CORRESPONDENCE

THROMBIN AND PLASMINOGEN ACTIVATOR INHIBITOR

To the Editor:

Colucci et al[1] recently reported a marked reduction of plasma levels of plasmin activator inhibitor (PAI) after infusion of bovine thrombin in rabbits treated with endotoxin (to induce an increase in fast-acting PAI). In contrast, other investigators reported an increase of PAI production by thrombin in human cultured endothelial cells.[2] Since PAI plays a pivotal role in the control of fibrinolysis,[3] it is important to know whether thrombin causes an increase or a decrease of plasma PAI level. In this respect, we (Table 1) and other investigators[4,5] have observed that plasma PAI activity is markedly elevated in patients with stable or unstable angina. In such patients, enhanced thrombin generation assessed by elevated plasma fibrinopeptide A level (a marker of thrombin generation[6]) was reported.[7-9] We have measured plasma PAI activity by a spectrophotometric method[10] in platelet-poor plasma of 43 subjects: 19 with unstable angina, 11 with stable angina, and 13 healthy controls. We have also observed that plasma PAI activity (adjusted to a platelet concentration of 2.5×10^8/mL) was markedly elevated in 11 patients with chronic myeloproliferative disorders (CMPD; four with polycythemia vera and seven with essential thrombocythemia) compared with controls (Table 1) or with five patients with reactive thrombocytosis. Eight of the CMPD patients suffered from peripheral vascular ischemia and three suffered from deep vein thrombosis, but none of the 11 patients had bleeding episodes. In CMPD patients, increased prothrombin consumption (indicating enhanced thrombin generation) was reported.[11]

Therefore, we can conclude that enhanced thrombin generation, which has been indicated (by other investigators) in stable or unstable angina[7-9] and in CMPD patients, is not associated with reduced plasma PAI activity but, rather, with an increased one. Moreover, plasma levels of tissue plasminogen activator in the three groups of patients did not differ significantly from control levels (Table 1). Therefore, the reduction by thrombin of plasma PAI levels in rabbits (reported by Colucci et al[1]) is probably not tenable in humans. This effect might be local and of short duration, or occurring only after induction of endotoxemia. Its importance in the control of fibrinolysis is still unclear.

Table 1. Plasma Tissue Plasminogen Activator Level and PAI Activity in Patients and Controls

	Age	Platelet Count	TPA (ng/mL)	PAI (IU/2.5 × 10^8 platelets)
Controls	52 (38-70)	2.5 ± 0.5	7.7 (2.9-13.3)	0.9 (0.0-5.0)
Stable angina	56 (38-72)	2.2 ± 0.7	8.5 (1.3-14.2)	16.6 (0.0-37.0)
P	NS	NS	NS	<.02
Unstable angina	57 (41-76)	2.5 ± 0.7	8.4 (5.4-14.2)	6.5 (0.0-21.0)
P	NS	NS	NS	<.02
CMPD	67 (24-84)	6.0 ± 3.2	8.9 (4.0-17.0)	5.1 (0.13-19.0)
P	NS	<.02	NS	<.05

Results are the mean and range. Probability measured by two-tailed Mann-Whitney U-Test comparing patients with controls.

Abbreviations: TPA, tissue plasminogen activator; NS, non-significant.

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RESPONSE

We appreciate the comments of Drs J. Zahavi and M. Zahavi. It is also our experience that in coronary artery disease, as well as in other clinical conditions known to be associated with enhanced thrombin generation, there is an increase in plasma PAI.[1-3] However, in our

opinion, these findings are insufficient to conclude that enhanced thrombin generation is associated with an increase in PAI and that our results in the rabbit "are probably not tenable in humans." First, thrombin formation is only one of the numerous events that may influence PAI production and/or release in patients with coronary artery disease or chronic myeloproliferative disorders. These events include release of platelet products (transforming growth factor-β is one of the most potent inducers of PAI-1 production), generation of cytokines, hypertrigliceridemia, vascular damage, etc.[4,5] Second, the observation that PAI levels in these patients are higher than in control "healthy" subjects is not incompatible with a profibrinolytic effect of thrombin, since plasma PAI could have been higher in the absence of thrombin generation and subsequent protein C activation (our data, indeed, indicate that the effect of thrombin on plasma PAI is mediated by protein C activation). In this respect, the data of Taylor et al[6] are of interest. They showed that infusion of *Escherichia coli* in baboons caused a coagulopathic response despite protein C activation. However, when activation of protein C was blocked by specific monoclonal antibodies, the coagulopathic response was markedly more pronounced and was associated with high mortality at sublethal doses of bacteria.[6] Third, the profibrinolytic effect of thrombin has also been reported in another animal species,[7] though the involvement of PAI, whose relevance in blood fibrinolysis was unknown at the time, was not considered.

We are aware that our results in rabbits cannot be directly transferred to human beings, and agree with Drs Zahavi and Zahavi that endotoxin treatment might have influenced the response to thrombin. However, we do believe that the clinical evidence available so far is not against the hypothesis that thrombin may induce in humans a reduction of PAI-1 via activation of protein C.

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