Glucagon-like Peptide-1 and Myocardial Protection: More than Glycemic Control

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ABSTRACT

Pharmacologic intervention for the failing heart has traditionally targeted neurohormonal activation and ventricular remodeling associated with cardiac dysfunction. Despite the multitude of agents available for the treatment of heart failure, it remains a highly prevalent clinical syndrome with substantial morbidity and mortality, necessitating alternative strategies of targeted management. One such area of interest is the ability to modulate myocardial glucose uptake and its impact on cardioprotection. Glucose-insulin-potassium (GIK) infusions have been studied for decades, with conflicting results regarding benefit in acute myocardial infarction. Based on the same concepts, glucagon-like peptide-1-[7–36] amide (GLP-1) has recently been demonstrated to be a more effective alternative in left ventricular (LV) systolic dysfunction. This paper provides a review on the current evidence supporting the use of GLP-1 in both animal models and humans with ischemic and nonischemic cardiomyopathy.

Introduction

The continuous requirement for high-energy phosphates to perform mechanical work burdens the heart with metabolic requirements not shared by other organ systems. As such, substrate availability, oxidative phosphorylation, and high energy phosphate transfer are critical to cardiac performance. While the heart is capable of utilizing a variety of available substrates to generate adenosine triphosphate (ATP), this metabolic flexibility is compromised under circumstances in which the heart is stressed, particularly by myocardial ischemia. Under these circumstances, the heart shifts its preference from nonesterified fatty acids (NEFA) to glucose to reduce the production of reactive oxygen species and minimize the added requirements for molecular oxygen associated with NEFA oxidation.[1] Despite widespread acceptance of these basic metabolic principles, clinical strategies designed to assist the injured heart in the uptake of glucose have failed to yield the predicted clinical benefits.

Although the transport of glucose into the myocyte is controlled by the glucose transporters GLUT-1 and GLUT-4, the number of transporters at the cell surface is influenced by insulin, energy demand, and oxygen availability. Major metabolic changes occur rapidly during an acute myocardial infarction (AMI). Increased circulation of free fatty acids and secretion of catecholamines contribute to the development of acute glucose intolerance and adversely influence the outcome of ischemic but viable tissue. In animal models, increased levels of free fatty acids increase myocardial oxygen utilization by 10 to 25% and inhibit glucose utilization. In addition, free fatty acids may exert arrhythmogenic effects on the hypoxic myocardium, increase membrane damage, and decrease cardiac function.[2] In the hypoxic state, an increase in glucose uptake and subsequent ATP generated through glycolysis help to sustain myocardial electrical and mechanical performance, maintain cellular ultrastructure, promote myocardial recovery, reduce myocardial creatine phosphokinase depletion, and slow mitochondrial injury.[2,3] Based on this premise, the proposed mechanism of enhancing myocardial energetic efficiency by increasing glucose availability and utilization has led to the vigorous pursuit of therapeutic approaches designed to augment glucose uptake and oxidation or reduce fatty acid uptake and oxidation as cardioprotective strategies in AMI and other clinical states of LV systolic dysfunction.

The Limitations of Glucose-Insulin-Potassium

Despite the compelling metabolic argument that indicates the benefits of increasing glucose uptake as an important therapeutic goal in the management of LV systolic dysfunction, the identification of effective strategy to modulate myocardial metabolism has proven elusive.

The effects of glucose-insulin-potassium (GIK) therapy in the treatment of AMI have been intriguing researchers for decades (Table 1).[4–7] Important studies such as ECLA (Estudios Cardiológicos Latinoamérica) and the Zwolle Infarct Study Group showed a significant decrease in mortality in AMI, though only selectively in those undergoing concomitant reperfusion therapy[4] or those without heart failure.[5] Recently, the CREATE-ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiológicos Latinoamérica)[6] and GIPS-II (Glucose Insulin Potassium Study II)[7] groups found no additional benefit in mortality or reinfarction at

