A Pilot Study to Assess Whether Glucagon-Like Peptide-1 Protects the Heart From Ischemic Dysfunction and Attenuates Stunning After Coronary Balloon Occlusion in Humans

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Background—The incretin hormone glucagon-like peptide-1 (GLP-1) has been shown to have cardioprotective properties in animal models of ischemia and infarction due to promotion of myocardial glucose uptake and suppression of apoptosis. We investigated whether GLP-1 protected the heart from dysfunction caused by supply ischemia during percutaneous coronary intervention (PCI).

Methods and Results—Twenty patients with normal left ventricular (LV) function and single-vessel coronary disease within the left anterior descending artery undergoing elective PCI were studied. A conductance catheter was placed into the LV through the femoral artery, and pressure-volume loops were recorded at baseline and during a 1-minute low-pressure balloon occlusion at the site of the stenosis. The patients were randomized to receive an infusion of either GLP-1(7–36) amide at 1.2 pmol/kg per minute or saline immediately after the first balloon occlusion. Coronary balloon occlusion caused LV stunning in the control group with cumulative LV dysfunction on subsequent occlusion that was not seen in the GLP-1 group. GLP-1 improved recovery of LV systolic and diastolic function at 30 minutes after balloon occlusion compared with control (delta dP/dtmax from baseline, 1.6% versus 12.2%; P=0.02) and reduced the LV dysfunction after the second balloon occlusion (delta dP/dtmax, −13.1% versus −25.3%; P=0.01).

Conclusions—In this pilot study, infusion of GLP-1 has been demonstrated to reduce ischemic LV dysfunction after supply ischemia during coronary balloon occlusion in humans and mitigates stunning. The findings require confirmation in a larger scale clinical trial.

Clinical Trial Registration—URL: http://www.isrctn.org. Unique identifier: ISRCTN 77442023.

Key Words: glucagon-like peptide-1 ■ angioplasty ■ myocardial ischemia ■ myocardial stunning

The incretin hormone glucagon-like peptide-1 (GLP-1) has been shown to have cardioprotective properties in animal models of ischemia and infarction.1–3 The pharmacological properties of GLP-1 are attractive because the effects of GLP-1 on the pancreas depend on the prevailing plasma glucose level, which minimizes the risk of hypoglycemia and obviates the need for the intensive monitoring and concomitant glucose infusion that was an important factor limiting metabolic manipulation with intravenous insulin, glucose, and potassium.4 The GLP-1 receptor is present in cardiac muscle,5 and it has been demonstrated that infusion of GLP-1 suppresses apoptosis2 and promotes myocardial glucose uptake, causing a shift in cardiac metabolism in favor of glucose.1,6 Myocardial metabolic efficiency is improved because fatty acid oxidation requires more oxygen to generate energy than does glucose. This reduces the risk of myocardial dysfunction during ischemia, and GLP-1 has been shown to enhance recovery from myocardial stunning after coronary occlusion in conscious dogs.3 There are limited data in humans, although infusion of GLP-1 improves myocardial contractility after primary angioplasty for acute myocardial infarction.7

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We have demonstrated previously that supply ischemia coronary due to occlusion of the coronary artery by the balloon during percutaneous coronary intervention (PCI) results in late myocardial stunning, with cumulative stunning...
after the second inflation. This may be particularly important in situations (e.g., left main or proximal vessel PCI) where a large territory of myocardium is rendered ischemic during the interventional procedure with multiple balloon inflations. Protection of the myocardium from this ischemic insult associated with PCI may reduce myocyte loss, and even in elective cases, there is troponin release in approximately one third, which is associated with subsequent cardiovascular events.

We have demonstrated previously that inhibition of dipeptidyl peptidase-4 (by sitagliptin) with a resultant increase in the plasma concentration of GLP-1(7–36) protects the heart against demand ischemia during dobutamine stress and reduces postischemic dysfunction. The present study, therefore, was undertaken to assess whether infusion of GLP-1(7–36) could protect the heart against ischemic dysfunction associated with coronary balloon occlusion during PCI and mitigate myocardial stunning.

