressive New York Heart Association class IV dyspnea, pedal edema, productive cough, and night sweats. His history included aortic valve replacement for a bicuspid aortic valve and mitral valve replacement for mitral regurgitation with 25- and 27-mm Carpentier Edwards Perimount BPVs (Edwards Lifesciences, Irvine, CA), respectively, 4 years prior. He also had paroxysmal AF, coronary artery disease with prior stent placement, hypertension, hyperlipidemia, and a 45-pack-year smoking history. Medications included apixaban 5 mg twice a day, metoprolol tartrate 150 mg twice a day, furosemide 40 mg/d, and a multivitamin.

He was treated for sepsis from presumed mitral valve endocarditis between two outside hospitals 5 months before the current presentation. He completed a 6-week course of intravenous (IV) ceftriaxone and vancomycin. Transesophageal echocardiography (TEE) after completion of IV antibiotics reported a concern for "old endocarditis" on the mitral valve leaflet, with mild mitral regurgitation.

On admission to our hospital, physical examination revealed a body temperature of 36.4°C, oxygen saturation of 98% on room air, a respiratory rate of 18 breaths/min, a heart rate of 108 beats/min, and blood pressure of 114/85 mm Hg. The patient had reduced air entry to the lung bases with inspiratory crackles in the lower two thirds bilaterally. Cardiovascular examination showed an irregularly irregular pulse, raised jugular venous pressure with a grade I diastolic murmur at the apex, grade II systolic murmur at the left upper sternal border, prominent P2, and 1+ pedal edema to the mid shin bilaterally.

Laboratory analysis revealed a white blood cell count of 7,600/L (normal range, 4,200–10,200/L) and a pro-calcitonin level of 0.08 ng/mL (normal range, ≤0.5 ng/mL). Brain natriuretic peptide was elevated at 8,216 pg/mL (normal range, ≤83 pg/mL). Blood cultures were drawn in the emergency department. Chest radiography showed small bilateral pleural effusions, mild interstitial pulmonary edema, and mild cardiomegaly. A clinical diagnosis of cardiogenic pulmonary edema was made, and the patient was treated with IV diuretics.

Initial transthoracic echocardiography was performed and showed a mobile mass on the mitral valve prosthesis with severe mitral valve stenosis (Figure 1) and thickening of the aortic valve prosthetic leaflets (Figure 2). Given these findings, TEE was pursued. TEE showed a large (4.5 × 1.5 cm) highly mobile homogeneous mass attached to the atrial aspect of the medial leaflet of the prosthetic mitral valve with marked prolapse from the ventricle to the atrium (Figure 3, Videos 1, 2, and 3). This was associated with severe stenosis (mean diastolic Doppler gradient, 18–27 mm Hg at a heart rate of 76–83 beats/min) and mild regurgitation. TEE also showed an echodense immobile mass attached to the aortic side of the aortic prosthetic valve annulus (1.0 × 0.9 cm) along the prosthetic right and noncoronary cusps, consistent with thrombus (Figure 4, Video 4). Severe left atrial and moderate right atrial enlargement was noted, with severe right ventricular enlargement and a moderate decrease in right ventricular systolic function. Left ventricular chamber size was normal, and ejection fraction was 55% to 60%.

The patient was treated with IV unfractionated heparin for BPVT. Other medications during his hospitalization included oral aspirin 81 mg/d, oral metoprolol 150 mg twice daily, and IV furosemide 40 mg/d. Blood cultures remained negative at 72 hours. A thrombophilia workup was negative, and brain magnetic resonance imaging was negative for embolic phenomena. Repeat TEE at 72 hours showed no improvement in valvular function or thrombus size, and thus the patient underwent surgical redo mitral and aortic tissue valve replacement with a 31-mm Medtronic Mosaic porcine heart valve (Medtronic, Minneapolis, MN) in the mitral position and a 23-mm Edwards pericardial tissue heart valve in the aortic position. Pathology showed noninfective bland thrombus associated with minimal organizing pannus and focal calcifications. The left atrial appendage was surgically excluded. Surgical specimens showed a large thrombus on the mitral valve that was mostly occlusive and a
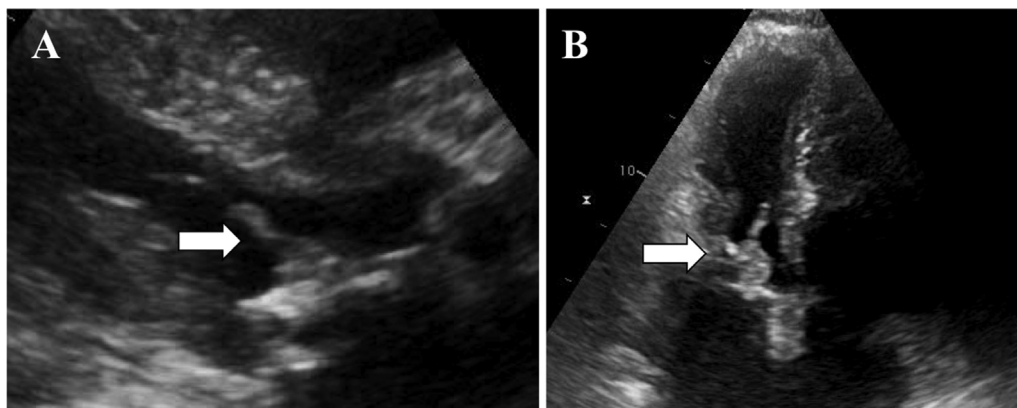
Figure 1 Transthoracic echocardiogram demonstrating mobile thrombus (*arrows*) on the mitral valve in the short-axis view **(A)** and four-chamber view **(B)**.
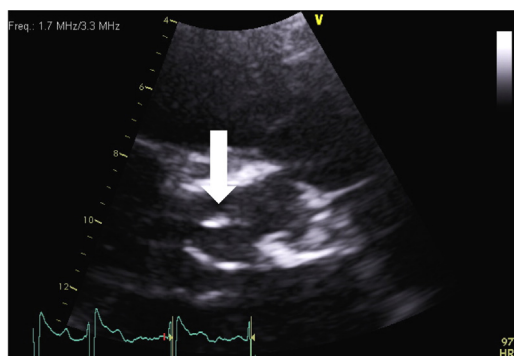