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Table 1. Clinical Trials of Glucose-Insulin-Potassium in Acute Myocardial Infarction

Trial	Patients	Follow-up	Intervention	Absolute risk (mortality), %	RR, HR, or OR (95% CI)	Results
ECLA[4] n = 407	Suspected AMI within 24 hours of symptoms	In-hospital mortality (average length of stay 9–11 days)	24-h infusion GIK (1.0–1.5 ml/kg/h)	6.7% (5.2% when combined with reperfusion)	RR 0.58 (0.30–1.10)	No overall differences between GIK and control. When combined with reperfusion, GIK reduced in-hospital mortality.
			Control	11.0% (15.2% when combined with reperfusion)	RR 0.34 (0.15–0.77) when combined with reperfusion	
Zwolle Infarct Study Group[5] n = 940	ST elevation MI within 24 hours of symptoms	30 days	8–12 h infusion GIK (3 ml/kg/h)	4.8% overall (1.2% in Killip Class 1)	RR 0.82 (0.46–1.46) overall.	No overall differences in mortality. In those without heart failure, GIK reduced mortality.
			Control	5.8% overall (4.2% in Killip Class 1)	RR 0.28 (0.1–0.75) in those without signs of heart failure (Killip Class 1)	
CREATE-ECLA[6] n = 20,201	ST elevation MI within 24 hours of symptoms	30 days	24-h infusion GIK (1.5 ml/kg/h)	9.7%	HR 1.03 (0.95–1.13)	No significant differences in mortality, cardiac arrest, cardiogenic shock, or reinfarction rates.
			Control	10.0%		
GIPS-II[7] n = 889	ST elevation MI within 6 hours of symptoms	30 days	12-h infusion GIK (2.0 ml/kg/h)	2.9%	OR 1.6 (0.7–4.0)	No significant differences in mortality, reinfarction, or need for revascularization.
			Control	1.8%		

Abbreviations: CREATE-ECLA, Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation — Estudios Cardiológicos Latinoamérica; ECLA, Estudios Cardiológicos Latinoamérica; GIPS-II, Glucose-Insulin-Potassium Infusion in Patients with Acute Myocardial Infarction Without Signs of Heart Failure: The Glucose-Insulin-Potassium Study (GIPS)-II; HR, hazard ratio; OR, odds ratio; RR, relative risk.

30 days with GIK compared to standard therapy in ST elevation MI.

Taken together, the preponderance of evidence now indicates that GIK treatment is an ineffective strategy for favorably influencing clinical outcomes in acute coronary syndromes. These findings raise several questions regarding metabolic modulation as a therapeutic target in acute or chronic left ventricular (LV) dysfunction. First, it is conceivable that favoring glucose as the metabolic substrate of choice is disadvantageous. However, a wealth of basic and experimental studies has demonstrated that the scientific basis for this is likely sound.[1,2] Alternatively, the therapeutic approach for increasing myocardial glucose uptake may be inappropriate and novel approaches are needed to achieve the putative benefits of adjuvant metabolic modulation in heart disease.

The Limitations of Insulin, Sulfonylureas, and Thiazolidinediones

A fundamental goal of type 2 diabetes management is glycemic control for the prevention of both microvascular and macrovascular complications. The United Kingdom Prospective Diabetes Study (UKPDS) [8] demonstrated that the various therapeutic approaches used to achieve glycemic control have different effects on these clinical outcomes. In this study of 3,867 patients with type 2 diabetes followed over 10 years, intensive treatment with insulin or sulfonylureas, both of which increase plasma insulin concentration, lead to an 11% reduction in glycosylated hemoglobin and a 25% risk reduction in microvascular endpoints, but had no impact on macrovascular events. Alternatively, in a similar study of metformin, an insulin-sensitizing agent that reduces plasma insulin concentration, there was a 32% reduction in overall diabetes-related endpoints, including macrovascular complications.[9]

Thiazolidinediones are another class of insulin-sensitizers that have been used in the management of type 2 diabetes. A recent meta-analysis[10] of 42 trials comparing rosiglitazone to control revealed odds ratios of 1.43 and 1.64 with regard to risk of myocardial infarction and death from cardiovascular disease, respectively. The recent controversy around thiazolidinedione use rekindles the debate as to the desired therapeutic profile of hypoglycemic drugs. Said differently, glycemic control may be necessary but insufficient to reduce cardiovascular mortality and how this glycemic control is achieved may be of substantial importance. With that in mind, we offer for consideration incretins as a therapeutic alternative that offers both excellent glycemic control and cardioprotection.

