Vitamin C and myocardial infarction: the heart of the matter

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Vitamin C has been associated with stress ever since Albert Szent-Gyorgi isolated it from the adrenal glands of oxen. More than 2 decades ago, investigators studying vitamin C in patients with the stress of an acute myocardial infarction showed that plasma and tissue concentrations declined within 1 d and increased again after 1 wk (1, 2). Others showed that vitamin C concentrations in leukocytes were lower in patients with angiographically proven coronary artery disease than in those without disease (3). Despite suggestions that some findings were due to changes in proportions of circulating neutrophils to lymphocytes, which have 2–3-fold different vitamin C concentrations, the findings of low plasma vitamin C remained unexplained.

Vitamin C is an electron donor for enzymes involved in collagen hydroxylation, biosynthesis of carnitine and norepinephrine, tyrosine metabolism, and amidation of peptide hormones; its deficiency causes scurvy. The amount of vitamin C necessary to prevent scurvy may not be adequate to maintain optimal health (4). The ability of vitamin C to donate electrons also makes it a potent water-soluble antioxidant that readily scavenges free radicals such as molecular oxygen, superoxide, hydroxyl radical, and hypochlorous acid. In this setting, several mechanisms could account for a link between vitamin C and heart disease. One is the relation between LDL oxidation and vitamins C and E. Vitamin C in vitro can recycle vitamin E, which can donate electrons to prevent LDL oxidation in vitro. As the lipid-phase vitamin E is oxidized, it can be regenerated by aqueous vitamin C (5). Other possibilities are that vitamin C could decrease cholesterol by mechanisms not well characterized, or could improve vasodilation and vascular reactivity, perhaps by decreasing the interactions of nitric oxide with oxidants (6, 7).

Although basic mechanisms support a role of vitamin C in heart disease, clinical data are less encouraging. Epidemiologic studies are inconsistent regarding vitamin C and coronary disease (4). Large doses of vitamin C induce vasodilatation in the brachial and coronary arteries (6, 7), but whether this has any bearing on such actions at physiologic concentrations of vitamin C found in patients with coronary artery disease is not known. A high dietary intake of vitamin C might reflect a healthy diet, or perhaps a healthy lifestyle. It is therefore uncertain whether the effects of vitamin C can be discerned clearly by epidemiologic studies alone.

In this context the goal of Riemersma et al (8) was to determine whether low plasma vitamin C concentrations conferred a risk of acute myocardial infarction. This Scottish study showed clearly that patients with acute myocardial infarction had lower plasma vitamin C concentrations than did control subjects, but not at recovery. These authors concluded that recovery concentrations reflected prehospitalization concentrations, and thus that subjects with low vitamin C concentrations did not have an increased risk of infarction. Other interpretations, however, are possible. The vitamin C concentrations in control subjects and in patients were relatively low compared with those of other populations. The assay used may overestimate vitamin C, so that the true concentrations may have been lower than reported (9).

To learn definitively whether vitamin C concentration affects risk, subjects with high concentrations would have to be compared with those with low concentrations immediately before and at the time of myocardial infarction. Prior experiments showed that when plasma concentrations of vitamin C are plotted against oral doses, the result is a sigmoidal relation, and the steep part of the curve corresponds to doses between 30 and 100 mg/d (10). Patients enrolled in the Scottish study had vitamin C intakes in this range. Thus, a small change in intake can produce a large change in plasma concentrations. Some patients did increase their vitamin C intakes after infarction, and this could have accounted for the observed postinfarction vitamin C concentrations. Therefore, we cannot be sure that vitamin C concentrations postinfarction are representative of those before infarction.

Despite these uncertainties, it is evident that patients with acute myocardial infarction have substantially lower plasma vitamin C concentrations than do control subjects (1, 2, 8). Why, and are there clinical consequences? One possibility is that vitamin C concentrations in the pre- or periinfarction period show a real decline, perhaps as a consequence of oxidative events associated with thrombosis, vascular spasm, or ischemia. In this case, we should determine whether preventing a fall in vitamin C concentration changes incidence, outcomes, or both. For example, related data suggest that only very low plasma vitamin C concentrations increase the likelihood that these events will occur (11). Another possibility is that vitamin C concentrations truly decline but are a consequence of redistribution of body stores or of altered renal excretion. In this case, it is uncertain whether maintenance of preinfarction concentrations would affect outcome. Still another possibility is that vitamin C declines in the test tube, but not in the person. Ascorbic acid is easily oxidized, and oxida-

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tion ex vivo would substantially reduce the true value. This is of even more concern in patients who are under oxidative stress, and it is possible that plasma components (i.e., oxidants) in the peri infarction period could render vitamin C less stable in processed plasma samples. If this were true, it would be essential to account for artifactual oxidation before planning other studies.

On the basis of mechanistic, physiologic, and epidemiologic studies, we have not resolved whether vitamin C has beneficial effects in coronary artery disease. Properly designed interventional studies can test this hypothesis. Before proceeding, we should be sure that the relation between myocardial infarction and low vitamin C concentrations is real. We must address measurement issues so that artifacts are eliminated. Accurate measurement, then, is the heart of the matter. To resolve the vexatious issue of peripatetic heavenly bodies, Galileo put his faith in accurate measurements and said, “Measure what is measurable, and make measurable what is not so.” We should remember Galileo’s words but temper them with the analysts’ reminder: “Vitamin C... is it there just like they say, or has it oxidized away...?”(12)

REFERENCES