EDITORIAL COMMENT

Vitamin C and Percutaneous Coronary Intervention*

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Percutaneous coronary intervention (PCI) is associated with a 15% to 35% incidence of periprocedural myocardial injury (PMI). Its spectrum ranges from obvious clinical myocardial infarction to subtle myocardial injury manifested by mild rises in cardiac enzymes. Even in the latter case, the resulting myocardial damage is clinically important, as multiple studies have consistently demonstrated that PMI is associated with increased long-term mortality with a graded risk related to the extent of creatine kinase-MB or cardiac troponin elevation. Despite extensive basic and clinical research and multiple therapeutic approaches, its incidence has not substantially decreased over the last 2 decades. Two patterns of PMI have been recognized by magnetic resonance imaging. Type I is near the intervention site consequent to side branch occlusion, and type II is in the downstream territory of the treated artery where perfusion is compromised mainly due to structural and functional microvascular dysfunction (1). PCI can be considered as an iatrogenic form of plaque rupture. It magnifies underlying or pre-existing microvascular disorders. It is thus not surprising that patients with pre-procedural abnormal coronary flow (2), high cardiovascular risk profiles, or high systemic inflammation markers, such as high sensitivity C-reactive protein, are most likely to have PMI and worse long-term outcomes (3).

Mechanisms of reduced microvascular perfusion after PCI are incompletely understood. Mechanical obstruction of the microvasculature due to plaque-derived emboli has been recognized in autopsy studies as a component of this syndrome (4). These microvascular plugs are formed by atheromatous debris, cholesterol clefts, apoptotic bodies, microparticles, platelets, neutrophils, sludge, or thrombus. However, the use of distal protection devices, anticoagulation, and powerful glycoprotein IIb/IIIa inhibitors does not fully prevent PMI, suggesting that the intricate interplay of other important mechanisms might be responsible for the mismatch between myocardial oxygen supply and demand. These include abnormal vasoreactivity, coagulation, inflammation, immunologic stimulation, neurohumoral activation, and oxidative stress (1). The acute trigger of these mechanisms is putatively linked to the downstream effect of biologically active molecules in the setting of an already compromised baseline microcirculatory function. Thus, numerous studies have demonstrated abnormal vasoreactivity in atherosclerosis characterized by impaired coronary blood flow in response to endothelium-dependent vasodilators. The presence of endothelial dysfunction as assessed by measurement of coronary flow reserve or by forearm blood flow studies is a strong predictor of future cardiovascular events (5). Increased oxidative stress via its ability to reduce nitric oxide bioavailability plays a crucial role in endothelial dysfunction and has been proposed to contribute to mechanisms of PMI.

PCI has been associated with an increase in oxidative stress as assessed by elevated coronary or systemic venous levels of F_2-isoprostane (6). The F_2-isoprostane family, and notably 8-iso-prostaglandin $F_{2\text{-alpha}}$ (8-iso-$PGF_{2\text{alpha}}$), are prostaglandin isomers formed by free radical–mediated oxidation of arachidonic acid in the membranes' phospholipids. Although they have inherent vasoconstrictor effects and are elevated after PCI, their role in PMI is unclear. In animal models of infarction/reperfusion inhibition of isoprostane $F_{2\text{alpha}}$ III failed to improve reflow (7). However, increased concentrations of circulating F_2-isoprostanes have been associated with coronary calcification (8) or markers of inflammation and endothelial dysfunction in young healthy adults in the CARDIA (Coronary Artery Risk Development in Young Adults) study (9). Thus, there is evidence that levels of isoprostane F_2 reflect overall redox status.