GLP-1 as a Therapeutic Alternative to Insulin-Mediated Glucose Uptake

What alternative options exist for influencing myocardial metabolism and specifically glucose utilization in cardiovascular disease? Recent scientific investigation into the role of incretin hormone biology has generated new enthusiasm for the clinical application of these naturally occurring peptides in the pursuit of glycemic control in type 2 diabetes. Specifically, glucagon-like peptide-1-[7–36] amide (GLP-1) is a member of the pro-glucagon incretin family with insulinomimetic, insulinotropic, and glucagonostatic actions whose metabolic effects favor glucose uptake.[11] Todd et al.[12] and Zander et al.[13] confirmed in trials of GLP-1 for type 2 diabetes that GLP-1 activity ceases at glucose levels<4 mM (72 mg/dl). This property obviates the need for concomitant glucose infusion. However, continuous intravenous or subcutaneous infusion is required secondary to short half life (1–2 minutes) as GLP-1-[7–36] amide is rapidly degraded to GLP-1-[9–36] amide through the actions of the ubiquitous peptidase, dipeptidyl peptidase-IV (DPP-IV).[11]

With the use of GLP-1, the importance of minimal infusion volumes (3–6 ml/day) has significant implications given the adverse trend in mortality seen with Killip class III-IV heart failure patients who could not tolerate the volume requirements of GIK therapy.[5] For these reasons, there has been increasing interest in GLP-1 as an alternative method to stimulate myocardial glucose uptake in an attempt to limit myocardial stunning, improve global and regional ventricular function, and ultimately impact long term cardiovascular outcomes including mortality.

Experimental Studies of GLP-1 in Myocardial Ischemia

Nikolaidis et al.[14] demonstrated that GLP-1 (1.5 pmol/kg/min) attenuates myocardial stunning after brief periods of myocardial ischemia in conscious, chronically instrumented dogs. Regional wall motion recovery occurred significantly earlier (6 versus 24 hours) and isovolumic left ventricular relaxation, an ATP-dependent process influenced by myocardial substrate metabolism, significantly improved compared to control as measured over 24 hours. GLP-1 had no effect on myocardial contractility, heart rate, or coronary blood flow. These data suggest that GLP-1 has salutary effects on post-ischemic contractile dysfunction in a relevant large animal model of ischemia and reperfusion.

A fundamental question arising from the experiments of Nikolaidis et al. was whether the effects of GLP-1 seen in ischemia and reperfusion were due to its direct action on the post-ischemic myocardium. Zhao et al.[15] perfused isolated, isovolumic rat heart preparations for 30 minutes, then subjected them to a globally reduced coronary perfusion pressure (5% of baseline coronary flow) for 30 minutes. GLP-1 (500 pmol/L) was infused one minute prior to inducing low flow ischemia and throughout reperfusion. The LV developed pressure (GLP-1: 98 ± 5 mm Hg vs control: 66 ± 6 mm Hg, $p<0.05$) and contractile performance ($LV\ dP/dt_{max}$) (GLP-1: 4081 ± 165 mm Hg·s^{-1}vs control: 2345 ± 112 mm Hg·s^{-1}, $p<0.05$) recovered faster and to a greater extent in the GLP-1 treated group following

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brief periods of global low flow ischemia, consistent with the findings by Nikolaidis et al[14] in conscious dogs. GLP-1 was associated with an increase in post-ischemic myocardial glucose uptake compared to control. Creatine phosphokinase release following reperfusion was less in the GLP-1 group compared to both the insulin and control groups. The GLP-1 mediated recovery of post-ischemic contractile dysfunction was of a magnitude similar to insulin infusion but without the concomitant risks of hypoglycemia.

