Scientific letter

Antithrombin deficiency as a cause of aortic valve thrombosis in a bicuspid aortic valve

Déficit de antitrombina como causa de trombosis valvular aórtica en la válvula aórtica bicúspide

To the Editor,

Hereditary deficiency of antithrombin (AT), previously called AT III, is a hereditary thrombophilia of low prevalence (0.02%-0.2%) that was first described in 1965 and has autosomal dominant inheritance and variable penetrance. Although it is one of the thrombophilia conditions with the highest risk of producing venous thromboembolic disease, thrombotic phenomena in arteries and/or valves are rare and have been reported in the presence of a previous valvular lesion, such as severe aortic regurgitation,[1] or in biological aortic valve replacements.[1]

Bicuspid aortic valve is the most common congenital heart disease (1%-2%) and carries a higher risk of complications such as valvular dysfunction, aortic dissection, and even aortic valve thrombosis, which is commonly related to hypercoagulable states such as protein S deficiency[2] and antiphospholipid syndrome,[3] and may even occur spontaneously.[4]

We describe a case of aortic valve thrombosis in the bicuspid aortic valve of a 56-year-old man with AT deficiency and a history of ulcerative colitis who was admitted for syncope of unknown etiology. Echocardiography disclosed a bicuspid aortic valve with moderate aortic regurgitation and elevated transvalvular gradients (peak gradient, 30 mmHg; mean gradient, 12 mmHg), as well as an aortic mass of unclear nature at the junction between the noncoronary and right coronary cusps (figure 1 and figure 2).

The differential diagnosis included infective endocarditis, nonbacterial endocarditis, valve thrombosis, and tumor origin of the mass. Blood cultures, serology and autoimmune assays, lupus anticoagulant, and tumor markers were all negative.

Positron-emission tomography/computed tomography ruled out findings consistent with infective endocarditis, whereas cardiac magnetic resonance showed a nodular image with no gadolinium uptake at the junction between the noncoronary and right coronary cusps. Because the patient reported distal dysesthesia in his right leg, brain MRI was also performed, showing small lesions in the deep white matter of the right frontal, left occipital, and bilateral convexity regions that were reported as subacute ischemic lesions, probably of embolic origin.

During the course of the patient's complete study, a more comprehensive family history revealed that, in addition to his father's death from bacterial endocarditis at age 42 years, he also had a nephew who had experienced embolic ischemia of the right leg at age 17 years. This family member had undergone a study at the time at another hospital that diagnosed AT deficiency and was receiving oral acenocoumarol therapy.

In view of the clinical suspicion of probable thrombosis in the bicuspid aortic valve due to a family history of this hereditary thrombophilia, the study was completed with a functional AT III assay, which yielded a result of 45%. Type I AT deficiency was confirmed after other causes of thrombophilia were ruled out due

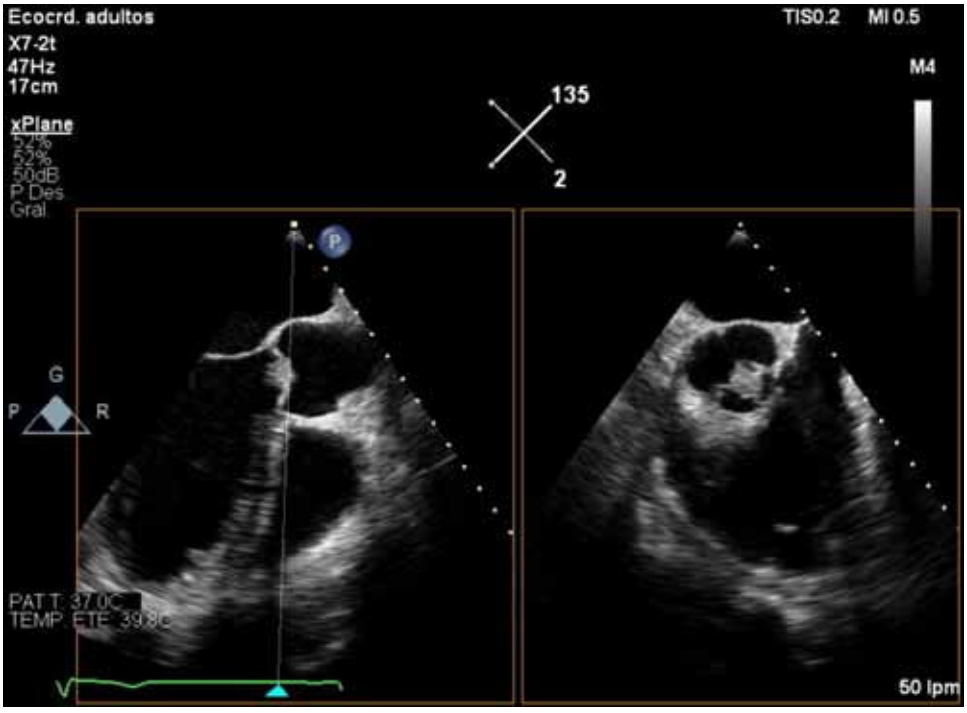

Figure 1. 2 D transesophageal echocardiography image of the aortic valve with orthogonal planes to the long axis (135°) and short axis (45°).

