

Glucagon-Like Peptide-1 Infusion Improves Left Ventricular Ejection Fraction and Functional Status in Patients With Chronic Heart Failure

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ABSTRACT

Background: Insulin resistance is present in the setting of congestive heart failure. Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin with both insulinotropic and insulinomimetic properties.

Methods and Results: We investigated the safety and efficacy of a 5-week infusion of GLP-1 (2.5 pmol/kg/min) added to standard therapy in 12 patients with New York Heart Association class III/IV heart failure and compared the results with those of 9 patients with heart failure on standard therapy alone. Echocardiograms, maximum myocardial ventilation oxygen consumption (VO_2 max), 6-minute walk test, and Minnesota Living with Heart Failure quality of life score (MNQOL) were assessed. Baseline demographics, background therapy, and the degree of left ventricular dysfunction were similar between groups. GLP-1 significantly improved left ventricular ejection fraction ($21 \pm 3\%$ to $27 \pm 3\%$ $P < .01$), VO_2 max ($10.8 \pm .9 \text{ ml/O}_2/\text{min/kg}$ to $13.9 \pm .6 \text{ ml/O}_2/\text{min/kg}$; $P < .001$), 6-minute walk distance ($232 \pm 15 \text{ m}$ to $286 \pm 12 \text{ m}$; $P < .001$) and MNQOL score (64 ± 4 to 44 ± 5 ; $P < .01$). Benefits were seen in both diabetic and non-diabetic patients. There were no significant changes in any of the parameters in the control patients on standard therapy. GLP-1 was well tolerated with minimal episodes of hypoglycemia and gastrointestinal side effects.

Conclusion: Chronic infusion of GLP-1 significantly improves left ventricular function, functional status, and quality of life in patients with severe heart failure. (*J Cardiac Fail* 2006;12:694–699)

Key Words: Insulin resistance, Diabetes, Congestive heart failure, Metabolism.

Recently, there has been growing recognition of altered myocardial metabolism as a potential therapeutic target in dilated cardiomyopathy (DCM). The normal adult heart possesses the ability to use numerous substrates for the generation of high-energy phosphates, including non-esterified fatty acids (NEFAs), glucose, and lactate,^{1,2} with NEFA being the preferred metabolic substrate because of the high

yield of adenosine triphosphate (ATP) when fully oxidized. However, under circumstances such as myocardial infarction and heart failure where myocardial work is increased and oxygen may be limited, the myocardial preference shifts to glucose due to the fact that glucose is an energetically more efficient fuel for ATP production. This metabolic adaptation is mediated by both physiologic and transcriptional mechanisms.³

There is a growing body of literature that supports the concept that left ventricle (LV) dysfunction not only predisposes to the development of myocardial insulin resistance, but whole body insulin resistance as well.^{4–10} Insulin resistance is present in heart failure even in the absence of overt diabetes.² In fact, abnormal glucose homeostasis has been observed in up to 43% of patients with CHF and correlates with New York Heart Association (NYHA) classification.⁴ Our laboratory has demonstrated the magnitude and cellular mechanisms underlying myocardial insulin resistance in conscious dogs with advanced DCM,¹¹ which suggests increased glucose utilization could improve cardiac function. Glucose-insulin-potassium (GIK) infusions have

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been studied as metabolic adjuvants in acute myocardial infarction in an attempt to enhance myocardial glucose uptake and oxidation with mixed results.^{12–15} The use of GIK infusions in the treatment of CHF is limited by the large volume of fluid required.¹⁵ An agent with similar effects on glucose uptake and less volume requirements would be an attractive alternative therapy. One such agent, glucagon-like peptide-1 (GLP-1 [7–36] amide), is a member of the proglucagon incretin family implicated in the control of appetite and satiety.¹⁶ GLP-1 has both insulinomimetic and insulintropic actions,^{17,18} predicated on ambient glucose concentration, minimizing risks of hypoglycemia and the need for glucose infusion. GLP-1 has been shown to be effective in the setting of acute myocardial infarction.¹⁹ The purpose of the present study was to determine if a 5-week continuous subcutaneous infusion of GLP-1 (7–36 amide) improved both LV ejection fraction (LVEF) and functional capacity in patients with NYHA class III/IV heart failure.

