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Pre-Treatment With Glucagon-Like Peptide-1 Protects Against Ischemic Left Ventricular Dysfunction and Stunning Without a Detected Difference in Myocardial Substrate Utilization

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ABSTRACT

OBJECTIVES This study sought to determine whether pre-treatment with intravenous glucagon-like peptide-1 (GLP-1)(7-36) amide could alter myocardial glucose use and protect the heart against ischemic left ventricular (LV) dysfunction during percutaneous coronary intervention.

BACKGROUND GLP-1 has been shown to have favorable cardioprotective effects, but its mechanisms of action remain unclear.

METHODS Twenty patients with preserved LV function and single-vessel left anterior descending coronary artery disease undergoing elective percutaneous coronary intervention were studied. A conductance catheter was placed into the LV, and pressure-volume loops were recorded at baseline, during 1-min low-pressure balloon occlusion (BO), and at 30-min recovery. Patients were randomized to receive an infusion of either GLP-1(7-36) amide at 1.2 pmol/kg/min or saline immediately after baseline measurements. Simultaneous coronary artery and coronary sinus blood sampling was performed at baseline and after BO to assess transmyocardial glucose concentration gradients.

RESULTS BO caused both ischemic LV dysfunction and stunning in the control group but not in the GLP-1 group. Compared with control subjects, the GLP-1 group had a smaller reduction in LV performance during BO (delta dP/dT_{max}, -4.3 vs. -19.0%, $p = 0.02$; delta stroke volume, -7.8 vs. -26.4%, $p = 0.05$), and improved LV performance at 30-min recovery. There was no difference in transmyocardial glucose concentration gradients between the 2 groups.

CONCLUSIONS Pre-treatment with GLP-1(7-36) amide protects the heart against ischemic LV dysfunction and improves the recovery of function during reperfusion. This occurs without a detected change in myocardial glucose extraction and may indicate a mechanism of action independent of an effect on cardiac substrate use. (Effect of Glucgon-Like-Peptide-1 [GLP-1] on Left Ventricular Function During Percutaneous Coronary Intervention [PCI]; ISRCTN77442023) (J Am Coll Cardiol Intv 2015;8:292-301) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Glucagon-like peptide-1 (GLP-1) is an incretin hormone, which regulates carbohydrate metabolism (1). As well as its effects on glucose homeostasis, the identification of GLP-1 binding sites in the heart has generated strong interest in a potential role on cardiovascular function (2). In animal models, GLP-1 attenuates ischemia-reperfusion injury (3-6), and clinical studies investigating the

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potential effects of GLP-1 modulation therapy are starting to emerge (7–12). However, there is uncertainty regarding its mechanisms of action.

The cardioprotective properties of GLP-1 are attractive as a potential therapeutic adjunct to support the heart during the multiple episodes of supply ischemia that occur with balloon inflations during percutaneous coronary intervention (PCI). We have previously used conductance catheter-derived pressure-volume loops to quantify left ventricular (LV) function during PCI, and we have demonstrated that 1-min coronary balloon occlusion (BO) results in late post-ischemic myocardial dysfunction (stunning), with further BO after 30 min resulting in cumulative LV dysfunction (13). This may be particularly important in patients with pre-existing LV impairment and in those with proximal coronary lesions subtending large territories of myocardium.

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In 1 of the few physiological studies investigating the cardioprotective efficacy of GLP-1 during supply ischemia in humans, we demonstrated that an intravenous infusion of GLP-1(7-36) amide, when commenced after an initial 1-min coronary BO, reduced ischemic LV dysfunction caused by subsequent BO, and mitigated myocardial stunning (9). However, it is not known whether these favorable cardiovascular effects are dependent on the activation of ischemic pre-conditioning pathways, or whether they are the result of a change in myocardial substrate use. This study was therefore undertaken to provide some mechanistic insights into the cardioprotective properties of GLP-1. Specifically, we sought to determine whether pre-treatment with intravenous GLP-1(7-36) amide, commenced before an ischemic insult, protected the heart during PCI and whether there were changes in the myocardial use of glucose and free fatty acids (FFA).

METHODS

STUDY POPULATION. Patients with preserved LV function (defined as an ejection fraction ≥50% by transthoracic echocardiography) and single-vessel disease awaiting PCI to the left anterior descending artery were invited to participate. Exclusion criteria included a history of myocardial infarction (as defined by the Third Universal Definition of Myocardial Infarction) (14) within the preceding 3 months, and patients with diabetes receiving insulin, dipeptidyl-peptidase 4 inhibitors, or GLP-1 receptor agonists. The study was approved by the local ethics committee (REC number 09/H0311/17) and complied with the guidelines set out in the Declaration of Helsinki. All participants gave written informed consent. The trial number was ISRCTN77442023.

PRE-STUDY PROTOCOL. Patients were asked to abstain from consuming caffeine, alcohol, nicotine, as well as nicorandil and oral/sublingual nitrates in the 24 h leading up to the procedure. No other cardiovascular medications were omitted. All subjects fasted for 6 h and received aspirin 300 mg and clopidogrel 300 mg at least 6 h before PCI.

CARDIAC CATHETERIZATION. One 7-F sheath was placed in the right femoral artery, 1 6-F sheath in the right femoral vein, and another 6-F sheath in either the right radial or left femoral artery. All patients were anticoagulated with heparin (70 to 100 U/kg as an initial bolus) and the activated coagulation time maintained >250 s throughout the procedure (**Figure 1**). Simultaneous coronary artery (CA) and coronary sinus (CS) blood samples were taken via a 6-F guide catheter positioned at the ostium of the left main coronary artery and a 6-F multipurpose or Amplatz Left 1 catheter (Johnson & Johnson Medical, Diegum, Belgium) positioned inside the ostium of the CS using fluoroscopic imaging. In all cases, selective engagement of the main CS trunk was verified using retrograde contrast injection and confirmed by measuring oxygen saturations sampled from the catheter to ensure minimal contamination by right atrial blood. No hemodynamic-altering medication was administered during the study. The conductance catheter technique was used to determine pressure-volume relations and provide a beat-to-beat assessment of LV performance. A 7-F 8-electrode conductance catheter (Millar Instruments, Houston, Texas) was inserted through the 7-F arterial sheath, advanced across the aortic valve into the LV apex, and placed along the longitudinal axis of the ventricle. The catheter was connected to a MPVS Ultra signal-conditioning unit (Millar Instruments) in series with an ADInstruments PowerLab 16/30 Series sixteen channel amplifier (ADInstruments, New South Wales, Australia). After measuring blood resistivity, the catheter tip was submersed in a saline bath and the pressure transducer was zeroed.

CONDUCTANCE CATHETER CALIBRATION. A 20-kHz current was applied to the proximal and distal electrodes and time-varying conductance (G^t) was calculated by measuring the sum of the conductance between the intervening 5 adjacent segments of the 6 central electrodes. G measured by the conductance

ABBREVIATIONS AND ACRONYMS

BL = baseline
BO = balloon occlusion
CA = coronary artery
CO = cardiac output
CS = coronary sinus
EF = ejection fraction
FFA = free fatty acids
GLP-1 = glucagon-like peptide-1
LV = left ventricular
MGU = myocardial glucose uptake
PCI = percutaneous coronary intervention
SV = stroke volume