In this regard, the findings of Basili et al. (10), in this issue of *JACC: Cardiovascular Interventions*, that intravenous ascorbic acid (vitamin C) infusion improves myocardial perfusion grade during elective PCI are noteworthy. Their working hypothesis is that vitamin C, by quenching free radicals, decreases myocardial oxidative stress and improves myocardial microcirculation. In this prospective placebo-controlled study, patients with stable angina and de novo 1-vessel disease were assigned to receive 1 g of ascorbic acid or placebo before PCI. Markers of oxidative stress that were measured in venous blood before and after the procedure included 8-iso-$PGF_{2\text{alpha}}$ and 8-hydroxy-2-deoxyguanosine (8-OHdG), a product of hydroxyl radical–deoxyribonucleic acid interaction (11). The corrected Thrombolysis In Myocardial Infarction (TIMI) frame count, when compared with baseline values, as expected, improved in both arms after coronary revascularization. However, this improvement was significantly better in the vitamin C group with more individuals in the treatment

group achieving lower-risk corrected TIMI frame count class (p < 0.0001). Similarly, microvascular perfusion as assessed by TIMI myocardial perfusion grade improved to a greater extent in the treated group. Thus, 79% of individuals receiving vitamin C reached TIMI myocardial perfusion grade III versus 39% in controls. This improvement correlated with reduced oxidative stress markers, whereas, in the placebo group, these were significantly higher than baseline. Even though the increase in cardiac troponin levels was the same in control subjects and treated patients, the data suggest that vitamin C improved microcirculatory function, potentially via its antioxidant effects. It is of note that the half-life of parenteral vitamin C is short, and one can speculate about whether continued vitamin C administration during PCI would have produced an improved effect.

Basili et al. (10) correctly point out that decreased F_2-isoprostanes can only putatively be linked to decreased myocardial oxidative stress. Furthermore, the potential role of reduced oxidative stress in the vitamin C induced improvement in TIMI myocardial perfusion grade cannot be established from this study. Quantitative measurements of reactive oxygen species and reactive nitrogen species are difficult in vivo and decreases of these lipid peroxidation end products may not reflect actual decreases in free radical generation. It is of note that Guan et al. (12) did not find a reduction in urinary 8-epi-PG_{alpha} levels after PCI in patients with acute myocardial infarction after infusion of 2 g of vitamin C. It is also relevant to note that despite increasing evidence for the association between increased oxidative stress and cardiovascular disease (13), the results of clinical trials of antioxidant therapy such as vitamin C have been mixed to negative (14). One potential explanation for these results is that scavenger activity of vitamin C is dependent on serum concentrations of 1 to 10 mmol/l or higher (15), which are not achieved with chronic administration. Furthermore, vitamin C has been reported to have paradoxical pro-oxidant effects (16).

The association of F_2-isoprostane levels and cardiovascular outcomes is also not straightforward. Thus, in a setting of patients undergoing elective PCI, Berg et al. (17) did not find any correlation between 8-iso-PGF_{2alpha} and post-PCI myocardial injury as defined by troponin release. Chronic administration of alpha-tocopherol (vitamin E) to individuals with coronary artery disease decreased inflammatory parameters such as high sensitivity C-reactive protein and reduced indices of oxidant stress such as urinary F_2-isoprostanes but failed to alter carotid intimal media thickness or cardiovascular events over 2 years (18). Similarly, vitamin C and E therapy reduced F_2-isoprostanes in high-risk individuals but failed to alter oxidized low-density lipoproteins or autoantibodies to oxidized low-density lipoproteins, or to improve endothelial vasomotor function over 6 months (19). On the contrary, omega-3 infusion in an animal model of cardiac ischemia-reperfusion injury

significantly reduced infarct size, and this correlated with a marked reduction in serum markers of oxidative stress, namely 8-isoprostanes (20). Furthermore, compared with placebo, oral administration of an inhibitor of xanthine oxidase, allopurinol, to patients with acute myocardial infarction undergoing PCI was also associated with reduced urinary 8-epi-PGF_{2alpha} with less coronary flow perturbation and improved left ventricular ejection fraction at 6 months (21). This latter study suggested that inhibiting the generation of oxygen-derived radicals during reperfusion therapy is beneficial to left ventricular function.

In summary, published data on potential beneficial effects of antioxidants on PMI are sparse and mixed. At the least, the interesting study of Basili et al. (10) is hypothesis-generating and will provide a rationale to further test the effect of antioxidants in the setting of coronary revascularization procedures.

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