Other laboratories have demonstrated similar salutary effects of GLP-1 in rodent models of myocardial infarction. Bose et al.[16] showed that GLP-1 treatment reduced infarct size compared to control both In Vitro (26.7 ± 2.7% vs 58.7 ± 4.1%) and in vivo (20.0 ± 2.8% vs 44.3 ± 2.4%) in rat models of permanent coronary artery occlusion (35 minutes of ischemia followed by 120 minutes reperfusion). Taken together, these data suggest that GLP-1 has direct effects on post-ischemic myocardium, and the effects are mediated through the myocardial GLP-1 receptor.

Experimental Studies of GLP-1 in Non-Ischemic Dilated Cardiomyopathy (DCM)

In addition to the beneficial effects of GLP-1 in post-ischemic myocardial injury, there is emerging evidence that GLP-1 has salutary effects in non-ischemic LV dysfunction. Nikolaidis et al.[17] infused GLP-1 over 48 hours in escalating doses (1.5 to 20 pmol/kg/min) in a group of conscious control dogs to determine hemodynamic effects of GLP-1 on normal hearts (measured for 48 hours after infusion was complete). There was no effect on LV systolic pressure, LV end-diastolic pressure (LVEDP), LV dP/dt, heart rate or mean arterial pressure. In contrast, GLP-1 (1.5 pmol/kg/min) markedly improved these hemodynamic parameters in conscious dogs with severe DCM induced by rapid pacing. These significant effects included increased LV dP/dt (+960 ± 47 mm Hg·s^{-1}), stroke volume (+14 ± 3 mL), cardiac output (+548 ± 39 mL·min^{-1}), and left ventricular ejection fraction (LVEF) (38 ± 5% vs 28 ± 1%), and decreased LVEDP (−11 ± 2 mm Hg), heart rate (−34 ± 5 min^{-1}), and systemic vascular resistance (−1122 ± 139 dyne·s^{-1}·cm^{-5}) (Figure 1). These investigators also