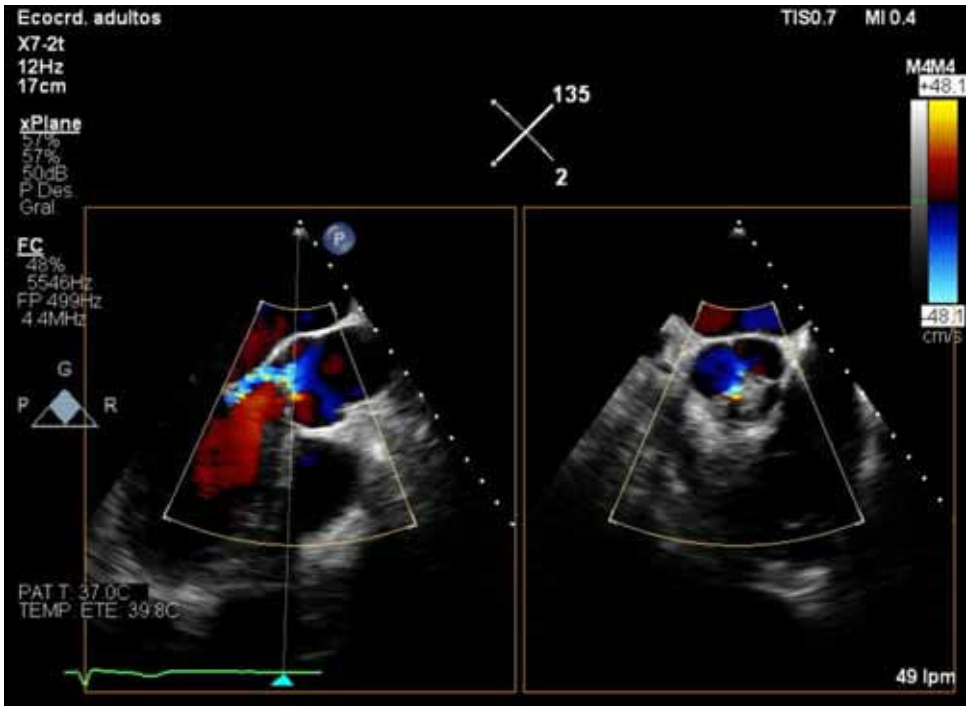

Figure 2. Color Doppler transesophageal echocardiography of the aortic valve with orthogonal planes to the long axis (135°) and short axis (45°).

to normal results for protein C, antigenic and functional protein S, activated protein C resistance, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-B_2 glycoprotein I), factor V Leiden mutations, and a G20210A prothrombin gene mutation.

Last, a molecular study on the *SERPINC1* gene revealed a heterozygous c.1154-14G>A pathogenic variant (NM_000488.3) already described in association with AT deficiency. This study confirmed the suspected diagnosis, and family genetic counseling was given.

Enoxaparin was started at therapeutic doses (taking into account the heparin resistance associated with AT deficiency), followed by oral acenocoumarol. A decision was made to continue long-term acenocoumarol according to current recommendations and in view of the high recurrence rate, although the scientific evidence remains weak.[5]

During follow-up, the patient remained asymptomatic. Eight months after treatment was started, the aortic valve thrombosis and mild residual aortic regurgitation had completely disappeared, and gradients were normal (gradient peak, 19 mmHg). This is the first published case of aortic valve thrombosis in a bicuspid aortic valve described in a patient with AT deficiency and illustrates the importance of a comprehensive family history to guide the clinical diagnosis of an aortic valve mass of unclear nature as an incidental finding. The appearance of aortic valve thrombosis could be explained by a situation of added risk, such as hemodynamic distortion of the aortic transvalvular flow conditioned by the bicuspid opening of the aortic valve, which raises the possibility of thrombus formation. Additionally, local flow turbulences produced by the bicuspid opening have been reported to promote repeated cycles of thrombus deposition, organization, and reendothelization with progressive valvular thickening,[6] which would have contributed to the initial appearance of elevated transvalvular gradients.

In summary, we describe an example of aortic valve thrombosis in a bicuspid aortic valve secondary to an additional hypercoagulable state (AT deficiency), in which a simple family history proved to be extremely helpful in guiding the diagnostic process and establishing appropriate treatment.

