To the Editor:

We read with interest the article by Ghebremariam et al1 demonstrating that proton pump inhibitors (PPIs) reduce endogenous formation of nitric oxide (NO) and impair vascular reactivity.1 This deleterious effect of PPIs occurred through inhibition of the enzyme dimethylarginine dimethylaminohydrolase, which degrades asymmetrical dimethylarginine, an endogenous NO synthase inhibitor.1 The authors discuss this as a possible mechanism explaining the increased risk of adverse cardiovascular events with prolonged PPI treatment.2 We bring up another mechanism by which PPIs may alter vascular NO homeostasis, with possible added deleterious effects in the cardiovascular system. Although classic formation of NO is from l-arginine and mediated by NO synthases, an alternative pathway for NO formation has been described more recently. The major oxidation products of NO metabolism nitrite and nitrate are recycled in blood and tissues through reductive pathways to again form NO and other bioactive nitrogen oxides.3 Nitrate is also found in our everyday diet, and studies have shown robust NO-like effects of nitrate ingestion, including a reduction in blood pressure and improvements in vascular function.4 These beneficial cardiovascular effects of dietary nitrate involve an entero-salivary circulation in which nitrate is rapidly absorbed in the gastrointestinal tract and then actively taken up by the salivary glands and concentrated up to 20-fold in saliva.5 Oral commensal bacteria then reduce salivary nitrate to nitrite, and when saliva enters the acidic stomach, much of the nitrite is rapidly protonated to form nitrous acid, which decomposes further to form NO and other nitrogen oxides.6 In addition, some nitrite is also absorbed systemically and reduced to NO in blood and tissues. The use of PPIs increases the gastric pH, and this contributes to impairments of the nitrate–nitrite–NO pathway described above. Indeed, a recent study in rats showed that the increases in gastric pH caused by the PPI omeprazole completely blunted the beneficial antihypertensive effects of oral nitrite.7 Intriguingly, nitrate also interacts directly with the pathway studied by Ghebremariam et al,1 as demonstrated by decreases in asymmetrical dimethylarginine levels in a rat model of chronic cardiovascular disease after treatment with dietary nitrate.8 In addition, PPI-induced inhibition of NO synthase will lead to a decrease in circulating levels of nitrate and nitrite, thereby affecting also the nitrate–nitrite–NO pathway. In aggregate, PPIs may disturb vascular NO homeostasis in 2 interconnected ways, both of which may contribute to the association between PPIs and cardiovascular risk.

Disclosures

Dr Lundberg is a named inventor on a pending patent application for medical uses of inorganic nitrate and nitrite. Dr Montenegro reports no conflicts.

Marcelo F. Montenegro, PharmD, PhD
Department of Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

Jon O. Lundberg, MD, PhD
Department of Physiology and Pharmacology
Karolinska Institute
Stockholm, Sweden

References

Letter by Montenegro and Lundberg Regarding Article, "Unexpected Effect of Proton Pump Inhibitors: Elevation of the Cardiovascular Risk Factor Asymmetric Dimethylarginine"

Marcelo F. Montenegro and Jon O. Lundberg

_Circulation_. 2014;129:e426
doi: 10.1161/CIRCULATIONAHA.113.005585

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/129/13/e426