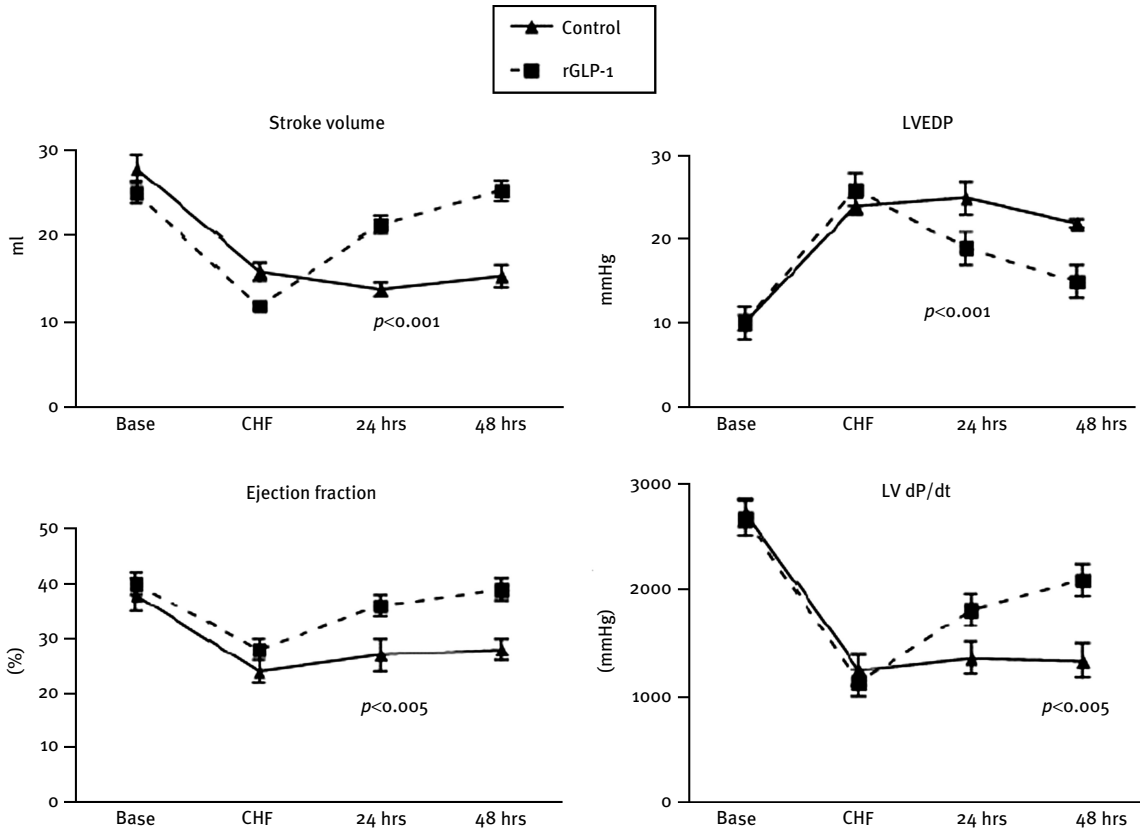

Figure 1. Effects of continuous infusion of GLP-1 (1.5 pmol·kg^{-1}min^{-1}) for 48 hours on Stroke Volume, LVEDP (left ventricular end-diastolic pressure), Ejection Fraction, and Contractility (LV dP/dt) in 16 conscious dogs with advanced DCM (dilated cardiomyopathy) compared with 8 conscious dogs that received equal amounts (3 ml/day) of saline as control.[17]

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continued

Table 2. Clinical Trials of Glucagon-like Peptide-1

Trial	Patients	Follow-up	Intervention	Data				Results
GLP-1 in AMI and LV dysfunction[18] n = 21	AMI and LVEF<40% after angioplasty	72 hours		LVEF (%)	r-WMSI (%)	g-WMSI (%)	mortality (%)	GLP-1 improved LVEF, global and regional wall motion scores, glycemic control, and decreased in-hospital mortality and length of stay
			72-h infusion GLP-1 (1.5 pmol/kg/min)	39	−21	−15	10	
			Control	29	4	0	27	
GLP-1 in chronic heart failure[19] n = 21	NYHA Class III or IV with LVEF ≤ 40%	5 weeks		LVEF (%)	VO_2 max (ml O_2/min/kg)	6-min walk (m)	MNQOL (score)	Chronic infusion of GLP-1 significantly improved LV function, functional status, and quality of life
			5-week infusion GLP-1 (2.5 pmol/kg/min)	27	13.9	286	44	
			Control	21	10.8	232	64	
GLP-1 in CABG[20] n = 20	Preserved LVEF undergoing CABG	7 days		LVEF (%)		Glycemic Control (mg/dl)		GLP-1 improved glycemic control and decreased need for inotropic support, vasoactive infusions, and antiarrhythmic drugs
			60-h infusion GLP-1 (1.5 pmol/kg/min)	61	95			
			Control	59		140		

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; g-WMSI, global wall motion score index; MNQOL, Minnesota Living with Heart Failure Quality of Life score; NYHA, New York Heart Association; r-WMSI, regional wall motion score index; VO_2 max, maximum myocardial oxygen consumption.

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demonstrated a constellation of favorable metabolic effects associated with GLP-1. Thus, GLP-1 improved LV systolic performance and stimulated myocardial glucose uptake in a large animal model of dilated cardiomyopathy.