Methods

This was a single-center, open-label, nonrandomized pilot study, designed to evaluate the safety and clinical efficacy of GLP-1 (7–36) amide (Restoragen, Inc., Lincoln, NE) at a dose of 2.5 pmol/kg/min in a group of patients with chronic heart failure. The study was approved by the Investigational Review Board of Allegheny General Hospital and was initially intended to be a 10-week dose escalation study but initial evaluation indicated no additional benefit to higher doses.

To be included, patients had to meet the following criteria: maximum medical therapy for at least 30 days prior to randomization, NYHA class III or IV CHF, LVEF of $\leq 40\%$, maximum myocardial ventilation oxygen consumption (VO_2) max of ≤ 15 ml O_2 /kg/min, and ineligibility for cardiac transplantation. Patients were excluded from the study if they had: 1) heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or active myocarditis; 2) conventional cardiac revascularization procedure, LV reduction procedure, or cardiomyoplasty within 30 days prior to enrollment; 3) evidence of intrinsic hepatic disease defined as liver enzyme values greater than 5 times the upper limit of normal, a prolonged prothrombin time in the absence of systemic anticoagulation therapy at the time of screening; 4) serum creatinine greater than 3.5 mg/dL or long-term dialysis; 5) type 1 diabetes mellitus; 6) presence of a condition other than heart failure that would limit survival to less than 1 year; or 7) hospitalization for acute decompensation of CHF in the past 60 days.

After screening eligible patients for enrollment, informed consent was obtained, and the first 12 patients meeting eligibility criteria received GLP-1 via continuous subcutaneous infusion. Patients were started on an initial dose of 1.25 pmol/kg/min for 1 week to assess tolerability of the drug, followed for 4 weeks at a higher dosage of 2.5 pmol/kg/min. End points were evaluated at baseline and upon completion of the 5-week infusion. The next 9 eligible patients were enrolled as control patients but did not receive GLP-1. All patients were on a stable heart failure medication regimen including angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, β -blocker, aldosterone antagonist, loop diuretic, and digoxin. Only diuretic doses were adjusted

during the protocol although patients with diabetes did undergo adjustment to their diabetes medications if plasma glucose levels fell below 70 mg/dL.

Primary end points included evaluation of LV function at rest assessed by 2-dimensional echocardiography and with exertion by VO_2 max measured by cardiopulmonary exercised treadmill test. Secondary end points included measures of the patient's quality of life as assessed by 6-minute walk distance and the Minnesota Living with Heart Failure questionnaire.

Echocardiograms were analyzed, and indices of systolic and diastolic function quantified by an expert echocardiographer blinded to the study drug. LV volumes and LVEF were calculated with the use of the Simpson's method on standard 2-dimensional images. The degree of mitral regurgitation was assessed using the methods established by the American Society of Echocardiography.²⁰ Non-invasive measures of blood pressure were determined prior to the echocardiogram study and cardiac output calculated as the product of the echo-derived stroke volume and heart rate. LV mass was calculated as previously described by the American Society of Echocardiography.²¹

Plasma glucose was measured using Beckman Glucose Analyzer 2 (Beckman Instruments, Fullerton, CA). NEFAs were measured in the plasma using an in vitro enzymatic colorimetric assay purchased from Wako Chemicals USA, Inc. (Richmond, VA). Plasma insulin levels were measured using radioimmunoassay kits purchased from Linco Research, Inc. (St. Charles, MO). B-type natriuretic peptide (BNP) was measured using immunoassay kits purchased from Biosite, Inc. (San Diego, CA).

Statistical Analysis

All data are reported as mean $\pm$ SEM. Baseline and 5-week measurements were compared in each group using either the paired *t* test or Wilcoxon signed rank test. All statistical tests were 2-tailed. A *P* value $< .05$ was considered statistically significant.

Results

The demographics of the study groups are depicted in Table 1. The majority of subjects were older patients with NYHA class III heart failure. There were more patients with diabetes and ischemic cardiomyopathy in the GLP-1-treated group (67%) compared with control subjects (56%), although the difference was not significant (*P* = .95). Fasting glucose levels and HgbA1C levels were higher in the GLP-1-treated patients compared with the control group. Patients in both groups were obese with average body mass index > 30 . Blood pressure measurements and BNP levels suggested that patients were compensated on standard medical therapy.