Methods

Study Population
Patients with single-vessel disease and normal left ventricular (LV) function awaiting elective PCI to the left anterior descending artery were invited to participate in the study. Exclusion criteria were a history of myocardial infarction within the previous 3 months, atrial fibrillation, and diabetes. The study was approved by the local ethics committee and the protocol complied with the guidelines of the Declaration of Helsinki. All participants gave fully informed written consent.

Prestudy Protocol
Patients were asked to abstain from consuming caffeine, alcohol, nicotine, and oral/sublingual nitrates and nicorandil for 24 hours before the procedure. All patients fasted for 6 hours and received aspirin 300 mg and clopidogrel 300 mg at least 6 hours before PCI.

Cardiac Catheterization
Sheaths were placed in both femoral arteries (7 F) and the right femoral vein (6 F), and heparin (70 to 100 U/kg) was administered to maintain an activated coagulation time of >250 s throughout the study (Figure 1). No hemodynamics-altering medication was administered during the procedure. The conductance catheter technique was used to determine pressure-volume relations and provide a beat-to-beat assessment of LV performance. A 6-F 8-electrode conductance catheter (Millar Instruments; Houston, TX) was inserted through a femoral arterial sheath then advanced across the aortic valve into the LV apex and placed along the longitudinal axis of the ventricle. The catheter was connected to an MPVS Ultra signal-conditioning unit (Millar Instruments) and calibrated.

Conductance Catheter Calibration
A 20-kHz current was applied to the proximal and distal electrodes, and the remaining 6 electrodes were used to measure time-varying conductance $G(t)$, which is the sum of the conductance between the intervening 5 pairs of adjacent electrodes. The catheter was calibrated according to the technique described by Baan et al. The time-varying LV volume $V(t)$ was calculated as follows: $V(t) = (1/\alpha) \times (L^2/\sigma) \times G(t) - V_c$, where $\alpha$ is the ratio of conductance-derived volume to true ventricular volume, $L$ is the interelectrode distance, $\sigma$ is the specific conductivity of blood that is measured by a calibrating cuvette, and $V_c$ is a volume correction to account for parallel conductance of structures surrounding the ventricular cavity. The $V_c$ was calculated from parallel conductance $G_p$ as follows: $V_c = (1/\alpha) \times (L^2/\sigma) \times G_p$. Parallel conductance, and hence $V_c$, was measured using the hypertonic saline injection technique through a multipur-

Table 1. Patient Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Control (n=10)</th>
<th>GLP-1 (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59.5±7.2</td>
<td>66.3±9.9</td>
</tr>
<tr>
<td>Male sex</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.4±3.7</td>
<td>33.3±7.0</td>
</tr>
<tr>
<td>Active or ex-smoker</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.9±0.9</td>
<td>4.2±1.4</td>
</tr>
<tr>
<td>Antianginal medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Calcium channel antagonist</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are presented as counts or mean±SD. BMI indicates body mass index; GLP-1, glucagon-like peptide-1; MI, myocardial infarction.
Table 2. Baseline LV Hemodynamics Data

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>61.9±11.1</td>
<td>66.7±14.8</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>95.4±10.6</td>
<td>87.8±17.1</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>13.8±4.3</td>
<td>16.9±4.2</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>126.5±31.7</td>
<td>134.3±43.5</td>
</tr>
<tr>
<td>LVE SV, mL</td>
<td>51.0±12.9</td>
<td>61.9±19.1</td>
</tr>
<tr>
<td>SV, mL</td>
<td>75.5±18.8</td>
<td>72.4±22.7</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.6±1.3</td>
<td>4.7±1.4</td>
</tr>
<tr>
<td>EF, %</td>
<td>59.7±6.2</td>
<td>57.5±11.8</td>
</tr>
<tr>
<td>LV dP/dt max, mm Hg/s</td>
<td>1387±253</td>
<td>1556±381</td>
</tr>
<tr>
<td>LV dP/dt min, mm Hg/s</td>
<td>−2009±415</td>
<td>−2173±394</td>
</tr>
<tr>
<td>LV tau, ms</td>
<td>51.8±10.5</td>
<td>53.1±7.7</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. CO indicates cardiac output; dP/dt max, maximum rate of isovolumic pressure increase; dP/dt min, minimum rate of isovolumic pressure decline; EF, ejection fraction; GLP-1, glucagon-like peptide-1; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEDV, LV end-diastolic volume; LVE SV, LV end-systolic volume; MAP, mean arterial pressure; SV, stroke volume.

