Nitrates are not only vasodilators but may also inhibit platelet aggregation. The mechanisms of this inhibition are not fully understood. However, it is well-established that nitroglycerin (NTG) inhibits platelet aggregation in vivo and in vitro. This is due to its ability to increase the availability of nitric oxide (NO), which readily diffuses across the cell membrane to inhibit platelet aggregation.

On the other hand, sodium nitroprusside (SNP) has been shown to inhibit platelet aggregation both in vivo and in vitro. However, there is evidence suggesting that platelets from patients with stable angina pectoris are resistant to the inhibitory effects of SNP. This resistance is likely due to the presence of nitrate-resistant platelets, which are more common in patients with stable angina pectoris compared to healthy individuals.

The article by Chirkov and colleagues clearly indicates that platelets in plasma samples from patients with stable angina are resistant to the inhibitory effects of SNP. This resistance is even more pronounced in patients with nitrate-resistant platelets. The authors point out that this observation does not necessarily reflect platelet resistance to NTG in vivo. However, even in the absence of nitrate resistance, organic nitrates are notably poor inhibitors of platelet aggregation because, unlike vascular tissue, platelets lack the necessary metabolic pathway for NO generation from nitrites. 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 than NTG, raising a theoretical concern about precipitation of aggregation. However, they are also more potent arteriolar dilators than NTG. Moreover, the clinical context suggests that SNP and platelet-selective NO donors such as S-nitrosothiols may be more suitable than NTG for therapeutic inhibition of platelet aggregation, as they are more potent than NTG and may reduce the potential for adverse effects. Moreover, the concentration of SNP required to inhibit platelet aggregation is likely to be lower than that of NTG, which may reduce the risk of adverse effects.

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, conversion in platelet-rich plasma produces sufficient NO to inhibit and reverse 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 clinical use. This disparity between efficacy of NTG in vivo and in vitro has never been adequately explained but may reflect the consequences of intense NO bioconversion in blood vessels, resulting in increased NO release.

Regarding the suggestion that SNP 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, 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.

Yuliy Y. Chirkov, PhD
Andrew S. Holmes, BSc Hons
Larissa P. Chirkova, PhD
John D. Horowitz, PhD
Department of Cardiology
The Queen Elizabeth Hospital
University of Adelaide
Adelaide, SA, Australia

Nitrate Resistance in Platelets From Patients With Stable Angina Pectoris
I. L. Megson and D. J. Webb

_Circulation_. 2000;102:e87
doi: 10.1161/01.CIR.102.11.e87
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/102/11/e87

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/