The D-dimer assay: A possible tool in the evaluation of atrial thrombosis

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Atrial fibrillation (AF) is a common arrhythmia seen in clinical practice, and affects more than 4% of the population older than 60 years of age. Peripheral thromboembolism contributes significantly to the observed morbidity and mortality. Symptomatic AF, before cardioversion to normal sinus rhythm, requires either exclusion of atrial thrombi using transesophageal echocardiography (TEE) or the conventional use of three weeks of adequate anticoagulation. The exclusion of atrial thrombi by TEE, a nontomographic technique but comparable with conventional treatment of AF in outcomes, has inherent limitations due to the complex three-dimensional multilobed anatomy of the left atrial appendage, where the majority of atrial thrombi arise. Also, the conventional treatment of three weeks of therapeutic anticoagulation before cardioversion reportedly does not always eliminate atrial thrombi. Plasma D-dimer constitutes an antigen-antibody reaction to the dimeric final degradation product of a mature clot. An elevated fibrin D-dimer has a high sensitivity for intravascular thrombosis and, hence, may improve the evaluation of a patient with AF before cardioversion in addition to a TEE. A case is presented in which a positive D-dimer resulted in performing TEE to document atrial thrombosis and the complications of previous bacterial endocarditis. In the present case, this involved aortic root abscess formation and acute aortic regurgitation because of flailing of the noncoronary cusp that resulted in recurrent pulmonary edema.

Key Words: Atrial fibrillation; Atrial thrombosis; D-dimer assay; Left atrial appendage; Thromboembolism; Transesophageal echocardiography

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice, and affects more than 4% of the population older than 60 years of age (1,2). Peripheral thromboembolism and ischemic stroke contribute significantly to the observed mortality and morbidity rates. AF contributes to 15% to 20% of all strokes (1,3), and emboli arise predominantly from the left atrial appendage (LAA) (4). Hence, there is a need to exclude atrial thrombi before cardioversion in symptomatic AF. A recent large, randomized controlled trial has shown that negative transesophageal echocardiography (TEE) results may obviate the need for prolonged anticoagulation before cardioversion, with no significant difference in embolic events compared with conventional therapy (5). Because of the complex multilobed configuration of the LAA and the minute size of clinically significant thrombi, there are inherent limitations in using a nontomographic technique for visualization of the LAA. Using the two-dimensional

Le dosage du D-dimère : Un outil possible pour évaluer la thrombose auriculaire

La fibrillation auriculaire (FA) est une arythmie courante en pratique clinique. Elle touche plus de 4 % de la population de plus de 60 ans. Une thromboembolie périphérique contribue de manière significative à la morbidité et à la mortalité observées. La FA symptomatique, avant cardioversion à un rythme sinusal normal, exige soit l'exclusion des thrombi auriculaires au moyen d'une échocardiographie transoesphagienne (ETO), soit le recours classique à une anticoagulation pertinente pendant trois semaines. L'exclusion des thrombi auriculaires par ETO, une technique non tomographique dont les issues sont comparables à celles du traitement classique de la FA, comporte des limites imputables à l'anatomie multilobe tridimensionnelle de l'appendice auriculaire gauche, où se produisent la majorité des thrombi auriculaires. De plus, l'anticoagulation thérapeutique classique de trois semaines avant la cardioversion n'éliminerait pas toujours les thrombi auriculaires. Le D-dimère dans le plasma est une réaction antigène-anticorps au produit de dégradation finale de D-dimère d'un caillot mature. La fibrine élevée du D-dimère est très sensible à la thrombose intravasculaire, ce qui peut améliorer l'évaluation d'un patient souffrant de FA avant cardioversion, en plus de l'ETO. Un cas est présenté selon lequel un D-dimère positif a donné lieu à une ETO pour documenter la thrombose auriculaire et les complications d'une endocardite bactérienne antérieure. Cet événement avait provoqué la formation d'un abcès de l'anneau aortique et une régurgitation aortique aiguë en raison du volet costal de la valvule non coronarienne responsable de l'œdème pulmonaire récurrent.

beam of TEE in visualizing the three-dimensional anatomy of the LAA is analogous to using a searchlight to visualize the entire roof of a cave, which is technically difficult to achieve completely. Studies have shown that embolism may presumably occur after cardioversion of AF, despite apparent exclusion of a pre-existing atrial thrombus by TEE (6). Plasma D-dimer constitutes an antigen-antibody reaction to the dimeric final degradation product of a mature clot. An elevated fibrin D-dimer has a high sensitivity for intravascular thrombus (7) and may improve the evaluation of a patient with AF before cardioversion.

CASE PRESENTATION

A 56-year-old man eight years post-renal transplant and four years post-coronary artery bypass surgery, as well as a history of adequately treated, methicillin-resistant *Staphylococcus epidermidis* bacteremia,

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Figure 1) Anteroposterior chest x-ray showing perihilar interstitial pulmonary edema two days after discharge from the coronary care unit

Figure 2) Transesophageal echocardiography showing left atrial appendage clot (arrow)

presented with left-sided, nonradiating chest pain, which was relieved by sublingual nitroglycerine. A physical examination revealed an afebrile white man with blood pressure of 139/62 mmHg, heart rate of 86 beats/min and respiratory rate of 20 breaths/min. His lungs were clear to bilateral auscultation. A cardiac examination revealed first and second heart sounds, with irregular rhythm and a grade 2/4 systolic ejection murmur radiating to the carotids. There was no jugular venous distension and no peripheral edema. The first set of cardiac enzymes was within normal limits. A 12-lead electrocardiogram showed AF with a controlled ventricular rate and nonspecific ST-T segment changes. He was transferred to the coronary care unit (CCU) for further treatment of his acute coronary syndrome. While in the CCU, his chest pain recurred with an elevated troponin I level of 1.1 µg/L. He was started on intravenous nitroglycerine and heparin drip and underwent coronary angiography, which showed patent grafts with good run off. The patient's clinical status improved with medical management. Three days after transfer to the step-down CCU, the patient developed an episode of acute shortness of breath, requiring transfer back to the CCU. A chest x-ray at that time showed diffuse interstitial pulmonary edema (Figure 1). Dipyridamole thallium-201 stress-redistribution imaging showed a small, 15% apicoinferior reprefusing defect. Transthoracic echocardiography revealed a left

