Vitamin C and Coronary Microcirculation

To the Editor:

In their study on the short-term effects of vitamin C on coronary microcirculation, Kaufmann et al.1 used adenosine to increase myocardial blood flow, which was assessed by positron emission tomography. When compared with controls, smokers showed an attenuated response that was corrected by 3 g of vitamin C given intravenously over 10 minutes. The authors conclude that cigarette smoke causes oxidant damage that is reversed by vitamin C.

Unfortunately, the study conditions are not physiological, which is a consequence of the sigmoidal vitamin C dose-concentration relationship. When vitamin C is given orally, it is completely absorbed until the dose exceeds 200 mg.2 Consumption of 200 mg of vitamin C daily, which occurs in a typical Mediterranean diet, results in a plasma concentration of ~70 μmol/L. Many cells, such as neutrophils, actively transport vitamin C and saturate before plasma. Saturation of cells by 70 μmol/L corresponds to the maximal velocity of the main tissue vitamin C transporter, sodium-dependent vitamin C transporter.3,4 Higher vitamin C doses do not increase long-term plasma vitamin C concentrations because of decreased absorption and increased renal excretion, which begin when plasma concentrations exceed 60 to 70 μmol/L. With an oral dose of 1.25 g, less than half the dose is absorbed, and all that is absorbed is excreted.5 In contrast, when vitamin C is given intravenously, the limiting absorptive mechanisms are bypassed, and much higher plasma concentrations are achieved. Thus, when 1.25 g of vitamin C is given intravenously over 5 minutes, a peak plasma concentration of 700 μmol/L is attained, which falls to 200 μmol/L in 2 hours.6 Almost the entire dose is excreted in the urine in 12 hours. We estimate that 3 g of vitamin C given intravenously, as was done in Kaufmann et al.’s study, will result in a plasma concentration of ~1500 μmol/L, which will fall by perhaps a few hundred micromoles per liter during the course of the study.

These vitamin C concentrations, which are 10 to 20 times those that can be obtained by oral intake, are clearly unphysiological. The response of the tissues to such pharmacological concentrations may have little bearing on vitamin C actions at the more modest physiological concentrations. Although this study demonstrates the utility of using high-dose intravenous vitamin C to produce antioxidant effects in experimental situations, it does not show that vitamin C has such actions at physiological concentrations and, unfortunately, it cannot form the basis for using vitamin C in primary or secondary prevention of coronary heart disease. A healthy diet containing at least 5 servings of varied fruits and vegetables a day will supply all the vitamin C we need.

Sebastian J. Padayatty, MRCP, PhD
Mark Levine, MD
Molecular and Clinical Nutrition Section
Digestive Diseases Branch
National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, MD 20892-1372
MarkL@intra.niddk.nih.gov


Response

We appreciate Drs Padayatty and Levine’s interest in our article.1 We share their concerns about the direct extrapolation of our experimental data into daily clinical practice. In fact, in the discussion section of the article, we stated that “our study design does not allow us to comment on the long-term effects of vitamin C.” However, the aim of our study was to prove the hypothesis that the noxious effects of cigarette smoke on the function of the coronary microcirculation are due, at least in part, to oxidative stress. Because smokers have reduced plasma and tissue levels of vitamin C, we thought to provide a supplement of this natural antioxidant at a dose that has previously been shown to improve endothelial dysfunction in smokers.2 Although we agree that the plasma concentration of vitamin C achieved after such a high intravenous dose is not physiological, it had no appreciable effect in nonsmokers. Therefore, we believe that the effect of vitamin C on flow reserve in smokers was indeed due to its scavenging and antioxidant properties and that, at least in our study population, the impairment of the coronary microcirculation in smokers was still reversible, as proven by the normalization of flow reserve observed after the intravenous administration of vitamin C.

Although we agree that higher vitamin C doses do not increase long-term plasma vitamin C concentrations in healthy volunteers because of decreased absorption and increased renal excretion, this does not necessarily apply to smokers, who have reduced plasma and tissue levels of this vitamin. This depletion is thought to be due to increased consumption as the result of greater oxidative stress and to dietary differences.3 This questions, in daily practice, the value of theoretically valid recommendations such as “a healthy diet containing at least 5 servings of varied fruits.” Therefore, we believe that only a study testing the potential effect of long-term supplementation of vitamin C on coronary flow reserve in smokers could properly address the concerns of Drs Padayatty and Levine.

Phyllip Kaufmann, MD
Paolo G. Camici, MD, FESC, FACC, FRCP
Tomaso Gneechi-Ruscone, MD
Marco di Terlizzi, MD
Hammersmith Hospital
Imperial College School of Medicine
London, UK

Thomas F. Luscher, MD, FESC, FACC, FRCP
Department of Cardiology
University Hospital
Zurich, Switzerland

Klaus P. Schäfers, MSc
Klinik und Poliklinik für Nuklearmedizin
Universität Muenster
Muenster, Germany

Vitamin C and Coronary Microcirculation
Sebastian J. Padayatty and Mark Levine

Circulation. 2001;103:e117
doi: 10.1161/01.CIR.103.23.e117
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 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/103/23/e117

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/