The individual results following GLP-1 compared with control are illustrated in Figure 1. LVEF improved from $21 \pm 3\%$ to $27 \pm 3\%$ (*P* $< .001$) in the GLP-1-treated patients but was unchanged in the control group ($21 \pm 4\%$ to $22 \pm 4\%$). Six-minute walk test improved significantly from 232 ± 15 to 286 ± 12 m (*P* $< .001$) in the treated patients but not in the control group (233 ± 21 to 258 ± 21 m). VO_2 max improved from $10.8 \pm .9$ to $13.9 \pm .6$ ml/kg/min (*P* $< .001$), but was unchanged in the control group ($13.3 \pm .9$ to 13 ± 1.0 ml/kg/min). Quality of life

Table 1. Baseline Characteristics

	Control	GLP-1
No. of patients	9	12
Sex (M/F)	6/3	7/5
Age (y)	60 ± 5	61 ± 4
Weight (kg)	101 ± 14	94 ± 5
BMI (kg/m ²)	35 ± 4	33 ± 2
Diabetics	5 (56%)	8 (67%)
Ischemic cardiomyopathy	5 (56%)	8 (67%)
NYHA class (III/IV)	8/1 (89%)	9/3 (75%)
Heart rate (beats/min)	68 ± 4	73 ± 3
Systolic blood pressure (mm Hg)	116 ± 5	120 ± 4
Diastolic blood pressure (mm Hg)	66 ± 4	62 ± 2
MAP (mm Hg)	83 ± 3	81 ± 2
BUN (mg/dL)	16 ± 2	27 ± 6
Serum Cr (mg/dL)	1.3 ± .1	1 ± .1
Fasting glucose (mg/dL)	113 ± 17	173 ± 32
HbA1C (%)	6.6 ± .6	7.7 ± .4
BNP (pg/mL)	296 ± 128	289 ± 90
Baseline medications		
ACE inhibitor/ARB	9/9 (100%)	11/12 (92%)
Beta-blocker	9/9 (100%)	12/12 (100%)
Loop diuretic	9/9 (100%)	12/12 (100%)
Spirolactone	9/9 (100%)	10/12 (83%)
Digoxin	7/9 (78%)	8/12 (67%)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; GLP-1, glucagon-like peptide-1; MAP, mean arterial pressure; NYHA, New York Heart Association.

improved significantly in the GLP-1-treated patients from 64 ± 4 to 44 ± 5 ($P < .001$) but not in the control group (52 ± 12 to 46 ± 12). The majority of patients in the GLP-1-treated group showed improvement in these end points including 9 of 12 (75%) with at least a 3% increase in LVEF, 10 of 12 (83%) with at least 25 m improvement in 6-minute walk distance, 11 of 12 (92%) with a at least 2 ml/kg/min improvement in VO_2 max, and 9 of 12 (75%) with at least a 10-point improvement in quality of life score (Fig. 1). Conversely, the control group was limited to 3 of 9 (33%) with improvement in LVEF, 4 of 9 (44%) with improvement in 6-minute walk distance, 2 of 9 (22%) with improvement of VO_2 max, and 3 of 9 (33%) with improvement in quality of life.

GLP-1 significantly reduced plasma glucose (baseline: 173 ± 32 ; 5 weeks GLP-1: 125 ± 17 mg/dL, $P < .05$) and NEFA levels (baseline: 760 ± 67 ; 5 weeks GLP-1: 524 ± 60 $\mu\text{mol/L}$, $P < .05$) in association with an increase in plasma insulin levels (baseline: 206 ± 94 ; 5 weeks GLP-1: 308 ± 101 pmol/L, $P < .05$). Plasma glucose (baseline: 113 ± 17 ; 5 weeks: 114 ± 15 mg/dL), plasma NEFA (baseline: 750 ± 92 ; 5 weeks: 647 ± 96 $\mu\text{mol/L}$), and plasma insulin (baseline: 199 ± 72 ; 5 weeks: 243 ± 107 pmol/L) levels were not significantly different in the control group. However, the functional improvements in GLP-1-treated patients were observed in both diabetic and non-diabetic patients (Table 2), although these trends were not statistically significant due to the small number of patients in each group when stratified by diabetic status.

