

Effects of Glucagon-Like Peptide-1 in Patients With Acute Myocardial Infarction and Left Ventricular Dysfunction After Successful Reperfusion

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Background—Glucose-insulin-potassium infusions are beneficial in uncomplicated patients with acute myocardial infarction (AMI) but are of unproven efficacy in AMI with left ventricular (LV) dysfunction because of volume requirements associated with glucose infusion. Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin with both insulinotropic and insulinomimetic properties that stimulate glucose uptake without the requirements for concomitant glucose infusion.

Methods and Results—We investigated the safety and efficacy of a 72-hour infusion of GLP-1 (1.5 pmol/kg per minute) added to background therapy in 10 patients with AMI and LV ejection fraction (EF) <40% after successful primary angioplasty compared with 11 control patients. Echocardiograms were obtained after reperfusion and after the completion of the GLP-1 infusion. Baseline demographics and background therapy were similar, and both groups had severe LV dysfunction at baseline (LVEF=29±2%). GLP-1 significantly improved LVEF (from 29±2% to 39±2%, $P<0.01$), global wall motion score indexes ($1.94\pm0.11\rightarrow1.63\pm0.09$, $P<0.01$), and regional wall motion score indexes ($2.53\pm0.08\rightarrow2.02\pm0.11$, $P<0.01$) compared with control subjects. The benefits of GLP-1 were independent of AMI location or history of diabetes. GLP-1 was well tolerated, with only transient gastrointestinal effects.

Conclusions—When added to standard therapy, GLP-1 infusion improved regional and global LV function in patients with AMI and severe systolic dysfunction after successful primary angioplasty. (*Circulation*. 2004;109:962-965.)

Key Words: myocardial infarction ■ insulin ■ heart failure ■ angioplasty

Glucose-insulin-potassium (GIK) infusions have been used as metabolic adjuvants in acute myocardial infarction (AMI)¹⁻⁵ in an attempt to enhance myocardial glucose uptake and oxidation and take advantage of the efficacy of this substrate in generating ATP.^{6,7} Recently, a group of Dutch investigators⁸ reported beneficial effects of GIK therapy in patients with AMI treated with percutaneous coronary intervention (PCI). However, the benefits were limited to those presenting in Killip class I. In the same study, patients with evidence of congestive heart failure (Killip class III-IV) after AMI exhibited an adverse trend with GIK therapy.

Glucagon-like peptide-1 (GLP-1 [7-36] amide) is a member of the pro-glucagon incretin family implicated in the control of appetite and satiety.⁹ GLP-1 has both insulinomimetic¹⁰ and insulinotropic¹¹ actions. These effects are predicated on ambient glucose concentration and are mitigated at plasma glucose concentrations <70 mg/dL, minimizing risks of hypoglycemia and the need for glucose infusion. Thus, the pharmacological properties of GLP-1 are attractive as a means to stimulate myocardial glucose uptake during postischemic contractile dysfunction.

The purpose of the present study was to determine if a continuous 72-hour infusion of GLP-1 improves global and regional ventricular function in the early postinfarction period in patients in Killip class III-IV after successful reperfusion in AMI.

Methods

This was a single-center, nonrandomized pilot study, designed to evaluate the safety and clinical efficacy of recombinant GLP-1 (7-36) amide (rGLP-1) in high-risk patients (n=10) with AMI and left ventricular (LV) systolic dysfunction after successful reperfusion with primary angioplasty. Patients presenting within 6 hours from symptom onset, with Killip class II-IV clinical presentation and LV ejection fraction (EF) <40%, who were treated with primary angioplasty, were eligible. Patients were excluded from the study if they (1) had coronary anatomy warranting coronary artery bypass surgery, (2) required hemodialysis, (3) had malignancy, HIV, or central nervous system disorder, (4) had cardiopulmonary resuscitation for >30 minutes, (5) had diabetic ketoacidosis, or (6) had symptomatic hypoglycemia of <60 mg/dL. A group of similar patients (n=11) receiving comparable medical and interventional therapy but who chose not to receive rGLP-1 served as control subjects. After successful reperfusion, informed consent was ob-

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tained from all patients. Evaluation of LV function was performed by echocardiography within 2 hours of successful angioplasty. After the baseline assessment of LV function, a 72-hour intravenous infusion of rGLP-1 (1.5 pmol/kg per minute, provided by D. Elahi, PhD, University of Massachusetts School of Medicine) was initiated. The average time between initiation of reperfusion and the start of rGLP-1 was 212 minutes. rGLP-1 (7–36) amide was produced by prokaryotic fermentation with a carboxy-terminal amide added to the peptide by transamidation (Restoragen). The preparation was >99% pure. Plasma GLP-1 levels, glucose, insulin, and nonesterified fatty acid (NEFA) were measured at baseline and at 24, 48, and 72 hours in the rGLP-1-treated group. Assessment of LV function by echocardiography was repeated within 6 to 12 hours after the completion of the rGLP-1 infusion. LV functional assessments were made at similar time points in the control group.