Study Design

After conductance catheter calibration, a guide catheter was inserted through the second femoral arterial sheath, and the target coronary lesion was crossed with a guidewire as per standard practice. Pressure-volume loops were recorded at baseline and then during a 1-minute low-pressure (<4 atm) balloon inflation at the site of the coronary stenosis (Figure 1). Patients were randomized to receive either an intravenous infusion of GLP-1(7–36) amide (Bachem; Weil am Rhein, Germany) at a dose of 1.2 pmol/kg per minute (GLP-1 group) or normal saline (control group) starting immediately after the first coronary balloon occlusion. The infusions were prepared externally so that the patient and operator were blinded to the treatment strategy (GLP-1 versus control). GLP-1 has a short half-life of only 1 to 2 minutes with a rapid onset and offset of action, and the infusion was commenced after the first occlusion rather than at the beginning of the procedure in order to provide a comparison between 2 ischemic episodes within each patient. After a period of 30 minutes, pressure-volume loops were recorded at a second baseline and then during a second 1-minute low-pressure balloon inflation at the site of the coronary stenosis. After the study measurements were completed, the lesions were treated conventionally by high-pressure balloon angioplasty and stenting, and the infusion of GLP-1 or saline was discontinued at the end of the procedure.

LV Hemodynamics Measurements

The conductance catheter data were analyzed off line by a reviewer blinded to the treatment strategy using PVAN software (Millar Instruments). Five cardiac cycles were recorded at baseline and after 1-minute balloon occlusion (just before balloon deflation). The parameters generated to measure systolic function were stroke volume, ejection fraction, and dP/dt max (maximum rate of isovolumic pressure increase). The parameters for diastolic function were dP/dt min (maximum rate of isovolumic pressure decline) and tau (time constant of isovolumic relaxation). To calculate tau, the conductance catheter-derived P (time constant of pressure relaxation) is measured from the time peak rate of pressure decline (dP/dt min) to 5 mm Hg above end-diastolic pressure. Tau is derived from the monoeXponential decay of the pressure waveform: $P(t) = Ke^{-t/\tau}$; where tau is the slope of the log P versus t relation (tau = −1/slope, assuming $P_e = 0$).

Biochemistry

Blood samples were taken to measure glucose, insulin, free fatty acids (FFA), and GLP-1(7–36) at baseline and immediately after each of the 2 balloon occlusions. The GLP-1 samples were drawn into syringes containing dipeptidyl peptidase-4 inhibitor (Millipore; Consett, County Durham, UK) to prevent GLP-1 degradation. Plasma GLP-1(7–36) levels were measured using a commercially available assay (Meso Scale Discovery, Gaithersburg, MD). Cardiac
troponin I levels were analyzed at 6 hours after the procedure (Bayer ADVIA IMS Troponin-I Ultra method; Leverkusen, Germany).

Statistical Analysis
Data are expressed as mean±SD, unless otherwise stated. LV hemodynamics data were converted to a percentage change from baseline to facilitate data comparison. Comparisons between control and GLP-1 were made using the unpaired Student t test for continuous variables and Fisher exact test for categorical variables. Comparisons within the groups were made using repeated-measures ANOVA. A P<0.05 was considered statistically significant.

Results
Twenty-one patients without diabetes were recruited into the study. In 1 patient, it was not possible to cross the aortic valve with the conductance catheter. Complete data sets were obtained in 20 patients (10 control and 10 GLP-1). Patient demographic data (Table 1) and baseline hemodynamics data (Table 2) were similar in the 2 groups.