Hemodynamic parameters improved significantly in the GLP-1-treated group after 5 weeks of therapy. Cardiac

output increased from $2.5 \pm .3$ L/min to $2.9 \pm .3$ L/min ($P < .05$), while there was no significant change in the control group ($2.5 \pm .4$ to $2.6 \pm .5$ L/min). The improvement in cardiac output in the GLP-1-treated group was also present when normalized for body mass index ($P < .02$). GLP-1 reduced the LV end diastolic volume index (EDVI) from 82 ± 7 to 73 ± 6 mL/m² ($P < .05$) and the LV end systolic volume index (ESVI) from 66 ± 8 to 55 ± 6 mL/m² ($P < .05$). The changes in cardiac volumes were less in the control group (LV EDVI: 90 ± 11 to 84 ± 13 mL/m²; LV ESVI: 71 ± 11 to 66 ± 13 mL/m²). There was a trend toward reduced LV mass index in the GLP-1-treated group (172 ± 14 g/m² to 159 ± 12 g/m²; $P = .56$) compared with control (179 ± 21 g/m² to 183 ± 25 g/m²; $P = .77$) although the difference did not reach statistical significance. Heart rate was also not significantly different between the GLP-1-treated group (73 ± 3 to 78 ± 4 beats/min) and the control groups (68 ± 4 to 71 ± 5 beats/min). There were no significant changes in mean arterial pressure in the GLP-1-treated group (81 ± 2 to 84 ± 2 mm Hg) or the control group (83 ± 2 to 79 ± 5 mm Hg), but calculated systemic vascular resistance was reduced significantly in GLP-1-treated patients (2604 ± 143 to 2299 ± 102 dyne·cm⁻⁵·sec⁻¹, $P < .05$) compared with control (2656 ± 212 to 2451 ± 296 dyne·cm⁻⁵·sec⁻¹). Mitral regurgitation was present by echo in 11 of 12 of the GLP-1-treated patients and 8 of 9 controls. The degree of mitral regurgitation was moderate in both groups and did not change significantly during the 5 weeks of the study.

The improvement in LV hemodynamics was associated with a decrease in BNP in the GLP-1-treated group (baseline: 289 ± 90 ; 5 weeks: 218 ± 102 pg/ml), although BNP values varied widely in this obese patient population. There was no change in BNP levels in the control group (baseline: 296 ± 129 ; 5 weeks: 285 ± 152 pg/mL). There were no changes in renal function as measured by blood urea nitrogen (BUN) and creatinine in either group, although two-thirds of the GLP-1-treated patients required a reduction in their diuretic dose during treatment (Table 3).

Adverse events were reported in both groups. There were 2 hospitalizations in each group during the study. There was an episode of asymptomatic, non-sustained ventricular tachycardia in each group, and 1 episode of atrial fibrillation in the GLP-1-treated group. The most common adverse effects in the treatment group were nausea and constipation, which occurred (8 episodes) in 5 patients. There were a total of 9 episodes of hypoglycemia (glucose 50–70 mg/dL) in 4 GLP-1-treated patients and 4 episodes of hypoglycemia in 2 control patients. The episodes of hypoglycemia occurred in diabetic patients receiving oral hypoglycemics or insulin, were asymptomatic, and responded to a reduction in these medications. Two diabetics in the GLP-1-treated group had their insulin requirements eliminated during GLP-1 infusion.

One patient was withdrawn from the study during the first hour of administration of GLP-1 secondary to hypoglycemia with the test dose of 1.25 pmol/kg/min. A second

