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The Effect of Sodium Nitroprusside upon Platelet Function

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To the Editor:—Hines and Barash[1] reported the important findings that sodium nitroprusside infusion increases bleeding time and decreases *in vitro* platelet aggregation. These data are consistent with the recent *in vitro* findings of other investigators,[2,3] but the discussion presented by the authors does not address the most likely mechanism explaining their observations, and their conclusion that nitroprusside creates dysfunctional platelets is not accurate.

Nitroprusside probably inhibits platelet aggregation through the same mechanism used by normal vascular endothelial cells in the modulation of hemostasis. Vascular endothelial cells are now known to release a labile substance (endothelial cell derived relaxing factor-EDRF) that relaxes vascular smooth muscle[4] and inhibits platelet aggregation.[5] This substance is very closely related to, or may be identical to, nitric oxide, which is considered to also be the active metabolite of nitroprusside.[6]

These smooth muscle and platelet responses, induced by nitroprusside, EDRF, or nitric oxide take place through the activation of soluble guanylate cyclase and production of cyclic-GMP.[3,7] Free hemoglobin, which binds EDRF and nitric oxide, abolishes the responses. Other organic nitrates, such as nitroglycerin or sodium nitrite, which use nitric oxide as their active metabolite, will probably also be found to decrease platelet aggregation.

Therefore, since the process of regulating platelet aggregation by endothelial cells can be considered physiological, the dysaggregation induced by nitroprusside cannot be considered platelet dysfunction but instead should be considered platelet inhibition.

With this in mind, a few questions arise that suggest several avenues for further study. First, since the nitrates and nitric oxide are very short acting, how long does the platelet inhibition persist following cessation of drug infusion? Second, since this is the first study demonstrating an increase in bleeding time with the use of nitroprusside, and the findings may be due to vasodilatory effects of nitroprusside instead of the platelet effects, would the same alterations in bleeding times be seen with a non-nitrate vasodilator such as trimethaphan? And third, if the platelet effects are clinically significant and platelet aggregation can be inhibited in some controlled fashion, could nitrates be used as titratable drugs that may be indicated for episodes of undesired platelet aggregation such as DIC, acute myocardial infarction, or stroke?

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In Reply:—Drs. Rivers and Johns have misstated our conclusion. Careful reading of our paper would reveal that we described the effect of sodium nitroprusside on platelet function as one of inhibition.[1]

"In summary, in situations in which SNP therapy is administered, the clinician must be aware of the potential for the *inhibition* (italics added) of platelet aggregation."

Indeed, we employ the term inhibition throughout the Discussion. The use of dysfunction in the title refers to the global process of platelet function: adherence, aggregation, and release.

Rivers and Johns raise an intriguing alternative hypothesis to account for the observed inhibition. However, the reports cited in their letter do not make the critical link to establish the EDRF hypothesis.

We too were concerned about hemodynamic effects of SNP on the bleeding time. In designing the study, patients in the control group (fentanyl anesthesia without SNP administration) had mean arterial pressure maintained at the same level as the SNP treated patients (MAP = 80 mmHg). In a subsequent study, we are preparing for publication, the effect of trimethaphan infusion under similar clinical and experimental conditions (as our SNP study) was evaluated. Using trimethaphan infusions 1–4 mg/min, we were unable to demonstrate abnormalities in bleeding time or platelet inhibition as assessed by ADP and epinephrine challenge. These results argue against a vasodilating effect, as responsible for the increase in bleeding time seen with SNP.

Due to the clinical situation (patients had to be studied before initiation of cardiopulmonary bypass), our protocol did not allow for evaluation of return of platelet aggregation. Obviously, if reversal of platelet inhibition is possible, then a new therapeutic spectrum is opened for the clinician employing nitrate therapy. The prospect of using platelet disinhibitory effect of nitrates in the treatment of TIA, myocardial infarction, or other hypercoagulable vascular states is an exciting one that has been previously addressed.[2] Certainly, this is an area that warrants further laboratory and clinical investigation.