Editorial

Plasminogen Activator Inhibitor-1 and the Calculus of Mortality After Myocardial Infarction

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There are numerous clinical factors that have been identified that are associated with an adverse outcome after acute myocardial infarction (MI). These factors include female gender, the presence of severe left ventricular dysfunction or congestive heart failure, a history of diabetes mellitus, age >70 years, infarct location (anterior versus inferior), and patency of the infarct-related artery. In this issue of Circulation, Collet and colleagues describe a previously unrecognized relationship between acute increases in plasma levels of plasminogen activator inhibitor-1 (PAI-1) in patients hospitalized with acute ST-elevation MI and risk of mortality during a 1-month period.

PAI-1 is the primary circulating inhibitor of tissue-type plasminogen activator and the urokinase-type plasminogen activator in plasma. Elevated plasma PAI-1 levels have been shown to be a predictor of recurrent MI and have been identified as an independent predictor of cardiovascular risk. When one considers the many factors that regulate plasma PAI-1 levels, it is not completely surprising that acute increases in the levels of PAI-1 in plasma might reflect increased risk of mortality after acute MI. The PAI-1 that circulates in plasma is derived from the composite output of several different cellular synthetic sites, including the liver, the vascular endothelium, and visceral adipose tissue. There are a number of factors that are known to directly affect PAI-1 production, including metabolic factors such as glucose, insulin, and VLDL, neurohumoral factors including angiotensin II and aldosterone, and inflammatory cytokines including tumor necrosis factor-α and interleukin-1. The remarkable relationship described in this study could reflect the impact of any or all of the previously listed mechanisms. For example, it has been shown previously that impaired glucose control is an independent predictor of risk after acute MI. Although the level of metabolic control in this population is not described, it certainly is possible that some of the mortality associated with elevated PAI-1 levels reported here may simply reflect poor glycemic control in the peri-infarct setting. PAI-1 is commonly and predictably elevated in individuals with insulin resistance and type II diabetes, and whereas diabetics made up ~19% of the population studied here, it is not clear whether they were overrepresented with regard to 1-month mortality.

Our group and others have shown a strong relationship between activation of the renin-angiotensin-aldosterone system (RAAS) and plasma PAI-1. It is known that the RAAS is activated after acute MI. The level of activation of the RAAS can also reflect the extent and severity of left ventricular dysfunction after acute anterior MI. In this context, PAI-1 may represent a circulating marker of activation of the RAAS that may be indirectly related to infarct size. PAI-1 is also a classic acute phase reactant and is strongly upregulated by inflammatory cytokines. Healing after MI involves an inflammatory process that is generally thought to occur later in the course of events after an MI, a process temporally delayed from the early increase in PAI-1 seen in this study, although some inflammatory contribution to these acute increases cannot be excluded.

There are several important limitations to this study. The population examined is relatively small in size, which precludes any definitive conclusions being drawn at present. The novelty of the associations suggests that these observations deserve to be validated in larger and better-characterized populations. Although the authors were successful in identifying a change in plasma PAI-1 as a predictor of risk, it is surprising that the well-known circadian variation patterns in plasma PAI-1 did not confound the results or diminish the differences between subjects who survived and those who died. There is also no accompanying information on the potential benefit of therapies, both pharmacological and nonpharmacological, that might prevent the acute increase in plasma PAI-1. These potentially include ACE inhibitors, insulin synthesizing agents, or other agents that improve endothelial function and nitric oxide production systematically.

Overall, this study suggests that the acute release of PAI-1 in ST-elevation MI helps identify patients at risk for undesirable outcomes. The novelty and statistical strength of the association reported are noteworthy and should provide a strong impetus for further investigation. It is tempting to speculate that additional therapeutic measures that reduce PAI-1 production or directly antagonize PAI-1 activity may eventually be of value in the setting of acute MI.

References


The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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