Clinical Studies of GLP-1

Against the backdrop of an expanding body of evidence suggesting salutary cardiovascular effects of GLP-1 in experimental animal models, there have been several phase 2 trials of GLP-1 in humans with cardiovascular disease (Table 2).[18–20] Nikolaidis et al.[18] reported on the effects of a 72-hour infusion of GLP-1 (1.5 pmol/kg/min) added to standard therapy in patients with AMI and LVEF<40% after successful (TIMI 3 flow) primary angioplasty. Effects were measured within 6–12 hours after completion of the 72-hour infusion. Global and regional wall motion scores improved in the GLP-1 treated group. Benefits of GLP-1 on LVEF (29 ± 2% to 39 ± 2%, $p<0.01$) were evident in both diabetic and non-diabetic patients, as well as in patients with anterior (left anterior descending artery) and non-anterior AMI (Figure 2). The in-hospital mortality rate and hospital length of stay were reduced (10% vs 27% and 6.1 vs 9.8 days, $p<0.02$, respectively) in the GLP-1 treated group.

Sokos et al.[19] was the first group to demonstrate that a long-term infusion of GLP-1 improves both LVEF and functional capacity in human patients with advanced heart failure. In a single-center pilot study, 21 obese patients with LVEF ≤40% and NYHA class III or IV heart failure were divided to receive a continuous subcutaneous infusion of GLP-1 or a small volume of saline as a control over 5 weeks. All patients in the study were on a standard, stable heart failure medication regimen, including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, aldosterone antagonist, loop diuretic, and digoxin. The group treated with GLP-1 had significantly improved LVEF (21 ± 3% to 27 ± 3%, $p<0.01$), maximum myocardial ventilation oxygen consumption (10.8 ± 0.9 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ to 13.9 ± 0.6 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, $p<0.001$), 6-minute walk distance (232 ± 15 m to 286 ± 12 m, $p<0.001$) and Minnesota Living with Heart Failure Quality of Life (MNQOL) score (64 ± 4 to 44 ± 5, $p<0.01$) (Figure 3). GLP-1 also lead to improved glycemic control with an increase in plasma insulin and decrease in plasma NEFA levels. Hemodynamic parameters that improved in the GLP-1 group included cardiac output (2.5 ± 0.3 $L \cdot min^{-1}$to 2.9 ± 0.3 $L \cdot min^{-1}$, $p<0.05$), LV end diastolic volume index (82 ± 7 $ml \cdot m^{-2}$ to 73 ± 6 $ml \cdot m^{-2}$, $p<0.05$), LV end systolic volume index