Biochemistry
There was no difference in the baseline plasma level of GLP-1(7–36), glucose, insulin, and FFA between the GLP-1 and control groups (Figure 2). After the first balloon occlusion (before GLP-1 infusion), there was no change in GLP-1(7–36), glucose, or insulin compared with baseline in either group. However, there was an increase in FFA in both the GLP-1 (P<0.02) and the control (P<0.02) groups compared with baseline. Intravenous infusion of GLP-1(7–36) achieved a mean 14-fold increase in the plasma concentration of GLP-1(7–36) at the time of the second balloon occlusion (P<0.001 versus control). The plasma concentration of glucose and FFA did not change between the first and second balloon occlusions in either group. In patients who received GLP-1, the plasma insulin concentration increased between first and second balloon occlusion (P=0.01), but no change was seen in the control group. There was a trend for postprocedure troponin I levels to be lower in the GLP-1 group than in the control group (0.27±0.23 versus 0.59±0.82 ng/mL, P=0.27).

LV Function
The first balloon occlusion caused a similar reduction in LV systolic and diastolic function in both the GLP-1 and the
control groups (Figure 3). In the control group, there was a reduction in \( \frac{dP}{dt_{\text{max}}} \) \((P=0.003)\), tau \((P=0.001)\), ejection fraction \((P=0.01)\), and stroke volume \((P=0.02)\) at 30 minutes after coronary balloon occlusion consistent with LV stunning. The second balloon occlusion caused cumulative LV systolic dysfunction with a greater reduction in \( \frac{dP}{dt_{\text{max}}} \) \((P=0.003)\), ejection fraction \((P=0.003)\), and stroke volume \((P=0.01)\) compared to the first balloon occlusion. These changes were not seen in the GLP-1 group (Figure 4), where stunning did not occur, and LV performance at 30 minutes after coronary balloon occlusion assessed with all parameters returned to baseline. LV dysfunction caused by the second balloon occlusion was reduced by GLP-1 compared with control \((\frac{dP}{dt_{\text{max}}}, P=0.01; \frac{dP}{dt_{\text{min}}}, P=0.02; \text{tau}, P=0.01; \text{ejection fraction}, P=0.03; \text{stroke volume}, P=0.04)\). Cumulative LV dysfunction did not occur in the GLP-1 group.

**Discussion**

Previous studies have shown that in humans undergoing PCI, coronary balloon occlusion significantly impairs LV systolic and diastolic function.\(^{15}\) Persistent, but reversible myocardial dysfunction after an ischemic insult despite restoration of normal flow is known as stunning.\(^{16}\) Repeated episodes of ischemia have a cumulative effect on stunning\(^{17,18}\), and we have shown previously that this occurs in humans after coronary balloon occlusion.\(^{8}\) The present study demonstrates that intravenous infusion of GLP-1(7–36) amide reduces ischemic LV systolic and diastolic dysfunction caused by a 1-minute balloon occlusion within a coronary artery in humans and improves the recovery of function, mitigating LV stunning.

The first balloon occlusion had no effect on the plasma levels of glucose, insulin, or GLP-1(7–36). However, there was a rise in plasma FFA likely because of the intravenous heparin given after the baseline samples had been taken. Heparin is known to produce a rise in FFA, which is maximal 10 minutes after administration.\(^{19}\) Myocardial ischemia due to coronary angioplasty also causes a rise in FFA\(^{20}\) and may contribute to this effect, although the samples were taken immediately after balloon deflation. There was no difference in FFA between the GLP-1 and the control groups.

**Cardioprotection by GLP-1**

There is now considerable evidence to suggest that shifting myocardial metabolism from fatty acids in favor of glucose can improve LV performance during ischemia and in heart failure.\(^{21}\) Fatty acids require 10% to 15% more oxygen to generate an equivalent amount of energy to glucose and have other detrimental effects on hypoxic myocardium, including lactate and proton accumulation in the ischemic cell.\(^{22}\) Attempts have been made to use this effect with insulin through glucose-insulin-potassium infusions, but these largely have been ineffective.\(^{4}\) This strategy involves intensive monitoring to control the plasma glucose concentration and avoid hypoglycemia. GLP-1 does not present the same problems, and work in animal models of ischemia,\(^{1,3}\) infarction,\(^{2}\) and nonischemic heart failure\(^{6,23}\) has shown considerable promise. In human pilot studies, intravenous GLP-1 improved LV function after acute myocardial infarction,\(^{7}\) and a subcutaneous infusion of GLP-1 over 5 weeks improved LV function, functional status, and quality-of-life scores in patients with severe heart failure.\(^{24}\)