LV function was assessed with the use of Simpson's method on standard 2D images obtained at the apical acoustic window. In addition, regional and global wall motion indexes were calculated with the use of the 16-segment model of the American Society of Echocardiography.¹² The global composite average of all myocardial segments constitutes the global wall motion score index (g-WMSI), whereas regional wall motion score indexes (r-WMSI) were defined for infarct-related territory. By definition, lower scores are associated with better contractile function. The echocardiogram reader was blinded as to the treatment.

All data are reported as mean $\pm$ SEM. Demographic parameters between groups were compared by means of the Student's *t* test for continuous variables and χ^2 test for categorical variables. Paired *t* tests were used to compare the change in LV function over time in the GLP-1 and control patients. A 2-tailed value of *P*<0.05 was considered statistically significant.

Results

The Table summarizes the demographics of the study population. The rGLP-1 group tended to be younger, with fewer women. The rGLP-1 group also had significantly higher peak creatine phosphokinase and a higher prevalence of multivessel disease. All LV volumes, regional and global indexes, and blood pressures were similar between the groups. The time from onset of symptoms to reperfusion was comparable between groups. Both groups received standard post-MI therapy after primary angioplasty, including aspirin, clopidogrel, heparin, glycoprotein IIb/IIIa inhibitors, β -blockers, ACE inhibitors, and statins.

Global LVEF improved from 29 $\pm$ 2% to 39 $\pm$ 2% (*P*<0.01) in the rGLP-1-treated patients but not in the control group (28 $\pm$ 2% to 29 $\pm$ 2%). Global LV function improved in all rGLP-1-treated patients, whereas the response was heterogeneous in the control group (Figure 1A). Similar results were observed in the peri-infarct zone (Figure 1B). Regional WMSI significantly decreased (–21 $\pm$ 2%, *P*<0.001) in the rGLP-1-treated group, whereas no change (+4 $\pm$ 4%) was noted in the control group. Global WMSI also improved (–15 $\pm$ 3%, *P*<0.001) in rGLP-1-treated patients but not in the control group (0 $\pm$ 3%). Regional GLP-1 had no effect on LV end-diastolic volume (90 $\pm$ 6 from 91 $\pm$ 9 mL) but did improve LV end-systolic volume (55 $\pm$ 5 from 64 $\pm$ 7 mL, *P*<0.01) and stroke volume (35 $\pm$ 2 from 26 $\pm$ 2 mL, *P*<0.02). There was no change seen in the control group. Figure 2 illustrates that the benefits of rGLP-1 on global and regional contractile functions were evident in both diabetic and non-diabetic patients (upper panel) as well as in patients with anterior (left anterior descending artery) and nonanterior MI (lower panel). The observed effects of rGLP-1 on LV

Patient Demographics

	r-GLP-1 (N=10)	Control Subjects (N=11)
Age, y (range)	58 $\pm$ 3 (42–79)	65 $\pm$ 4 (42–84)
Gender, male/female, n	7/3	4/7
Body mass index, kg/m ²	28.8 $\pm$ 1.4	29.5 $\pm$ 1.7
Body surface area, m ²	1.92 $\pm$ 0.05	1.90 $\pm$ 0.05
Diabetes, n (%)	5 (50)	4 (37)
Anterior location (left anterior descending), n of N (%)	5 of 10 (50)	7 of 11 (63)
Time from symptom onset to reperfusion, min	381 $\pm$ 36	358 $\pm$ 42
Multivessel coronary artery disease, n of N (%)	9 of 10 (90)	7 of 11 (64)
Killip class	3.0 $\pm$ 0.1	3.1 $\pm$ 0.2
Creatine kinase peak, U/L	2893 $\pm$ 698	1894 $\pm$ 563
Creatine kinase–MB peak, ng/mL	250 $\pm$ 55	181 $\pm$ 50
Systolic blood pressure, mm Hg	119 $\pm$ 7	118 $\pm$ 6
Diastolic blood pressure, mm Hg	74 $\pm$ 6	64 $\pm$ 4
Mean blood pressure, mm Hg	89 $\pm$ 6	81 $\pm$ 4
Intra-aortic balloon pump, n of N (%)	1 of 10 (10)	2 of 11 (18)
Inotrope use, n of N (%)	2 of 10 (20)	3 of 11 (27)
LV ejection fraction, %	29 $\pm$ 2	28 $\pm$ 2
LV end-diastolic volume, mL	91 $\pm$ 9	90 $\pm$ 9
LV end-systolic volume, mL	64 $\pm$ 7	65 $\pm$ 8
SV, mL	26 $\pm$ 2	24 $\pm$ 2
g-WMSI	1.94 $\pm$ 0.11	1.98 $\pm$ 0.06
rWMSI-IZ (regional infarct zone)	2.53 $\pm$ 0.08	2.59 $\pm$ 0.10

