Postprandial Microvascular Dysfunction

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Endothelial cells play diverse biological roles, such as maintaining vascular tone and structure, regulating intravascular hemostasis, permeability, tissue repair, cell adhesion and migration. Recent progress in vascular biology has revealed that the endothelium releases a large number of vasoactive substances, which can be divided into 2 classes: endothelium-derived relaxing factors (EDRFs), and endothelium-derived contracting factors (EDCFs). It has been shown that EDRFs, such as nitric oxide (NO), protect the vasculature from atherogenic insults, whereas EDCFs, such as endothelin, have the opposite effect and participate in the progression of cardiovascular diseases. Exposure to coronary risk factors decreases the bioactivity of EDRFs and increases the release of EDCFs. Endothelial dysfunction caused by an imbalance between EDRFs and EDCFs precedes and promotes atherosclerosis by several mechanisms, such as adhesion of monocytes and platelets, increased vascular permeability, and the proliferation and migration of smooth muscle cells. These processes result in plaque formation and intimal thickening. Thus, coronary risk factors impair the bioactivity of NO derived from endothelium and increase the release of EDCFs. Endothelial dysfunction, superoxide anion is reduced to hydrogen peroxide. Reactive oxygen species (ROS) have detrimental effects on vascular function through several mechanisms. First, as a direct effect, ROS, especially hydroxyl radicals, injure cell membranes and nuclei. Second, by interacting with endogenous vasoactive mediators formed in endothelial cells, ROS modulate vasomotion and atherogenic processes. For instance, superoxide anions rapidly react with endothelium-derived NO and inactivate its effects. In addition, ROS oxidize lipid components, leading to formation of oxidized low-density lipoprotein (LDL), which is a key mediator of atherosclerosis. Oxidized LDL is not only incorporated into macrophages, leading to the formation of foam cells, but also stimulates production of cytokines from vascular tissues. These cytokines induce phenotypic changes of vascular smooth muscles cells and stimulate monocyte migration and platelet activation. Like hydroxyl radicals, oxidized LDL is also directly cytotoxic to vascular cells, thus promoting the release of lipids and lysosomal enzymes that further aggravate tissue injury. Indeed, it has been previously reported that acute removal of oxidized LDL by a single session of apheresis restored endothelial function in patients with familial hypercholesterolemia. In addition, oxidative stress stimulates synthesis of alternative risk factors of atherosclerosis, such as homocyst(e)ine and an endogenous inhibitor of NO synthase. Collectively, oxidative stress induced by ROS and their reactants may impair the biological activities of endothelium-derived NO, leading to progression of atherosclerosis.

As the frontline of systemic homeostasis, the endothelium has a highly flexible nature against dynamic changes in hemodynamics and cellular/humoral factors. Endothelial function alters beat-by-beat in the cardiac cycle, and diurnal variation has been reported. During daily activities, a number of vascular stresses, such as emotional agitation or vigorous exercise, also impair endothelial function. Of these, the Western diet has been advocated as a most tough villain against endothelial health because of the concept that repeated exposure to high-fat meals per se may damage the endothelial cells, hence promoting atherosclerosis. This issue, “postprandial endothelial dysfunction” has been a major topic in the field of clinical research for a decade. In 1997, Vogel and his colleagues has demonstrated that flow-mediated vasodilation (FMD) was transiently impaired after loading healthy volunteers with a single high-fat meal (ie, “big Mac”), and was restored by pretreatment with antioxidant vitamins. High-fat meals cause transient hypertriacylglyceridemia and hyperglycemia, leading to inflammation and oxidative stress, especially in the process of digestion and absorption of oxidized fat. Methionine-rich meat may also induce transient hyperhomocysteinemia during which in vivo exfoliation of endothelial cells has been experimentally reported. It has been previously demonstrated that endothelial dysfunction induced by transient hyperhomocysteinemia was restored by co-administration of folic acid. Thus, it has been suggested that antioxidant vitamins may reduce cardiovascular events by amelioration of postprandial endothelial dysfunction, although several large clinical trials failed to demonstrate beneficial effects of supplemental vitamins.

Three-hydroxyl-3-methylglutanyl coenzyme A reductase inhibitors (statins) significantly decrease the cardiovascular mortality associated with hypercholesterolemia. In vitro studies have shown that statins inhibit leukocyte rolling/
adhesion and stabilize endothelial NO synthase post-translationaly. A randomized clinical trial showed that fluvastatin, but not colestimide, restored endothelium-dependent vasodilation and diminished LDL oxidation and leukocyte activity, indicating that statins protect the endothelium through pleiotropic antioxidant/antiinflammatory activities. In this issue of the Journal, Arao et al report the effects of a lipid-lowering agent, pitavastatin, on postprandial vascular assaults, such as oxidative stress or vascular dysfunction in patients with coronary artery diseases (CAD). Both the baseline and postprandial postischemic hyperemic responses of forearm blood flow were deceased in the CAD patients. Six months of pitavastatin therapy improved the lipid profile and reactive hyperemia (RH), increased the adiponectin levels and lowered those of urinary 8-OHdG, a marker of oxidative stress. Post-ischemic RH is not only determined by the microvascular structure but is also associated with the combined effects of flow- and ischemia-induced vasodilators, such as NO, adenosine, and endothelium-derived hyperpolarizing factor, as well as the local myogenic response. Accordingly, RH likely provides an integrated measure of vascular function that is not confined to endothelium-derived products. Recent data from the Framingham study revealed that RH was more strongly related to cardiovascular risk factors in that population than was FMD, which has been advocated as a clinical index of endothelial function. Thus, it is possible that statin may restore global microvascular dysfunction, including endothelium-independent smooth muscle cell dysfunction, by inhibiting the oxidative stress experienced after a high-fat meal.

The concept of meal-associated vascular dysfunction sounds unique and interesting, but an important issue needs to be solved; that is, whether postprandial endothelial dysfunction predicts, or whether intervention in this process improves, future cardiovascular events. Because the content of meals varies day by day, any long-term prospective protocols may not be feasible and large cohort studies seem to be incompetent on this issue. At the present time, vascular function tests, such as RH or FMD, have been applied in 3 areas: (1) clinical trials examining the effect of interventions, (2) health check-up program for asymptomatic subjects, and (3) clinical utilities for outpatient care, or pre-operative risk assessment in the vascular laboratory. Further clinical application of vascular function test as surrogate markers, which may translate early vascular insults into long-term cardiovascular outcomes, are highly warranted.

References
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