

Thrombotic Risk in Patients with Aortic Bioprostheses

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Thrombosis of Mosaic aortic valve bioprostheses occurring at more than one month after surgery occurs in 0.8% (95% CI 0.33-1.67%) of patients. In the two cases reported here, each patient had risk factors for thrombus formation, namely severe left ventricular impairment in one patient, while the other patient was heterozygous for prothrombin variant G20210A. The cases were treated successfully, by thrombolytic therapy with streptokinase in the first case, and by

repeat aortic valve replacement in the second case. Thrombosis of bioprosthetic valves in the aortic position is rare, and a period of anticoagulation postoperatively does not invariably protect against this serious complication. In conclusion, patients with risk factors for thrombus formation should be considered for long-term anticoagulation.

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Thrombosis of prosthetic valves is an accepted complication associated with mechanical valves, especially when implanted in the mitral and tricuspid positions (1), and this has been reported previously for bioprosthetic valves (2-5) and for abnormal native valves (6). Thrombosis causing malfunction and stenosis of aortic valve prostheses occurs rarely, however, with no incidences in one series of 599 cases reported from Vancouver (7), and only two cases out of 694 St. Jude Medical valve implants reported from Denmark (8). The role of prothrombotic risk in patients with bioprosthetic valves has not previously been well characterized. Here, two cases of thrombosis of Mosaic aortic bioprostheses are reported, in which patients received oral anticoagulants for a minimum of one month postoperatively. A brief review of the relevant literature is also provided.

Case 1

A 76-year-old man was scheduled for aortic valve replacement at Green Lane Hospital, Auckland, New Zealand following a history of progressively increasing breathlessness over the preceding five months. This included an admission to hospital in Australia

with pulmonary edema when a systolic murmur was noted, with further investigation recommended on his return home. Transthoracic echocardiography (TTE) showed a mean aortic valve gradient of 27 mmHg, a marked restriction of valve opening, and severe global left ventricular (LV) impairment (estimated ejection fraction 30%); taken together, these findings supported a diagnosis of severe aortic stenosis. Coronary angiography showed only mild coronary artery disease, with no flow-limiting stenoses.

At operation, the aortic valve was noted to be extensively calcified, and was replaced with a 27 mm Medtronic Mosaic bioprosthesis. The patient's postoperative recovery was uncomplicated, and he was started on warfarin (8 mg) on the first postoperative day, and discharged on this agent with the plan to continue this for six weeks, aiming for a target International Normalized Ratio (INR) of 2-3. However, after four weeks the warfarin was discontinued, prior to a transurethral resection of the prostate being performed. The surgery was uneventful, and prophylactic antibiotics were given, but anticoagulation was not restarted following the procedure. Aspirin was not given at any time. At the initial follow up examination, at 10 weeks after aortic valve replacement, the patient was asymptomatic and mobilizing well.

At six months after surgery, over the course of one week, the patient developed increasing breathlessness on exertion, associated with paroxysmal nocturnal dyspnea and orthopnea. On examination, the patient was breathless on minimal effort and was tachycardic

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with a blood pressure of 96/70 mmHg, but the clinical findings were otherwise unremarkable and revealed no stigmata of infective endocarditis. TTE showed that the patient's LV dysfunction had worsened compared to the preoperative evaluation, with a calculated ejection fraction of 20%. The mean gradient across the aortic valve was only 14 mmHg, the leaflets were thickened, and the opening was restricted. This was considered abnormal in the context of markedly reduced cardiac output. Transesophageal echocardiography (TEE) subsequently demonstrated that one cusp of the valve was markedly bulky and restricted, consistent with thrombosis.

In view of the patient's age, severe LV impairment and low-output state, and the perceived risk of reoperation, it was decided in the first instance to administer thrombolytic therapy with the option of subsequent aortic valve replacement if clinical improvement did not occur. A regime of streptokinase (1 MU over 1 h, followed by 0.1 MU per hour for 5 h) was used, with subsequent anticoagulation with intravenous heparin (APTT 50-70 s) followed after 48 h by warfarin, with a target INR of 2-3. The patient tolerated this treatment well, and TTE performed at 24 h after thrombolytic therapy showed the mean gradient to have fallen to 8 mmHg. Additional TEE performed three days later showed all leaflets to be thin and fully mobile. A thrombophilia screen performed prior to thrombolysis suggested the presence of Lupus anticoagulant, with a dilute Russell's Viper Venom time of 57 s, though anticardiolipin antibodies (IgG and IgM) were negative. Genetic testing for Factor V Leiden and prothrombin variant G20210A was negative.