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Prospective validation and comparison of new indexes for the assessment of coronary stenosis: resting full-cycle and quantitative flow ratio

Validación prospectiva y comparación de los nuevos índices de evaluación de las estenosis coronarias: resting full-cycle *y* quantitative flow ratio

To the Editor,

Coronary physiological indices are not widely used, despite evidence supporting their utilization.[1] This is largely because of confidence in the adequacy of angiographic assessment and because measurement of these indices requires coronary guidewire manipulation[2] or, in the case of fractional flow reserve (FFR), induction of hyperemia.[3]

A number of simplified indices have been developed to increase the use of functional assessment. These include instantaneous wave-free ratio [iFR], diastolic resting pressure ratio [dPR], resting full-cycle ratio [RFR], and quantitative flow ratio (QFR).[4] The success of iFR spawned the development of other indices not requiring hyperemia induction, such as RFR, which has been shown to have good correlation and agreement with iFR and FFR in retrospective analyses.[5] In addition, QFR does not require the use of a guidewires as it is based on 3-dimensional analysis of the coronary anatomy. It has also been found to have good correlation and agreement with FFR.[6] No prospective studies, however, have compared RFR or QFR with FFR. The aims of this study were to evaluate and compare the ability of RFR and QFR to predict FFR in a prospective sample and, based on our results, to propose a combined algorithm for minimally invasive functional assessment.

Following approval of the study by the research committee, we consecutively included patients scheduled for functional assessment in 3 high-volume hospitals. The physiological parameters requiring an invasive approach were measured using the Abbott Vascular guidewire (Abbott Vascular, USA). RFR was calculated using the dedicated Coroventis AB (Sweden) software program. Hyperemia was then induced to calculate FFR. Angiographic images captured using recommended procedures[6] were reconstructed to calculate QFR (Medis, Netherlands).

Pearson correlation analysis was used to assess correlations between QFR, RFR, and FFR. The level of agreement between the 3 indices was analyzed using the Bland-Altman method and the intraclass correlation coefficient. The ability of each index to predict significant stenosis was analyzed using receiver operating characteristic curves with a predefined cutoff value of ≤ 0.80 for FFR and QFR and ≤ 0.89 for RFR.

A total of 101 vessels (77 patients) were studied. The mean ± SD age of the patients was 69.3 ± 10 years and 70.1% were male. The most common diagnosis was stable angina (40.3%).

The mean percent diameter stenosis based on visual estimation was 54% ± 14%. Mean FFR was 0.84 ± 0.09 and, based on this index, 30.7% of the vessels had significant stenosis. RFR identified significant stenosis in 51.5% of the vessels and the mean value was 0.88 ± 0.09. Assessment of stenosis by QFR was possible in 89 vessels (88.1%). The mean value was 0.86 ± 0.08 and 27% of the vessels had significant stenosis.

The intraclass correlation coefficients between QFR and FFR and RFR and FFR were 0.92 (95% confidence interval [95%CI], 0.88-0.95) and 0.76 (95%CI, 0.67-0.84), respectively. The mean differences between the indices were 0.04 ± 0.006 for RFR and FFR and 0.01 ± 0.03 for QFR and FFR (figure 1A,B). RFR produced 20 false positive (30.3%) and 1 false negative (3%). By contrast, just 1 of the vessels (1.6%) identified as significant by QFR did not have significant stenosis and 5 (17.9%) of the vessels considered nonsignificant by QFR had an FFR ≤ 0.80 (figure 1C,D).

Assessment of the diagnostic accuracy of visual estimation to detect FFR with a cutoff of ≤ 0.80 (stenosis > 70% of diameter) showed a sensitivity of 34.4% and a specificity of 87.5%. The respective results for RFR and QFR were 96.7% and 82.15% for sensitivity and 67.7% and 98.36% for specificity (figure 1E). Although QFR and RFR had extreme diagnostic accuracy values of 100% and 84.4%, respectively, for values close to the cutoff point (FFR of between 0.75 and 0.85), their accuracy for values at or below the cutoff point was lower: 80% for QFR and 68.6% for RFR.

Our proposed combined algorithm-based approach is shown in figure 2. The accuracy of QFR at extreme values would have eliminated the need for a coronary guidewire in 61 lesions (42 patients, 54.5%). RFR should be used for values near the cutoff point and for cases where QFR cannot be measured. The diagnostic accuracy of this combined approach to detect FFR ≤ 0.80 was 97.03%.

This is the first prospective study to compare RFR and QFR with FFR. Our combined approach showed excellent diagnostic accuracy compared with FFR. Apart from overconfidence in the adequacy of visual estimation, the main reasons for not using coronary physiological indices are the need to induce hyperemia[1] and difficulties with guidewire manipulation.[2] Use of the algorithm shown in figure 2 would have avoided hyperemia induction in 100% of patients and use of a coronary guidewire in more than 50%.

Although our study has significant limitations, such as a lack of comparison with other resting coronary physiological indices and not knowing how consistent these data would be if measured by clinicians with less training in QFR analysis, our approach could be useful for increasing the use of functional assessment of coronary lesions. Further studies are needed to confirm our proposed strategy.