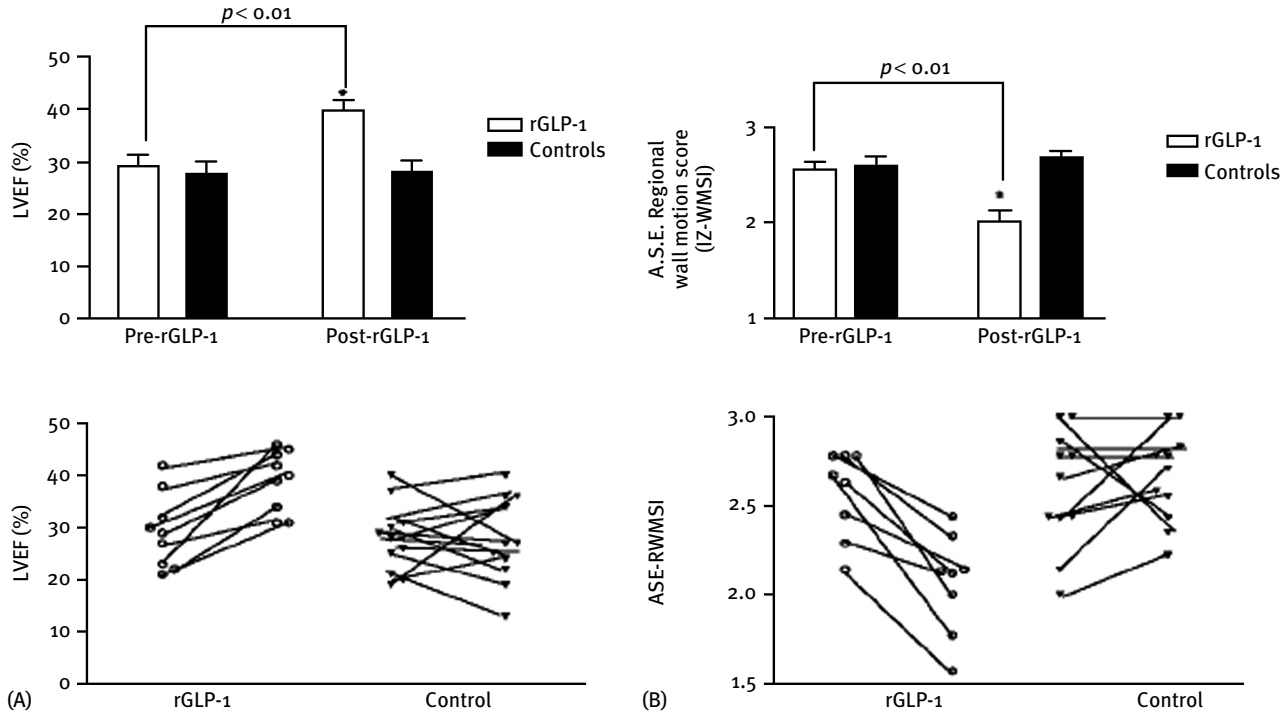

Figure 2. A. Changes in LVEF (left ventricular ejection fraction) after 72 hours of GLP-1 infusion versus control subjects. Lower panel illustrates individual data. B. Changes in regional wall motion score at the peri-infarct zone in GLP-1 treated patients versus control subjects. Lower panel illustrates the individual data.[18]

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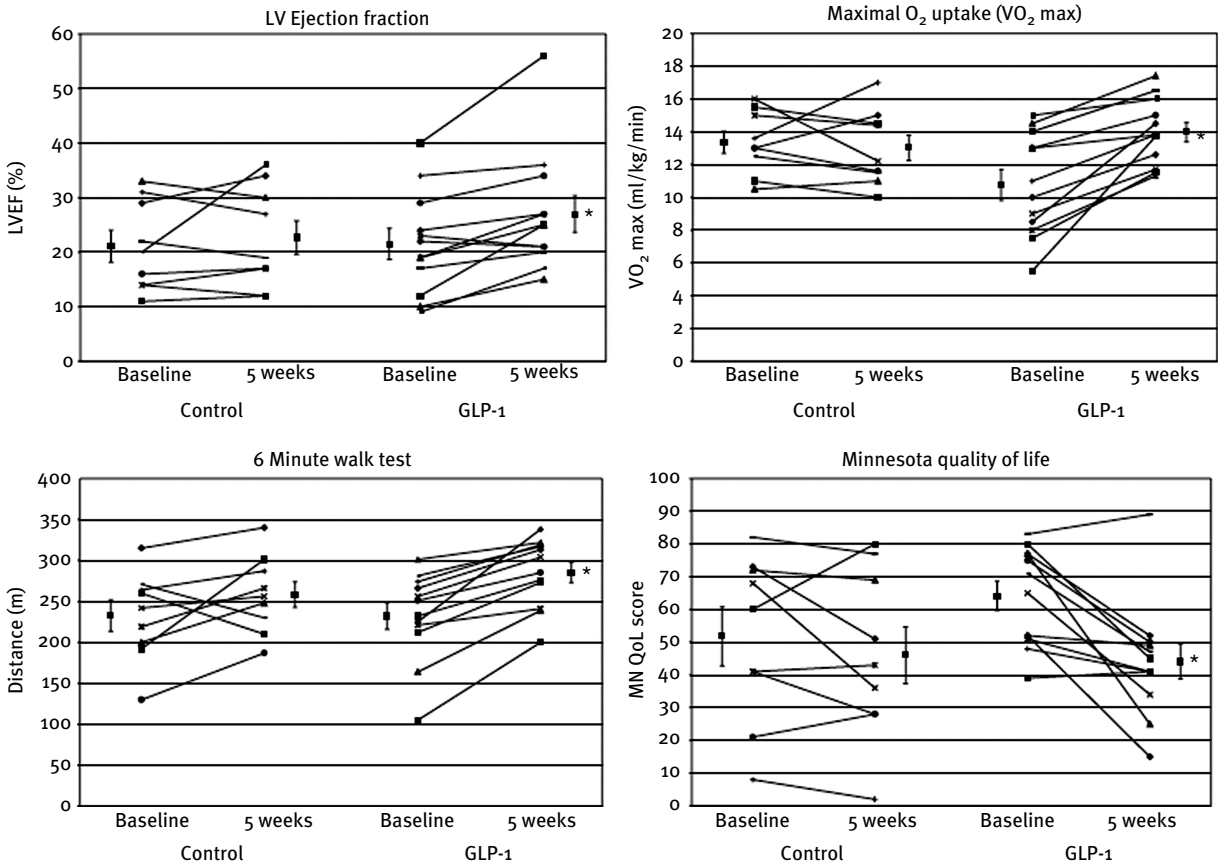