The patient was discharged on warfarin, with a target INR of 2-3, aspirin 150 mg, and treatment for LV impairment. At follow up 10 weeks later, he was well and returning to normal activities. TTE showed a mean aortic gradient of 6 mmHg, with a significant improvement in LV function (calculated ejection fraction 34%).

Case 2

A 63-year-old man presented with a 12-month history of worsening dyspnea and angina. He was known to have coronary artery disease, having previously had myocardial infarctions in 1982 and 1987, and percutaneous balloon angioplasty in 1987. Angiography in 2001 showed severe three-vessel coronary artery disease, with both aortic and mitral regurgitation and a LV ejection fraction on left ventriculography of 56%. Intraoperative TEE demonstrated moderate aortic regurgitation secondary to prolapse of the right coronary cusp and moderate mitral regurgitation secondary to posterior leaflet prolapse.

At operation, four arterial grafts were placed. A 29

mm Medtronic Mosaic valve was implanted in the aortic position, and the mitral valve was repaired with a quadrangular posterior leaflet resection and placement of a Cosgrove flexible annuloplasty band. Bypass was easily discontinued, and recovery was uncomplicated. Postoperative TTE showed normal Mosaic valve function, with a mean gradient of 13 mmHg, no aortic regurgitation, and no residual mitral regurgitation. The LV function was mildly depressed, with an estimated ejection fraction by echocardiography of 50%. There was no history of postoperative atrial arrhythmias, with sinus rhythm being recorded at discharge.

Warfarin was commenced on the first postoperative day, and at discharge it was planned that this be continued for three months, aiming for a target INR of 2-3. However, anticoagulation was continued for six months. Compliance with therapy was good, and at no time was anticoagulation known to be subtherapeutic, with all recorded INR values >2.0. Treatment with aspirin 50 mg was given concurrently with warfarin and continued thereafter. At one month following the cessation of anticoagulation, the patient's symptoms of dyspnea and angina recurred acutely, without new electrocardiographic changes. Coronary angiography showed that all four arterial grafts were patent. Aortography demonstrated abnormal leaflet movement of the Mosaic valve. TEE showed thrombosis of the aortic prosthesis (Fig. 1), with a mean gradient of 30 mmHg associated with severe LV dysfunction. A thrombophilia screen showed that the patient was heterozygous for the prothrombin variant 20210 G to A (antithrombin III assay, protein C assay, activated protein C resistance (and Factor V Leiden), protein S assay and Lupus anticoagulant screen were negative). Of note, there was no prior history of venous thrombosis or thromboembolism.



Figure 1: Transesophageal long-axis image of the prosthetic valve showing marked restriction of leaflet motion (top arrows) and thrombus associated with the valve (bottom arrow).

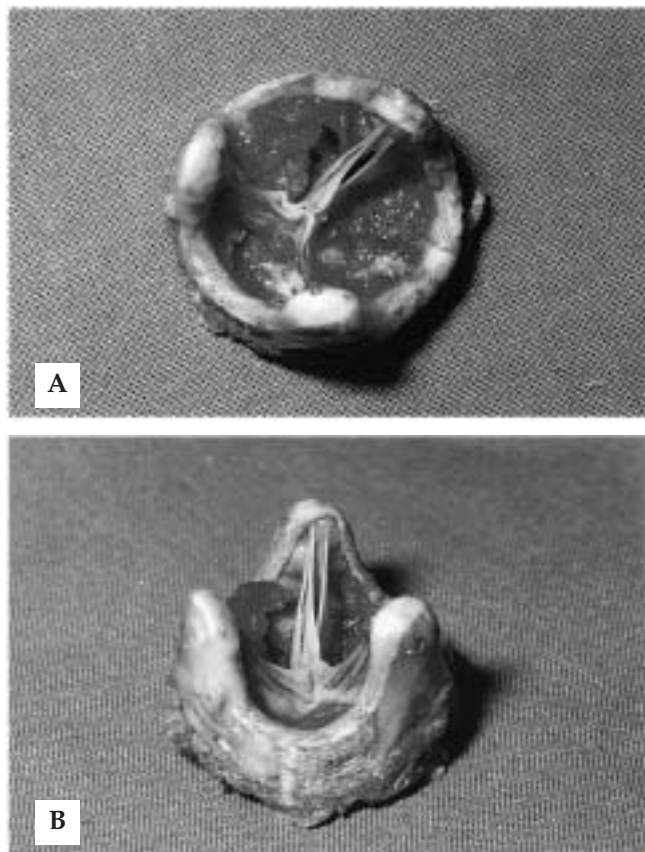


Figure 2: (a, b) Explanted Mosaic bioprosthesis, showing thrombus in all three sinuses of Valsalva.