Figure 3) Thickened aortic leaflets with flailing of noncoronary cusp (open arrow) and cavity of aortic root abscess (closed arrow)

ventricular ejection fraction of 40% to 45%, with no thrombus or spontaneous echo contrast, and a suggestion of mild to moderate aortic stenosis. The patient was treated appropriately for acute pulmonary edema. Two days later, the patient developed another episode of pulmonary edema. At this point, despite the absence of tachycardia, it was elected to attempt cardioversion to normal sinus rhythm because of a concern that his recent AF was playing a major role in the congestive heart failure recurrence. In view of atrial fibrillation for greater than 48 h, the authors were required to exclude left atrial clot by TEE before cardioversion. Permission was requested from the patient to perform TEE. The patient initially refused, but the treating physicians were able to negotiate with him; he then agreed to undergo TEE if D-dimer estimation was positive for a clot. The D-dimer assay obtained was markedly elevated (2000 µg/L). When presented with this evidence of a possible intracardiac thrombus, the patient agreed to undergo TEE, which revealed an LAA clot (Figure 2) with spontaneous echo contrast. Of major clinical importance, the TEE also showed flailing of the noncoronary cusp of the aortic valve, with moderate to severe aortic regurgitation, thickened immobile leaflets (Figure 3) and an aortic root abscess (Figure 4). It was determined that acute aortic regurgitation was the cause of the patient's recurring pulmonary edema, thus he proceeded to emergent aortic valve replacement. His clinical status improved after surgery, reverting back to normal sinus rhythm with no further episodes of pulmonary edema.

DISCUSSION

The D-dimer assay is reflective of the level of thrombin generation and plasmin activity on cross-linked fibrin. It has a half-life of 48 h, and the assay has a high sensitivity for intravascular thrombi (7). The development of monoclonal antibodies specific for D-dimer has enabled accurate quantification of cross-linked fibrin degradation products. The role of the D-dimer assay in the diagnosis and prognosis of cardiovascular disease has been extensively studied (7,8). We have presented a case in which the D-dimer assay was used in the inclusion and exclusion of atrial thrombosis before cardioversion in a patient with AF who refused to undergo TEE.

The conversion of AF to sinus rhythm is associated with an annual ischemic stroke rate of 3% (9). This postcardioversion embolism may be due to unrecognized preformed atrial thrombi that are dislodged into the circulation. In AF, thrombi almost always originate in the LAA. Although TEE is more sensitive than transthoracic echocardiography in the detection of atrial appendage thrombi, it has a number of

limitations. The LAA is multilobed, with unpredictable projections, making it difficult to completely interrogate all aspects to exclude a clot. The LAA had two or more lobes in 80% of 500 normal hearts in an autopsy study (10). This emphasizes the importance of carefully searching for all the lobes, which invariably lie in different planes. The sensitivity of TEE may be further reduced when LAA thrombi, which are minute but clinically significant, exist. Studies have shown that the exclusion of a pre-existing atrial thrombus by TEE does not eliminate the risk of thromboembolism after cardioversion of AF (6). There have been reported cases in which three weeks of anticoagulation to therapeutic levels not only failed to eliminate left atrial clots, but, in fact, converted them to a higher-risk appearance (11). Because both conventional use of anticoagulation and TEE in the management of AF have documented pitfalls, there is a need to improve the evaluation of patients before cardioversion. A prospective study (8) analyzing the D-dimer assay as a screening tool for the exclusion of atrial thrombi has shown that it may be a better single marker of overall thromboembolic risk than TEE. Low levels of D-dimer have been shown to exclude atrial thrombi (8); hence, the D-dimer assay is a possible adjunctive tool in the diagnostic evaluation of atrial thrombosis in addition to TEE. In a recent prospective animal study (12), we showed a potential role of minidose tissue plasminogen activator in enhancing the D-dimer signal in situ in deep venous thrombosis. This may eventually be applicable in the diagnostic evaluation of stable atrial thrombus in humans before cardioversion of AF and warrants further study. There is an interaction between D-dimer levels and inflammation, which might have contributed to D-dimer elevation in our patient. Note that our patient had a normal white cell count and differential, was afebrile and had repeated negative blood cultures after a complete four-week course of treatment for his previous methicillin-resistant *S epidermidis* infection. Our patient only had a residual local infection with a walled-in abscess, as documented during surgery, a few days after his D-dimer estimation. In this situation, the localized tissue infection is unlikely to be the cause of the marked D-dimer elevation. In any event, D-dimer levels tend to be lower in sepsis unless severe multiorgan failure supervenes (13,14).

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Figure 4) Thickened aortic leaflets with flailing noncoronary cusp (open arrow) and aortic root abscess (closed arrow)

CONCLUSION

The D-dimer assay is a measure of the antigen-antibody reaction to the final degradation product of a mature clot. A negative value appears to exclude the presence of a thrombus complicating AF (8). The role of a positive D-dimer assay is less defined. The positive result obtained in the present case was helpful in arriving at a crucial clinical diagnosis, which resulted in excellent patient outcome. Further prospective studies are needed to define the role of a positive D-dimer assay in the management of patients with potential atrial thrombosis.