

Early Mechanical Mitral Valve Thrombosis in a Patient with Warfarin Resistance

Ayse Saatci Yasar, Yucel Balbay, Orhan Maden, Hatice Sasmaz

Turkiye Yuksek Ihtisas Hospital, Department of Cardiology, Ankara, Turkey

Warfarin, an oral anticoagulant, is the therapy of choice to maintain anticoagulation. An individual requiring five- to 20-fold higher dosage than average for anticoagulation may be considered as having resistance to warfarin. In order to evaluate a subtherapeutic response to high-dose warfarin, the clinician must consider many possible causes of resistance, such as non-compliance, drug interactions, or pharmacokinetic changes. When these factors have been

eliminated, an hereditary warfarin resistance might be considered responsible. The case is reported of a 49-year-old woman who received warfarin after mitral valve replacement and experienced mechanical mitral valve thrombosis due to inadequate anticoagulation, possibly caused by warfarin resistance.

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Warfarin is a commonly used oral anticoagulant (1), due to its excellent bioavailability and good pharmacokinetics. Following its rapid and complete absorption, warfarin is highly bound to plasma proteins, in particular to albumin. Warfarin functions by inhibiting the vitamin K-dependent carboxylation of the precursors of Factors II, VII, IX, and X, which results in a reduced synthesis of these clotting factors (2). Occasionally, however, some patients may have an inadequate anticoagulation response at warfarin doses exceeding those commonly used - a condition which is referred to as 'warfarin resistance' and has been described as either acquired or hereditary in nature.

Hereditary warfarin resistance is thought to be due to the presence of abnormal enzymes or defective receptors which either have an increased affinity for vitamin K or a decreased affinity for warfarin. Hereditary warfarin resistance has been reported in few cases (3-6). Here, the case is presented of a woman who suffered an early mechanical mitral valve thrombosis and was shown to be resistant to oral anticoagulation therapy.

Case report

A 49-year-old woman with a prosthetic mitral valve was admitted to the authors' institution for adjustment of her warfarin dosage. One month previously, she had undergone surgery for mitral valve stenosis with replacement of the mitral valve using a St. Jude Medical prosthesis. On admission, her daily medication included 10 mg warfarin sodium and 50 mg metoprolol. The patient's vital signs were normal, and she had normal prosthetic valve clicks and an apical grade 1-2/6 systolic ejection murmur. There were no other abnormalities on physical examination. Her International Normalized Ratio (INR) had ranged from 1.2 to 1.4 on weekly determinations throughout the previous month, despite receiving 10 mg warfarin daily. The laboratory data on admission included an INR of 1.4, and an activated partial thromboplastin time (aPTT) of 30 s (normal 22-34 s). The complete blood count, serum urea nitrogen, total protein, albumin, and SGOT, SGPT and lactic dehydrogenase activities were all normal. Electrocardiography revealed a normal sinus rhythm, while echocardiography demonstrated normal valve function with no signs of thrombosis, stenosis, or regurgitation.

The patient neither had a diet rich in vitamin K, nor used alcohol or any medications other than those prescribed. She did not smoke or drink alcohol, and denied the use of any herbal preparations or dietary or vitamin supplements. She also denied missing any warfarin doses. Hence, warfarin resistance was sus-

Address for correspondence:
Ayse Saatci Yasar, TSK Rehabilitasyon Merkezi Lojmanlari, V1 Blok
No. 9, Bilkent, Ankara, Turkey
e-mail: drasaatciyasar@yahoo.com

pected and, following hospitalization because of inadequate anticoagulation with warfarin, intravenous heparin (1,000 U/h) was substituted and her aPTT was maintained at 1.5 to 2.5 times normal. Although the warfarin dosage was increased gradually from 10 mg to 40 mg per day, this still failed to extend her INR levels beyond 1.5. At this point the patient's plasma warfarin level (7.8 mg/l) was much higher than the normal range required to achieve a therapeutic effect (0.8-2.4 mg/l) (7).

At two weeks after hospitalization, the patient developed dyspnea. On physical examination, her prosthetic valve clicks were found to be muffled. Transthoracic echocardiography showed the mechanical mitral valve to have an abnormal leaflet motion, while transesophageal echocardiography (TEE) revealed a soft and irregular mass at the mitral valve position (Fig. 1). The mitral peak velocity was 2.5 m/s, and the mean gradient 16 mmHg (Fig. 2). Following a diagnosis of acute prosthetic valve thrombosis, the patient was treated with streptokinase, administered as a 250,000 U bolus over 30 min, followed by an infusion of 100,000 U/h for 48 h. At 24 h after the discontinuation of infusion, TEE showed that the thrombus had not resolved and that the mitral valve gradient had not changed.

In view of the patient's poor response to thrombolysis, her mechanical mitral valve was replaced with a bioprosthetic valve, thus eliminating the need for anticoagulant therapy as she had no concomitant risk factors that would indicate a need for oral anticoagulation. Postoperatively, the patient was discharged from the hospital in a stable condition.