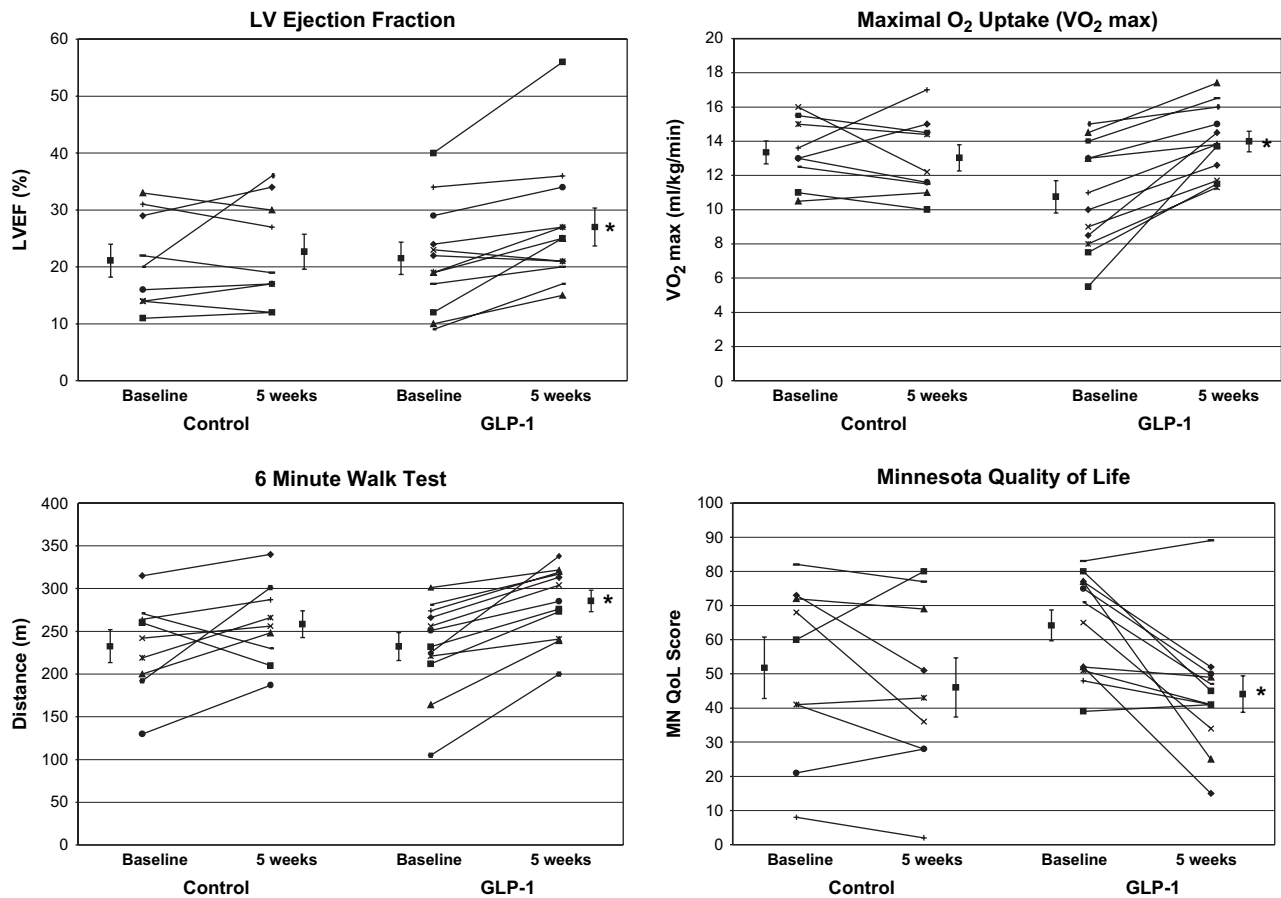


Fig. 1. Changes in left ventricular ejection fraction (LVEF), maximum myocardial ventilation oxygen consumption (VO₂ max), Minnesota Quality of Life score (MNQOL), and 6-minute walk after 5 weeks of glucagon-like peptide-1 (GLP-1) infusion versus control in subjects. These illustrations represent individual data in both groups of patients.

patient withdrew from the study 1 day after starting treatment secondary to his inability to use the infusion pump appropriately. There was 1 death in the GLP-1-treated group in a patient with class IV heart failure secondary to severe aortic stenosis that was deemed inoperable. The patient received 17 days of GLP-1 therapy before withdrawing from the study. The patient developed clinical decompensation due to low cardiac output and decided to forego aggressive treatment. The patient died 18 days after GLP-1 was discontinued.

Discussion

We report the hemodynamic and metabolic benefits of a novel insulinotropic and insulinomimetic agent, GLP-1, in patients with severe CHF. We observed significant improvements in both LVEF and functional status. The improvement in LVEF in the GLP-1-treated patients could not be accounted for by changes in blood pressure and was observed in patients with and without diabetes. The enhanced insulin responses resulted in reductions in NEFA and glucose.

Table 2. Effects of GLP-1 on Diabetic and Non-Diabetic Patients

	Control (n = 9)				GLP-1 (n = 12)			
	Non-DM (n = 4)		DM (n = 5)		Non-DM (n = 4)		DM (n = 8)	
	Baseline	5 weeks	Baseline	5 weeks	Baseline	5 weeks	Baseline	5 weeks
LVEF (%)	18.75 ± 3	18.25 ± 3	23 ± 4	26.2 ± 5	17.5 ± 2	25.25 ± 2	23.5 ± 3	27.9 ± 4
VO ₂ max (ml/kg/min)	14.4 ± .6	13.8 ± 1	12.5 ± 1	12.4 ± 1.0	9.9 ± 1.1	13.5 ± .4	11.2 ± .9	14.3 ± .6
MQOL	35 ± 12	27 ± 8	66 ± 8	61 ± 10	54 ± 4	45 ± 1	69 ± 4	44 ± 6
6 MWT (m)	214 ± 26	249 ± 19	248 ± 18	266 ± 24	212 ± 10	260 ± 7	243 ± 17	299 ± 12
BNP (pg/mL)	412 ± 170	446 ± 205	203 ± 78	156 ± 73	443 ± 14	441 ± 168	211 ± 74	106 ± 27
HbA1C (%)	5.6 ± .1	5.7 ± .1	7.35 ± .7	7.48 ± .6	6.2 ± .2	6.1 ± .2	8.09 ± .4	7.36 ± .4

