Response to Letter Regarding Article, “L-Arginine Supplementation in Peripheral Arterial Disease: No Benefit and Possible Harm”

We thank Dr. Teerlink for his comments regarding the unexpected results of our study. Pre-clinical studies and short-term trials in patients with coronary or peripheral arterial disease showed that supplemental L-arginine improved endothelium-dependent vasodilation and increased nitric oxide (NO) production. Accordingly, we hypothesized that long-term administration of L-arginine would improve vascular function and enhance collateral blood flow, thereby increasing walking distance in patients with peripheral arterial disease. To our surprise, long-term L-arginine supplementation tended to impair vascular function and to limit the improvement in walking distance over time in patients with peripheral arterial disease.

As Dr. Teerlink commented, the metabolic fate of L-arginine is highly complex and tightly regulated. However, plasma L-arginine levels rose in the supplemented group, so it is unlikely that induction of intestinal arginase activity fully explains our findings. Despite the increased plasma L-arginine levels, citrulline did not rise in the L-arginine–treated group. Furthermore, as compared with the placebo group, there was a significant decrement in endothelium-dependent vasodilation and nitric oxide production. These observations indicate the presence of a countervailing mechanism that opposed an arginine-induced increase in NO production. The apparent reversal of arginine-induced NO production could be due to an opposing increase in asymmetric dimethylarginine (the endogenous NOS inhibitor). Although plasma asymmetric dimethylarginine levels were elevated at baseline in both peripheral arterial disease groups, there were no group differences after treatment. Another possible explanation may be that vascular arginase expression and/or activity was increased, as Dr. Teerlink suggested. Increased endothelial arginase II expression has been shown to downregulate endothelial NO synthase activity. It is also possible that an increase in arginine metabolites such as ornithine may have led to adverse vascular effects as Dr. Teerlink suggests. However, this would not explain the failure of citrulline and NO to rise in the L-arginine–treated group, unless the elevated ornithine levels somehow led to NO synthase inhibition.

Whatever mechanisms are invoked to explain the surprising findings in this double-blind, randomized clinical trial, the results are clinically relevant, as L-arginine supplements are available over the counter and are currently being taken by a range of subject groups. We agree with Dr. Teerlink that alternate explanations for lack of benefit or even potential adverse effects should be sought.

Disclosures

Dr. Cooke is the inventor of patents owned by Stanford University for diagnostic and therapeutic applications of the NO synthase pathway from which he receives royalties. Dr. Cooke is a consultant to Ajinomoto and United Therapeutics. The other authors report no conflicts.

Andrew M. Wilson, MBBS, PhD
Randall K. Harada, MD
Nandini Nair, MD, PhD
Naras Balasubramanian, PhD
John P. Cooke, MD, PhD
Division of Cardiovascular Medicine
Stanford University School of Medicine
Stanford, Calif

References

Response to Letter Regarding Article, "L-Arginine Supplementation in Peripheral Arterial Disease: No Benefit and Possible Harm"
Andrew M. Wilson, Randall K. Harada, Nandini Nair, Naras Balasubramanian and John P. Cooke

_Circulation_. 2008;117:e158
doi: 10.1161/CIRCULATIONAHA.107.739052

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/117/6/e158

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/