Discussion

Patients who have received a prosthetic heart valve require lifetime treatment with an oral anticoagulant in order to reduce their high risk of thrombosis; moreover, their coagulant activity must be carefully and routinely monitored. Warfarin - which today is the therapy of choice to maintain anticoagulation - is metabolized by hepatic microsomal enzymes, with inactive metabolites being excreted in the urine. The effect of warfarin is monitored by measuring the patient's prothrombin time, expressed as the INR, and the dose necessary to achieve a therapeutic INR is found to vary. Resistance to the activity of warfarin is a rare phenomenon, with both acquired and hereditary resistances having been described. Acquired warfarin resistance may develop as a result of non-compliance, of the exogenous consumption of vitamin K, and by the concurrent ingestion of other agents known to reduce warfarin's effects. In assessing a patient with a demonstrated resistance to warfarin, all of the above factors should be considered.

The first well-documented case of warfarin resistance was reported by O'Reilly and colleagues, who were also the first to identify a genetic basis for the resistance (3). Subsequently, other studies provided supportive evidence for an hereditary transmission of the resistance (4-6). Warfarin targets blood coagulation by inhibiting the vitamin K epoxide reductase multi-protein complex (VKOR) (9); this complex recycles vitamin K hydroquinone, a cofactor that is essential for the post-translational gamma-carboxylation of several



Figure 1: Transesophageal echocardiogram showing thrombus at the mitral valve position (arrow).
LV: Left ventricle.

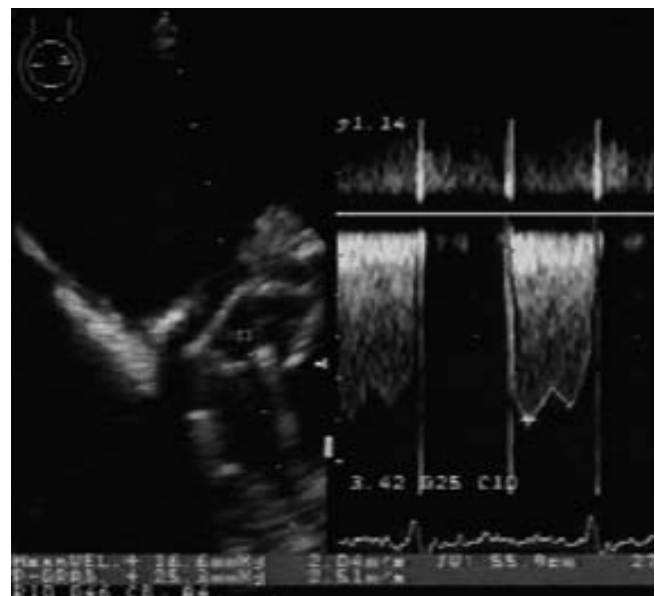


Figure 2: Continuous-wave Doppler echocardiography of the mitral prosthesis, showing a mean gradient of 16 mmHg.

blood coagulation factors (9,10). VKOR has been proposed to be involved in warfarin resistance. In this regard, Rost and colleagues were able to single out the gene encoding a protein of the VKOR complex by studying patients and rats with inherent defects in VKOR activity in whom mutations in the VKOR gene were found (11). At present, it remains unclear as to how this mutation causes warfarin resistance *in vivo*, but the effect is most likely the result of an interference with the binding of warfarin.

In the case of the present patient, neither her concomitant drugs, disease state or lifestyle factors were likely to have contributed to the warfarin resistance. Non-compliance and an excess of vitamin K intake were excluded as etiologic factors for poor response by admitting the patient to the hospital and monitoring plasma warfarin levels. A high level negated the possibilities of poor compliance, reduced absorption, or increased elimination. In addition, the patient's serum albumin level was normal, thereby eliminating the possibility that hypoalbuminemia might increase the free fraction of warfarin, with an enhanced rate of clearance of the drug leading to a decreased plasma half-life (12). On admission to the authors' institution, the patient was not taking any drugs that might have caused the enzymatic breakdown of warfarin, nor of any binding protein. Hence, these data suggest that the reason for unsatisfactory INR levels of the present patient might be an hereditary resistance to warfarin, and that this was an important contributory factor in the development of the valve thrombosis. Previously, Halvorsen et al. (13) described a 76-year-old woman receiving warfarin following aortic valve replacement who experienced prosthetic valve thrombosis. The reason for this was a reduced anticoagulant effect of warfarin during concomitant administration of warfarin and dicloxacillin. To the best of the authors' knowledge, the present case is the first report of a patient suffering from acute prosthetic valve thrombosis because of hereditary warfarin resistance.

Hereditary resistance to oral anticoagulant therapy is rare; the true incidence is unknown, and will probably remain so, as the defect does not predispose the patient to any clinically recognizable disorder. Any individual requiring a five- to 20-fold excess over the average dose to maintain anticoagulation should be considered as being resistant to warfarin, and should be investigated. Moreover, if familial-type resistance were to be suspected, the family members should be

educated as to the possibility that they, too, might be resistant to the benefits of warfarin anticoagulants. In addition, in patients with warfarin resistance a bio-prosthesis should be used instead of a mechanical prosthesis in order to avoid valve thrombosis.

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