Figure 3. Changes in LVEF (left ventricular ejection fraction), VO_2 max (maximal myocardial ventilation oxygen consumption), 6 Minute Walk Test, and MNQOL (Minnesota Living with Heart Failure Quality of Life) score after 5 weeks of GLP-1 infusion versus control. These illustrations represent individual data in both groups of patients.[19]

(66 ± 8 ml·m^{-2} to 55 ± 6 ml·m^{-2}, $p<0.05$), and systemic vascular resistance (2604 ± 143 dyne·cm^{-5}·sec^{-1}to 2299 ± 102 dyne·cm^{-5}·sec^{-1}, $p<0.05$).

The promising results from the above clinical studies raise the question of whether GLP-1 may have favorable effects in cardiovascular disease states not directly related to acute ischemia or heart failure. Sokos et al.[20] examined its effect on glycemic control and LV function in patients with known coronary artery disease and preserved LVEF undergoing coronary artery bypass grafting. Twenty patients were divided to receive standard therapy alone compared to standard therapy with GLP-1 (1.5 pmol/kg/min) for 12 hours before surgery and continuing for 48 hours thereafter. Although there were no significant differences in LVEF ($61 \pm 4\%$ vs $59 \pm 3\%$) or cardiac index (3.0 ± 0.2 L·min^{-1}·m^{-2}vs 3.3 ± 0.4 L·min^{-1}·m^{-2}), the control group required greater use of inotropic support and vasoactive infusions (5 in control group vs 2 in GLP-1 group) and antiarrhythmic drugs (2 in control group vs none in GLP-1 group) to achieve the same hemodynamic results as the group treated with GLP-1. GLP-1 also resulted in better postoperative glycemic control, with a 45% decrease in insulin requirement (95 U/patient in control group vs 42 U/patient in GLP-1 group). These data suggest that GLP-1 is effective in improving both metabolic and hemodynamic outcomes in humans with AMI, NYHA class III or IV heart failure, and coronary artery disease requiring bypass grafting.

Conclusion

Metabolic modulation of post-ischemic myocardium and advanced LV systolic dysfunction is an important and emerging area of therapeutic investigation. Conventional approaches using insulin have proven ineffective, calling for new approaches to increase glucose uptake. Recent experimental and human studies using GLP-1 offer considerable promise in this regard. This incretin-based therapy has had a promising impact on hemodynamic parameters including

ejection fraction, cardiac output, infarct size, and regional wall motion in both ischemic and nonischemic animal models and humans with LV systolic dysfunction. Furthermore, cellular studies suggest that GLP-1 may activate cardioprotective and pro-survival pathways contributing to its beneficial effects.[15,16] More basic investigation and clinical studies are needed to confirm and advance this potentially important therapeutic approach.

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