BNP, B-type natriuretic peptide; DM, diabetes mellitus; GLP-1, glucagon-like peptide-1; LVEF, left ventricular ejection fraction; MQOL, Minnesota Quality of Life score; VO₂ max, maximum myocardial ventilation oxygen consumption; 6 MWT, 6-minute walk test.

Table 3. Effect of GLP-1 on Renal and Metabolic Function

	Control (n = 9)		GLP-1 (n = 12)	
	Baseline	5 weeks	Baseline	5 weeks
BNP (pg/mL)	296 ± 128	285 ± 152	289 ± 90	218 ± 102
HbA1C (%)	6.6 ± .6	6.7 ± .6	7.7 ± .4	6.9 ± .4
[Na ⁺] (mmol/L)	141 ± 1	140 ± 1	140 ± 1	141 ± 1
BUN (mg/dL)	16 ± 2	23 ± 7	27 ± 6	27 ± 3
Cr (mg/dL)	1.0 ± .1	1.1 ± .1	1.3 ± .1	1.4 ± .2

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; GLP-1, glucagon-like peptide-1.

The effects of GLP-1 in humans with type 2 diabetes mellitus are well established in several trials.^{22,23} To date, studies demonstrating the efficacy of GLP-1 in both experimental and clinical cardiovascular disease states are limited. Our laboratory has demonstrated that administration of GLP-1 limits myocardial stunning following coronary occlusion and reperfusion in conscious canines.²⁴ In addition, Bose et al²⁵ were able to reduce infarct size in isolated rat hearts by infusing GLP-1 prior to coronary occlusion. GLP-1 has also been shown to limit accumulation of pyruvate and lactate in the ischemic and non-ischemic porcine myocardium.²⁶ Our laboratory has also demonstrated improvement in LV function with a continuous infusion of GLP-1 in dogs with pacing-induced DCM.²⁷

We have previously demonstrated the benefits of GLP-1 in patients with severe LV dysfunction following acute myocardial infarction and reperfusion.¹⁹ Significant improvement in LV function and regional wall motion abnormalities were seen in patients treated with a 72-hour IV infusion of GLP-1 with limited side effects. The current study is the first in humans to demonstrate the benefit of GLP-1 in patients with severe CHF.

Paolisso et al^{5,6} demonstrated that insulin-mediated glucose uptake is an independent prognostic factor in heart failure. Our laboratory has shown that GLP-1 increases myocardial glucose uptake in conscious dogs with pacing-induced heart failure,²⁷ but myocardial glucose uptake was not measured in this study. Other experimental studies have observed variable inotropic properties^{28,29} and improvements in endothelial function^{30,31} suggesting both direct and indirect myocardial effects. We cannot determine whether the beneficial effects of GLP-1 were due to direct effects on the myocardium or more general systemic effects. The decrease in cardiac volumes and systemic vascular resistance and the increase in cardiac output in the GLP-1-treated group are consistent with peripheral unloading and similar to effects observed in conscious dogs with advanced DCM.²⁷

It is conceivable that better glycemic control in the GLP-1-treated group may have contributed to the improvement in function. However, the improvement in non-diabetic subjects was of a comparable magnitude, suggesting effects over and above glycemic control. It is important to note that our study population was obese (BMI > 30) and that these results may not be applicable to heart failure patients with cachexia. We did not observe an improvement in renal

function as approximated by the plasma BUN and creatinine, but the reduction in diuretic requirements suggests a more effective diuresis in the GLP-1-treated group. The requirement for a reduction in diuretic dose suggests improved absorption or delivery consistent with the observed beneficial hemodynamic effects. We did not observe a qualitative difference in mitral regurgitation at rest.

Conclusion

GLP-1, an insulinotropic and insulinomimetic peptide, improves LVEF and functional status in patients with systolic heart failure. The safety and benefits are seen in both diabetic and non-diabetic patients. These results warrant further study in a large double-blind randomized trial of patients with advanced heart failure.

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