disease. This could impact the PCI group as compared to the bypass surgery group, which would have vascular conduits bypassing large areas of potentially obstructable diseased coronary arteries.[11] This suggests that drug-eluting stents alone may not be sufficient in reducing events during follow-up.

Revascularization with either bypass surgery or angioplasty in diabetic patients is associated with a less favorable outcome. Whether early intervention would be of value will be assessed in the ongoing BARI 2D Trial. However, it remains to be determined whether the widespread use of glycoprotein IIb/IIIa drugs in diabetic patients receiving stents and possibly drug-eluting stents will significantly alter results so that outcomes become similar to those receiving bypass surgery. For the present, it seems prudent not only to consider bypass surgery with LIMA grafting in diabetic patients with severe multivessel disease, but also to consider angioplasty in selected patients who have more discrete and less severe disease. ■

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Angina

Folate Treatment to Prevent Nitrate Tolerance

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Long-acting nitrates have been used for the treatment of angina and congestive heart failure for decades. Clinicians are well aware that the major limitation of long-term therapy using nitroglycerin is nitrate tolerance. Nitrate tolerance is defined as the tachyphylactic response when nitrate is used in a chronic fashion without a nitrate-free period. This tolerance is manifested as the loss of the blood pressure–lowering effect as well as the heart rate–raising response. Systemic venous vasodilatory effect is attenuated markedly after 48 hours of continuous nitrate infusion. It has been well demonstrated that after prolonged continuous nitrate use, the clinical effectiveness against angina pectoris is lost.

To avoid nitrate tolerance, patients are instructed to build in a nitrate-free period during their chronic therapy. Long-acting mononitrates are given in a once-a-day or in an asymmetric b.i.d. fashion; nitrate patch is applied to the skin for 12 hours and then removed for 12 hours. The provision of this nitrate-free interval seems to attenuate the nitrate tolerance. Other methods for reducing nitrate tolerance include the use of diuretics or angiotensin-converting enzyme inhibitors to counter fluid retention and depletion of thiols (-SH) groups. Often nitrate dosage has to be increased over time, especially when nitrate is given in a continuous intravenous fashion. However, despite these maneuvers nitrate tolerance continues to counter the actions of the organic nitrates and reduce the efficacy and compliance of this class of drug.

The mechanisms of nitrate tolerance have been studied by a variety of investigators for some time and include the depletion of thiols, an increase in venous blood volume limiting vasodilator response, and increased generation of reactive oxygen species. Evidence is mounting that nitrate tolerance is associated with an increase in production of superoxide anion in the vascular wall. The sources of these superoxides include membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase as well

as endothelial nitric oxide synthase (eNOS) itself; the latter is crucial in the production of nitric oxide (NO), which is the endogenous endothelial dependent vasodilator. The switch of eNOS from the production of NO to superoxides reduces the production of NO. Superoxides generated by the organic nitrates also inactivate both the nitrate-derived NO as well as the endothelium-derived NO, reducing the bioavailability of NO.

How do organic nitrates induce production of super-oxides? The mechanisms are complex and involve the redox state of thiols in the vascular smooth muscle or platelets. In simplified terms, organic nitrates need to go through reductive denitrification for these drugs to be active. In this reductive process, NADPH and tetrohydro-biopterin are depleted. These are essential cofactors for eNOS, leading eNOS to produce reactive oxygen species instead of NO.

Folic Acid Prevents Nitroglycerin-Induced Nitric Oxide Synthase Dysfunction and Nitrate Tolerance: A Human In Vivo Study

Gori T, Burstein JM, Ahmed S, et al.
Circulation. 2001:104:1119–1123.

In this article, Gori et al showed that folic acid supplementation (10 mg once daily) can prevent nitroglycerin-induced tolerance. Eighteen healthy volunteers were randomized to either folic acid or placebo for 1 week while receiving continuous transdermal nitroglycerin. Three hours after nitroglycerin administration, both groups of subjects manifested a decrease in blood pressure and a rise in

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The observation that this simple intervention with folate improves endothelial function and prevents nitrate tolerance has great clinical implications.

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heart rate. On visit 2 after 6 days of continuous nitrate treatment, systolic blood pressure and heart rate returned back to baseline in the placebo group but not in the folate group. The blood flow responses to acetylcholine in the forearm were significantly blunted in the placebo group (123% vs 583%) as well as to nitroglycerin (93% vs 183%). This suggested chronic nitrate therapy impairs vascular responses to endothelium-dependent and -independent vasodilators and that these responses can be normalized by folate therapy.

The mechanisms of how folate restores endothelial function are not clear. Folic acid possesses antioxidant

properties and can reduce superoxide production from xanthine oxidase. One potential mechanism is also that folate enhances the enzymatic regeneration of tetrahydro-biopterin, thus enhancing the production of NO.

Whatever the precise mechanism, the observation that this simple intervention with folate improves endothelial function and prevents nitrate tolerance has great clinical implications. It implies that patients with angina can enhance the effectiveness of nitrate therapy with folate supplementation. Patients with unstable angina treated with intravenous nitrates can also prevent tachyphylaxis by being given supplementary folates. Whether this is clinically effective in patients with coronary artery disease remains to be determined, but the outlook is certainly promising.

Atherosclerosis

Triglycerides and Coronary Atherosclerosis: Implications for Treatment of Mixed Dyslipidemias

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The goals of medical treatment of patients with mixed dyslipidemias remain controversial. Whether therapy should focus solely on reduction of low-density lipoprotein (LDL-C) or consideration given to raising levels of high-density lipoprotein (HDL-C), reducing triglyceride levels or converting the small dense LDL-C to the less atherogenic large LDL-C particle remains controversial. This issue becomes more important in the context of treating patients with diabetes, a disease whose prevalence is increasing at near epidemic proportions. It is common for the diabetic patient to present with the mixed picture of elevated small dense particle LDL-C, triglycerides, and low HDL-C levels. A review of two selected journal articles will deal with the importance of triglycerides as a risk factor for coronary artery disease and the difference between the effects of the statin atorvastatin and the fibric acid derivative fenofi-