A direct cardioprotective effect of GLP-1 has been demonstrated in isolated heart studies that may not be entirely independent of insulin, glucagon, FFA, and neural outflow. The effects are, however, believed to be mediated through GLP-1 receptor-dependent and -independent pathways.\(^{25}\) The predominant effect occurs by GLP-1(7–36) binding to its receptor and improving myocardial glucose uptake, although activation of subcellular pathways involved in ischemic preconditioning signaling and the suppression of apoptosis also have been implicated.\(^{2}\) Infusion of GLP-1 stimulates...
insulin secretion, and although we believe that an important direct effect on the heart is likely, we cannot exclude a smaller postconditioning effect mediated though rapid metabolism to GLP-1(9–36), which is believed to occur through a nitric oxide pathway.25

Clinical Implications
This pilot study demonstrates that GLP-1 may protect the heart from ischemic LV dysfunction after coronary balloon occlusion during PCI. Left main and proximal vessel interventions expose a large volume of myocardium to ischemia. In addition, many procedures, particularly multivessel or complex cases, involve multiple balloon inflations. A strategy to provide cardioprotection in these settings may be a useful clinical tool. Furthermore, GLP-1 may abrogate ischemic LV dysfunction responsible for stunning outside the catheterization laboratory and may have a beneficial therapeutic effect in the treatment of heart failure.

Troponin release after elective PCI is associated with a worse prognosis.10 We observed a trend for reduced troponin release with GLP-1, although the study was not powered for this end point. Larger studies clearly are warranted to assess whether infusion of GLP-1 can provide clinical benefits during elective and nonelective PCI and in other settings of myocardial ischemia and infarction. For example, GLP-1 may improve LV recovery after primary PCI for acute myocardial infarction, and this merits further investigation.

Limitations
The study was designed to assess the effects of GLP-1 on ischemic LV dysfunction and was not powered to assess any clinical end points. We were unable to confirm that LV function returned to baseline after the second balloon occlusion because of time and safety limitations. The definition of stunning requires that coronary flow is normal. We did not assess this but have shown previously that flow normalizes 30 minutes after occlusion.8 In addition, we cannot confirm that myocardial necrosis was absent after balloon inflation. It is believed that the majority of procedure-related embolic injuries occur at the time of stent implantation,26 and the normalization of flow in the previous study suggests that there is minimal microembolic injury from low-pressure balloon inflation. We continued the infusion of GLP-1 throughout stent implantation and observed a trend for the reduction of troponin release, although further work is needed to assess whether GLP-1 is protective against periprocedural necrosis.

Conclusions
GLP-1 protects the heart against ischemic LV dysfunction and attenuates stunning after balloon occlusion within the coronary artery in humans.

Acknowledgments
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Disclosures
None.

References
CLINICAL PERSPECTIVE

The incretin hormone glucagon-like peptide-1 (GLP-1) has been shown to have cardioprotective properties in animal models of ischemia and infarction due to promotion of myocardial glucose uptake and suppression of apoptosis. This study investigated whether GLP-1 can protect the heart during supply ischemia associated with percutaneous coronary intervention. Cardiac performance was assessed by a conductance catheter placed into the left ventricle through the femoral artery, and pressure-volume loops were recorded at baseline and during a 1-minute low-pressure balloon occlusion at the site of the stenosis. The patients then received an infusion of GLP-1(7–36) amide or saline for 30 minutes before the coronary artery was occluded again, and the effect on LV performance was recorded. GLP-1 improved the ability of the heart to recover from the first ischemic insult and to protect the heart against the cumulative stunning that was seen in the control patients. This preliminary study supports the use of GLP-1 as a metabolic cardioprotective agent that may have utility in protecting the heart during percutaneous coronary intervention, especially in patients undergoing high-risk intervention and those with type 2 diabetes. Further studies are required to assess the role of agents that modulate GLP-1 in humans with coronary disease before clinical trials are undertaken to determine whether GLP-1 has utility in clinical cardiology practice.
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