function were not attributed to changes in heart rate or mean arterial pressure in either group. Follow-up echocardiograms within 120 days after the AMI were available in 4 of the rGLP-1-treated patients, all of whom demonstrated sustained benefit (LVEF, 36 $\pm$ 3%) and in 4 control patients in whom LVEF remained depressed (27 $\pm$ 3%).

Plasma GLP-1 levels increased promptly and remained elevated through the 72-hour infusion (62 $\pm$ 11 to 168 $\pm$ 21 pmol/L, *P*<0.05). NEFA decreased from 478 $\pm$ 82 to 402 $\pm$ 82 μ mol/L (*P*<0.03) at 72 hours. Plasma glucose also tended to decrease during the first 48 hours (162 $\pm$ 26 to 126 $\pm$ 18 mg/dL), accompanied by a parallel decrease in plasma insulin levels (184 $\pm$ 31 to 118 $\pm$ 23 pmol/L) consistent with the insulinomimetic effects of rGLP-1. When patients resumed eating on day 3, plasma glucose increased to 168 $\pm$ 29 mg/dL, now accompanied by a robust insulin response (302 $\pm$ 81 from 184 $\pm$ 31 pmol/L, *P*<0.05), consistent with the insulinotropic effect of rGLP-1.

In-hospital mortality rate was 27% (3 of 11) in the control group and 10% (1 of 10) in the rGLP-1-treated group. There were no cardiovascular deaths in the GLP-1-treated group and 2 in the control group (18%): 1 from ventricular fibrillation and 1 from cardiogenic shock. Hospital length of stay was significantly reduced in the rGLP-1-treated group compared with control subjects (6.1 $\pm$ 1.3 versus 9.8 $\pm$ 1.5 days,

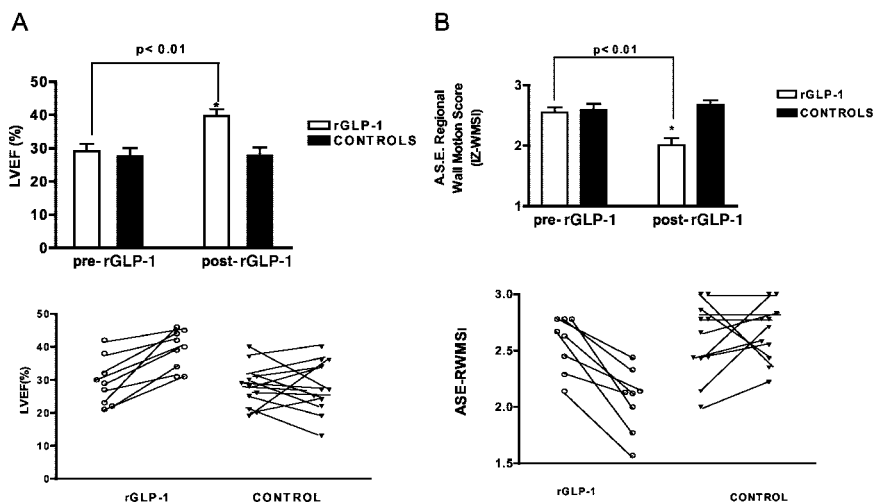


Figure 1. A, Changes in LVEF after 72 hours of rGLP-1 infusion versus control subjects. Lower panel illustrates individual data. B, Changes in regional wall motion score at the per-infarct zone in rGLP-1-treated patients versus control subjects. Lower panel illustrates the individual data.

$P < 0.02$), and there was a trend toward decreased coronary care unit length of stay (3.1 ± 1.4 versus 5.1 ± 1.0 days).

Minor reversible side effects occurred primarily in nondiabetic patients receiving rGLP-1. These included nausea (4 patients), vomiting (2 patients), constipation (2 patients), and decreased appetite (3 patients). Asymptomatic hypoglycemia was noted in 2 nondiabetic patients (58 and 52 mg/dL, respectively) but resolved after temporary interruption of the infusion for 1 hour and resumption at a lower dose (1 pmol/kg per minute) for the duration of the study. Both of these patients exhibited comparable benefit in global LVEF and regional wall motion score compared with entire rGLP-1 group.