Figure 2 Short-axis view of the aortic valve demonstrating thickening of the bioprosthetic aortic valve leaflets, particularly in the noncoronary cusp (*arrow*). Restricted motion of the noncoronary cusp is also noted.

subvalvular thrombus on the aortic valve with a thin laminar thrombus on the noncoronary cusp (Figure 5).

Postoperative transthoracic echocardiography showed well-seated and functional aortic and mitral prostheses. The aortic valve prosthesis systolic mean Doppler gradient was 8 mm Hg, and the mitral valve prosthesis diastolic mean Doppler gradient was 8 mm Hg (heart rate 80 beats/min). Our patient was discharged to a rehabilitation center on postoperative day 7 on warfarin therapy with a target international normalized ratio of 2.0 to 3.0. There was no valve thrombosis on repeat transthoracic echocardiography at 3-month follow-up.

DISCUSSION

Surgical repair of VHD with either a mechanical prosthesis or a BPV is performed in appropriately selected patients, with growing popularity of BPVs, which now account for nearly 80% of all surgical aortic valve replacements in the United States.[3] Anticoagulation strategies, although well established for mechanical valve prostheses, are not well defined for BPVs despite their increasing popularity. Particular considerations for anticoagulation with BPV are (1) prevention of early BPVT, (2) treatment of established BPVT, and (3) selection of anticoagulation in patients with BPVs and AF. The role of DOACs in these scenarios is unknown because of a lack of randomized controlled trials.

Although the risk for thrombosis in BPVs is significantly less than with mechanical valve prostheses, it is not negligible. Recent data suggest that the risk for BPVT could be as high as 10% to 12%, and it is most likely to occur in the first 1 to 2 years after valve implantation.[5] The 2017 American Heart Association (AHA) and American College of Cardiology (ACC) guidelines on VHD recommend the use of a VKA with a target international normalized ratio of 2.5 after either aortic or mitral bioprosthetic implantation for 3 to 6 months after surgery in patients at low risk for bleeding.[4]

Following this initial high-risk period, VKAs are the recommended choice for anticoagulation to treat BPVT.[4] Although the safety of DOACs in this setting is not established, there are several studies exploring their possible role in prevention or treatment of thrombosis. A study by Chakravarty *et al.*[6] in 2017 suggested that both DOACs and VKAs were effective in the prevention and treatment of subclinical BPVT, and both were superior to dual antiplatelet therapy. However, there was no significant reduction in stroke rates with DOACs, and the study did not address bleeding risk. Of the patients with BPVT, 16% had AF, and 8% of patients were on anticoagulation at the time of BPVT diagnosis; 5% were taking VKAs and 3% DOACs. The study did not differentiate if patients with AF received VKAs, DOACs, or antiplatelet therapy for the treatment of subclinical BPVT. Two randomized clinical trials, GALILEO (ClinicalTrials.gov identifier NCT02556203) and ATLANTIS (ClinicalTrials.gov identifier NCT02664649), are ongoing to evaluate the use of rivaroxaban and apixaban, respectively, in preventing BPVT in patients with transcatheter aortic valve replacements. The ATLANTIS trial will also include a subgroup of patients with coexisting AF.

AF is the most common cardiac arrhythmia and is implicated in 15% of all strokes in the United States.[7] The introduction of DOACs has expanded the therapeutic options for primary and secondary stroke prevention in patients with nonvalvular AF (NVAF).[8] Selection of anticoagulation in AF depends first on whether AF is valvular or not; however, society guidelines and landmark trials adopt different definitions of NVAF. The presence of a BPV is not formally categorized as valvular or NVAF in the most recent ACC/AHA updated VHD guidelines, and they do not explicitly address preferred anticoagulation in these patients.[4] In this document, VKAs are recommended in patients with rheumatic mitral stenosis and mechanical prosthetic valves only, and DOACs are permitted in patients with native VHD. This is a change from the ACC/AHA/Heart Rhythm