Nitrate Resistance in Platelets From Patients With Stable Angina Pectoris

To the Editor:

The article by Chirkov and colleagues1 clearly indicates that platelets in plasma samples from patients with stable angina are resistant to the inhibitory effects of pharmacological concentrations of the nitric oxide (NO) donor drugs nitroglycerine (NTG) and sodium nitroprusside (SNP). Resistance was reversed by superoxide dismutase, suggesting that the effect might be due to superoxide-mediated inactivation of NO derived from NTG and SNP in the platelets of patients.

As the authors point out, this interesting observation does not necessarily reflect platelet resistance to NTG in vivo. However, even in the absence of nitrate resistance, organic nitrates are notoriously poor inhibitors of platelet aggregation2 because, unlike vascular tissue, platelets lack the necessary metabolic pathway for NO generation from nitrates.3 This issue is highlighted by the need to use high concentrations (100 μmol/L) of NTG to inhibit platelet aggregation in this study; the maximum estimated plasma concentration with transdermal and sublingual NTG is several orders of magnitude lower (=2 and =20 nmol/L, respectively). Clearly, NTG is unlikely to have an impact on platelet aggregation in angina pectoris, irrespective of nitrate resistance. It is noteworthy that SNP is a significantly more potent inhibitor of platelet aggregation; perhaps we should be looking to SNP and platelet-selective NO donors such as S-nitrosothiols4 as vasodilators with antithrombotic activity, rather than organic nitrates.

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Response

We thank Drs Megson and Webb for their interest in our article. With regard to the phenomenon of “nitrate resistance,” it is certainly correct that reduced responsiveness to sodium nitroprusside (SNP) at the level of platelet aggregation in whole blood must have implications for endogenous nitric oxide (NO). Thus, we agree that one of the major conclusions to be drawn from our study is that patients with stable angina pectoris are more predisposed toward platelet aggregation by virtue of decreased platelet responsiveness to endogenous NO.

With regard to the implications of our findings for pharmacotherapy with NO donors, we do not agree that the antiaggregatory effects of nitroglycerin (NTG) are either nonexistent or trivial in the clinical context. There are numerous studies (for example, References 1 and 2) documenting in vivo and ex vivo antiaggregatory effects of NTG in both animals and humans. Although washed platelets do not bioconvert NTG, bioconversion in platelet-rich plasma produces sufficient NO to inhibit5 and reverse2 platelet aggregation.

We acknowledge that the concentrations of NTG and SNP utilized in our study for evaluation of inhibition of aggregation in vitro were far higher than those occurring with optimal clinical use of these agents. This disparity between efficacy of NTG in vivo and in vitro has never been adequately explained but may reflect the consequences of intense NTG bioconversion in blood vessels,6 resulting in increased NO release.

Regarding the suggestion that SNP or S-nitrosothiols may be more suitable than NTG for therapeutic inhibition of platelet aggregation, it is certainly true that these agents are more potent than NTG. However, they are also more potent arteriolar dilators than NTG,4 raising a theoretical concern about precipitation of coronary “steal.” In view of unimpressive outcomes of clinical trials with SNP and with the “direct” NO donor linsidomine in acute myocardial infarction, we hesitate to make recommendations based on antiaggregatory effects in isolation.

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