Discussion

We report for the first time the benefits of a novel insulinotropic and insulinomimetic agent, rGLP-1, in patients with extensive MI and severe LV dysfunction after successful reperfusion. We observed significant salutary effects of rGLP-1 on global LVEF as well as regional functional recovery in the peri-infarct zone. The favorable impact of rGLP-1 could not be accounted for by changes in blood pressure or heart rate and was seen in both diabetic and nondiabetic patients. The enhanced insulin responses and

reductions in NEFA were observed without significant hypoglycemia.

There are several important differences between our study and the recent Dutch GIK study⁸ in which no benefit of GIK therapy was seen in patients with LV dysfunction. First, we achieved successful reperfusion (TIMI 3 flow) in all patients, compared with 82% in the Dutch trial. Second, we began the infusion within 2 to 4 hours after successful PCI, in contrast to other GIK studies that administered treatment before reperfusion. We infused rGLP-1 for 72 hours, as opposed to insulin infusion for 8 to 12 hours. The proportion of diabetes was also higher in our study compared with the Dutch study⁸ or Estudios Cardiológicos Latinoamericana (ECLA)², although it was not exclusively a diabetic group, as in the Diabetes mellitus Insulin-Glucose infusion in Acute Myocardial Infarction (DIGAMI) study.¹³ Our "onset of symptoms to reperfusion" time was comparable in both groups but longer than in the Dutch trial,⁸ reflecting the fact that all of our patients were referred from outside hospitals. Despite the longer time to reperfusion, our outcomes with rGLP-1 were quite favorable. rGLP-1 exerts pleiotropic metabolic effects, including glucagon suppression and non-insulin-mediated glucose uptake, in addition to insulinotropic actions.⁹ Whether these

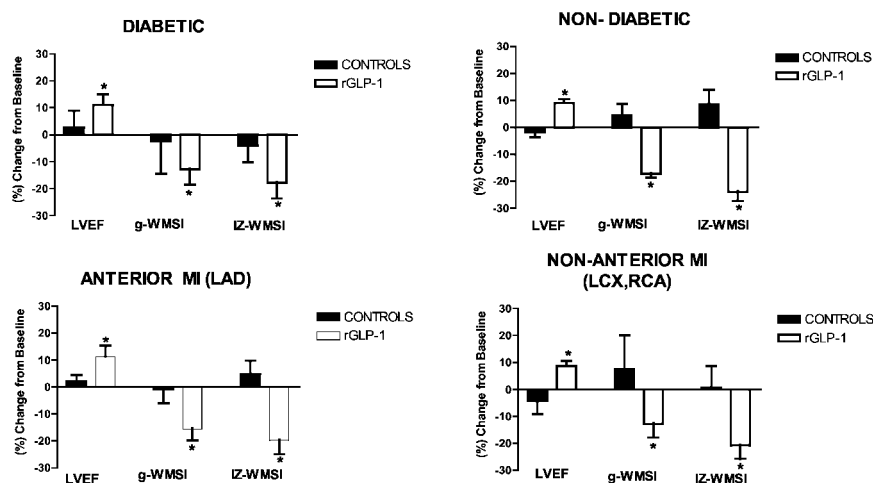


Figure 2. Impact of rGLP-1 on LVEF, g-WMSI, and regional (IZ-WMSI) wall motion in diabetic versus nondiabetic subjects (upper panel) and in patients with anterior versus nonanterior myocardial infarction (lower panel).

additional mechanisms are implicated in the observed cardiovascular benefits is unknown.

A prior study in anesthetized pigs demonstrated that pretreatment with rGLP-1 decreased the accumulation of lactate and pyruvate in ischemic myocardium but had no effect on functional parameters.¹⁴ However, recovery from the ischemic insult was only assessed for 2 hours. It is also conceivable that rGLP-1 may contribute to improved outcomes through non-glucose-dependent mechanisms. These include reductions in plasma NEFA levels that have been implicated in arrhythmogenesis.¹⁵ Alternatively, rGLP-1 may improve endothelial function and microcirculatory integrity, as suggested by the higher peak creatine phosphokinase, consistent with greater washout, in the rGLP-1-treated patients, despite comparable baseline regional and global LV dysfunction in both groups.

We demonstrated that rGLP-1 administration was safe in this precarious clinical setting. The side effects were minor, reversible, and more frequent in nondiabetic patients. Nevertheless, rGLP-1 was well tolerated in nondiabetic patients. No clinically significant hypokalemia occurred.

Limitations

This was a pilot trial in a small number of patients with AMI and severe LV dysfunction after primary angioplasty. Because the design of this study was limited to the first 72 hours after MI, we cannot speculate as to whether continued rGLP-1 infusion could have conferred greater cardiovascular benefits. Even if the benefits were limited to accelerated recovery from early myocardial stunning, this would be clinically important in post-MI patients with severe LV dysfunction, as reflected in the trend toward lower mortality rates and decreased length of stay.

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