At reoperation, thrombus was seen in all three sinuses of Valsalva (Fig. 2a and b), and the Mosaic valve was replaced with a mechanical valve. Histology of the explanted valve demonstrated thrombus with minimal fibrin content on the outflow surface of all three leaflets of the valve. Histological and microbiological examination revealed no other abnormality of the prosthesis.

Surgery was complicated by a perioperative cerebrovascular event, and a computed tomography scan demonstrated a right parieto-occipital cortical infarct. The patient made a slow recovery, but at the three-month follow up he was well, with no residual neurological deficit.

Discussion

Thrombosis of bioprosthetic valves has only rarely been reported in the literature, and the present report details two cases of thrombus formation causing stenosis of Mosaic bioprosthetic aortic valves, with different likely etiologies of thrombosis. These two cases of valve thrombosis, both of which occurred after a minimum of one month of postoperative warfarin therapy, represent 0.7% (2/283) of the Mosaic valves implanted

in the aortic position at the present authors' institution. A previous study from Europe (9) reported four instances of aortic Mosaic valve thrombosis among 461 valves implanted (0.9%). Therefore, although the Mosaic has shown favorable clinical and echocardiographic results (10,11), in these two series the combined frequency of thrombosis was 0.8% (95% CI 0.33-1.67%) when this prosthesis was implanted in the aortic position.

In previously reported cases of thrombosis of aortic bioprostheses, which occurred between 10 weeks and six months postoperatively, the majority of patients received either no anticoagulation or it was subtherapeutic (2-4). In the absence of any long-term indication for anticoagulation, oral anticoagulation is recommended for the first three months following bioprosthetic valve replacement (12,13), although for bioprostheses in the aortic position this is only an AHA/ACC grade 2C recommendation (12). The use of aspirin as long-term therapy for patients in sinus rhythm is also recommended (12,14,15). However, there have been reported cases of thrombosis in patients receiving therapeutic anticoagulation for three months (5). Both of the present patients were therapeutically anticoagulated for at least four weeks after valve replacement, but both developed valve thrombosis following the cessation of anticoagulation.

Inherited thrombophilias are known to be risk factors for venous thromboembolism. In addition, the inherited thrombophilias Factor V Leiden and /or prothrombin variant G20210A have been shown to be increased in frequency in young patients with acute coronary syndromes, including those without flow-limiting coronary stenoses (16,17). It is conceivable that inherited thrombophilias may contribute to thrombotic risk in other clinical situations such as prosthetic heart valves, including bioprostheses. However, there are no current guidelines on the role of thrombophilia screening in these patients. In the second of the present cases, an expensive and hazardous operation could potentially have been avoided had the patient's prothrombotic risk profile been discovered prior to the cessation of anticoagulation. As the frequencies of Factor V Leiden and prothrombin variant G20210A in populations of predominantly Northern European origin are 5% and 2% respectively, studies involving several thousands of patients would be required to demonstrate or exclude significant associations between the inherited thrombophilias and the risk of bioprosthetic valve thrombosis.

The most appropriate treatment of bioprosthetic valve thrombosis is unclear, and although cases of successful treatment with anticoagulation (18,19) or thrombolysis (20) have been reported, the disease process may be extremely rapid and urgent surgery is

often indicated. In many of the reported cases the progress from first reported symptoms to cardiovascular collapse or death was measured in hours rather than days or weeks.

These two cases show that routine discontinuation of short-term anticoagulation following bioprosthetic aortic valve replacement may not be appropriate. It is concluded that patients with risk factors for thrombus formation, such as significant LV dysfunction, should be considered for long-term anticoagulation, though whether thrombophilia screening should be undertaken for patients in whom discontinuation is contemplated is unlikely to be tested in prospective studies. While thrombosis is more common with mechanical prostheses than with bioprostheses, this diagnosis should be considered in any patient with a prosthetic valve who presents with new symptoms.

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