Prevention of Myocardial Stunning During Percutaneous Coronary Interventions

Novel Insights From Pre-Treatment With Glucagon-Like Peptide-1*

Brigitta C. Brott, MD

Patients undergoing high-risk percutaneous coronary interventions (PCIs) are at increased hazard of persistent hypotension and left ventricular (LV) dysfunction as a result of myocardial stunning. With the development of stunning, support devices and inotropes are frequently called upon to support the patient during and after procedures. Myocardial stunning is defined as the persistence of LV dysfunction after ischemia, in the absence of irreversible damage (1). Its duration is variable, but it often persists beyond 30 min, and repeated balloon occlusions prompt additional LV dysfunction (2). The mechanism of this persistent dysfunction is not known; proposed mechanisms include generation of oxygen-derived free radicals (3) or calcium overload (4). To date, no medications have proven effective in preventing this transient but potentially serious deterioration in function.

The discovery that glucagon-like peptide-1 (GLP-1) provides myocardial protection has generated significant scientific interest. GLP-1 is a 30 amino acid peptide produced in the intestinal epithelium in response to food intake (5). It is rapidly metabolized by dipeptidyl peptidase-IV (DPP-4) to its primary metabolite GLP-1(9-36), and the half-life of GLP-1 in plasma is 2 to 3 min (6). The primary action of GLP-1 is to stimulate insulin secretion and inhibit glucagon secretion, and it appears to regulate appetite and food intake (5). In addition to pancreatic islets, the GLP-1 receptor has been identified in the brain, peripheral nervous system, intestinal tract, lung, kidney, and heart (7). Two widely used classes of type II diabetes therapies are degradation-resistant GLP-1 agonists and DPP-4 inhibitors (8).

Animal and human studies suggest cardioprotective effects of GLP-1 infusion and with GLP-1 analogue and DPP-4 inhibitor administration. Proposed cardiovascular effects include protection from ischemia reperfusion injury, improved LV function in dilated cardiomyopathy, myocardial arterial vasodilation, improved glucose metabolism, reduced blood pressure, reduction in atherosclerotic lesions, and anti-inflammatory effects (9,10). Importantly, the GLP-1 receptor appears to play a direct role in enhanced cardiomyocyte survival in ischemia reperfusion injury via the reperfusion injury survival kinase pathway (9).

Myocardial metabolism is a complex process and varies depending on level of stress and availability of the substrates glucose and free fatty acids (FFA) (11). During stress, the myocardium shifts toward glucose metabolism (12). The mechanisms by which GLP-1, its degradation-resistant analogues, and DPP-4 inhibitors provide cardioprotection are not completely understood, although at least some of this effect is thought to be via the GLP-1 receptor associated with increased myocardial glucose uptake (12). Recent data in a mouse model suggests 2 different GLP-1 dependent pathways of myocardial protection (13). A GLP-1 receptor-dependent mechanism provides an inotropic effect, increased glucose uptake, and ischemic pre-conditioning. There appears to be a GLP-1 receptor-independent effect as well, which may involve ischemic pre-conditioning and vasodilation. The primary metabolite of GLP-1, GLP-1(9-36), was

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previously thought to be inactive. However, more recent evidence points to an additional cardiac protective effect (9), including vasodilation through a nitric oxide–dependent mechanism and cardioprotection from ischemia reperfusion injury (9,13). How GLP-1(9–36) exerts its effects is not clear, because a specific receptor for GLP-1(9–36) has not yet been identified.

Clinical studies have demonstrated cardio-protective effects with GLP-1 in a number of settings. There is evidence for greater myocardial salvage in the setting of ST-segment elevation myocardial infarction (14,15). DPP-4 inhibition or GLP-1 infusion improves LV function during dobutamine stress echocardiography in patients with coronary artery disease (16-18). In the setting of PCI, GLP-1 infusion started after balloon occlusion provides improved LV function and mitigates myocardial stunning (19).

Unanswered questions in the published studies include: what are the settings in which GLP-1 administration is cardioprotective? Are the myocardial effects mediated via the GLP-1 receptor and glucose metabolism, or are there other pathways? In the setting of myocardial ischemia and cardiac stunning during PCI, is GLP-1 protective given in advance or does it work via ischemic pre-conditioning/antiapoptotic mechanisms and, therefore, only after the initiation of ischemia?

In this issue of JACC: Cardiovascular Interventions, McCormick et al. (20) set up an elegant clinical trial to assess whether GLP-1 administration prior to balloon occlusion mitigates stunning at 30 min. The investigators measured pressure volume loops in patients with LAD lesions and normal LV function. Twenty patients were randomized to control versus GLP-1 infusion initiated prior to balloon occlusion. Those who received saline control developed a decrease in LV function during ischemia that persisted at 30 min. However, in those who received GLP-1 infusion, there was no decrease in LV function at either time point. Pressure-volume loops revealed reduced LV systolic function and impaired LV relaxation (Tau) with control infusion during balloon occlusion, which largely persisted at 30 min, consistent with stunning. With GLP-1 infusion, all LV function parameters were not impaired and remained at baseline, indicating a prevention of stunning. Administration of GLP-1 led to anticipated changes in systemic metabolic parameters. However, the investigators also obtained blood samples from the coronary arteries and the coronary sinus to look at glucose and FFA extraction by the heart. Surprisingly, there was no difference in the amount of glucose or FFA extracted by the heart after GLP-1 or control administration, indicating that the cardioprotective effect was independent of glucose uptake by the heart.

These findings demonstrate that there may be an additional myocardial metabolic pathway beyond glucose metabolism by which LV function can be protected from stunning in the setting of PCI. Although this cardiac protection could be the result of protection from ischemia reperfusion injury, this is unlikely because this injury response is not initiated until after balloon occlusion. This is a small study of 20 patients, but it provides important clues to the existence of an alternative metabolic pathway for GLP-1 effects. This could eventually lead to the development of new therapies for the prevention of myocardial stunning. What is not known from this study is whether this protection is a direct effect of GLP-1 or its metabolite GLP-1(9–36), or if degradation-resistant GLP-1 receptor agonists or DPP-4 inhibitors would have a similar effect.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Brigitta C. Brott, Interventional Cardiology, FOT 907, 1720 2nd Avenue South, University of Alabama at Birmingham, Birmingham, Alabama 35294-3409. E-mail: bbrrott@uabmc.edu.

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