Letter by Roldán et al Regarding Article, “Plasminogen Activator Inhibitor-1 as a Predictor of Postoperative Atrial Fibrillation After Cardiopulmonary Bypass”

To the Editor:

Pretorius et al report that elevated plasminogen activator inhibitor-1 (PAI-1) levels are independent predictors of the development of atrial fibrillation (AF) after cardiopulmonary bypass, raising the possibility that postoperative AF is secondary to inflammation and fibrosis. PAI-1 also could promote myocardial remodeling by reducing matrix metalloproteinase activity because PAI-1 inhibits tissue plasminogen activator (tPA) and consequently plasmin, which is a potent activator of matrix metalloproteinases. There also is a link between fibrinolysis and inflammation, but elevated PAI-1 levels are part of various pathophysiological interactions. For example, elevated PAI-1 levels are found in the insulin resistance syndrome, so its prognostic value in different conditions often disappears after adjustment for body mass index, triglycerides, and high-density lipoprotein cholesterol. As we have previously reviewed, the increased PAI-1 levels in AF have raised different hypotheses, including implications for thrombosis, endothelial damage/dysfunction, inflammation, or other confounders. Elevated PAI-1 levels also are reported in patients with mitral stenosis, including those in sinus rhythm, and more recently, high baseline PAI-1 activity has been shown to be a strong predictor of AF recurrence after electric cardioversion.

The different facets of PAI-1 in AF merit some discussion. The fibrinolytic system plays an important role in preventing intravascular thrombosis; hence, the fibrinolytic function in the vasculature is dependent on the rate of secretion of tPA, the inhibition of tPA by PAI-1 and other inhibitors, and the hepatic clearance of tPA. The improvement in fibrinolytic markers in AF after “steady-state” oral anticoagulation supports the prothrombotic role of PAI-1.

Because endothelial cells also release tPA and PAI-1, it has been suggested that these indexes could be related as markers of endothelial cell damage or dysfunction. Rather than being a measure of fibrinolysis, tPA and PAI-1 antigen levels may therefore be a surrogate for vascular injury. Given that AF is associated with a reduced expression of NO synthase and NO bioavailability with a significant increase in PAI-1 expression in left atrium, PAI-1 abnormalities may simply reflect endothelial damage.

Thus, there are several explanations for the significance of high PAI-1 levels in AF, reflecting the complex pathophysiology of this common arrhythmia. Pretorius et al may be simplistic in attributing a causal role in predicting AF development to PAI-1. Of note, matrix metalloproteinase-9 concentration, a more established marker of matrix remodeling, offers no predictive information in their study.

Disclosure

None.

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