Cardiovascular Effects of Glucagon-Like Peptide 1

A. Papazafiropoulou[1], S.I. Pappas[1], D. Papadogiannis[1] and N. Tentolouris*[,2]

[1]*Third Department of Internal Medicine and Diabetes Center, General Hospital of Nikaia, Piraeus, Greece*

[2]*First Department of Propaedeutic and Internal Medicine, Athens University Medical School, Athens, Greece*

Abstract: Glucagon-like peptide-1 (GLP-1) is involved in satiety control and glucose homeostasis. Besides, GLP-1 has cardiovascular effects. In experimental models, GLP-1 increases cardiac output and exerts a direct vasodilatory effect. In animals with dilated cardiomyopathy GLP-1 improves left ventricular performance. Human data demonstrated that GLP-1 reduces arterial blood pressure, improves endothelial function in individuals with diabetes and left ventricular function in patients with heart failure. Administration of GLP-1 increases ejection fraction in acute myocardial infraction and reduces ischemia-reperfusion myocardial injury. Although more research is needed, these data suggest that GLP-1 may be used with promising results in patients with heart failure, acute myocardial infarction and revascularization procedures in addition to the standard therapy.

Keywords: Arterial blood pressure, cardiovascular, endothelium, glucagon-like peptide 1, heart failure, left ventricular function, type 2 diabetes mellitus.

INTRODUCTION

Recently a new category of antidiabetic medication has been added to the existing treatments for type 2 diabetes mellitus (T2DM) with effects beyond metabolic control; they include glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-IV (DPP-IV) inhibitors [1]. GLP-1 analogues are administered subcutaneously while DPP-IV inhibitors orally [1]. These drugs reduce glycosylated hemoglobin A_{1c} levels by 0.4-1% in patients with T2DM, with GLP-1 analogues having a stronger glucose lowering effect [1]. In addition, GLP-1 analogues reduce appetite and delay gastric emptying [1]. The major advantages of this new class of antidiabetic medications are the low risk of hypoglycemic events, the favourable (GLP-1 analogues) or neutral (DPP-IV inhibitors) effect on body weight, and a potential protective role on β-cell preservation [1].

Many patients with T2DM are complicated by macrovascular disease, and cardiovascular events are the leading cause of morbidity and mortality in these patients [2]. A growing body of evidence, mainly from experimental studies, suggests that GLP-1 analogues exert certain favorable cardiovascular effects. The aim of this review is to provide current literature data on the cardiovascular effects of GLP-1. Towards this aim, we performed a systematic search in the PubMed and EMBASE databases using the terms 'glucagon-like peptide 1, 'GLP-1', 'exenatide', liraglutide', 'type 2 diabetes mellitus', 'cardiovascular', 'myocardial function', 'blood pressure' and 'endothelial function' alone and in combination to retrieve available data.

*Address correspondence to this author at the First Department of Propaedeutic and Internal Medicine, Athens University Medical School, 17 Agiou Thoma Street, GR-11527, Athens, Greece; Tel: +30 210 745 6448; Fax +30 210 746 2640; E-mail: ntentol@med.uoa.gr

GLP-1

The native GLP-1 is an incretin hormone secreted mainly by the L cells in the distal ileum and colon after a meal [1]. GLP-1 exists in two circulating equipotent molecular forms, GLP-1(7-37) and GLP-1(7-36) amide, although GLP-1 (7-36) amide is more abundant in the circulation after eating [1]. GLP-1 secretion occurs within minutes of nutrient ingestion, enhancing endogenous insulin secretion and thereby reducing blood glucose excursions [1]. GLP-1 also inhibits glucagon secretion, gastric emptying, and appetite [3].

GLP-1 has a short half-life of minutes, being rapidly degraded by DPP-IV and renal clearance [4]. As a result of DPP- IV activity, intact, biologically active GLP-1 represents only 10–20% of total plasma GLP-1 [5]. GLP-1 acts through its binding with its receptor. The GLP-1 receptor (GLP-1R) is a G protein–coupled receptor [6]. Distribution of the GLP-1R includes pancreatic β-cells, kidney, stomach, brain and, heart [7]. Activation of GLP-1R on β-cells leads to rapid increases in levels of cAMP and intracellular calcium followed by insulin exocytosis in a glucose-dependent manner [8]. More sustained GLP-1R signaling is associated with activation of protein kinase A, induction of gene transcription, enhanced levels of insulin biosynthesis, and stimulation of β-cell proliferation [9].

EXPERIMENTAL STUDIES

Experimental studies have investigated the effects of GLP-1 on blood pressure, heart rate and cardiac structure and function. Barragán *et al.* [10] showed that GLP-1-(1-37) in rats produced a moderate increase of systolic and diastolic arterial blood pressure and heart rate, while GLP-1-(7-36) amide induced the greatest increase these parameters in a dose-dependent manner. The same investigators showed that both GLP-1 (7-36) amide given at 10 ng and exendin-4, a GLP-1 agonist, given at 10 ng, produced a dose-dependent increase in systolic and diastolic arterial blood pressure as

1389-5575/11 $58.00+.00

well as in heart rate, with exendin-4 having a more prolonged action [11]. In addition, the administration of 3000 ng exendin (9–39), an antagonist of the GLP-1 (7–36) amide, blocked the effect of the latter two peptides on arterial blood pressure and heart rate. They concluded that the hemodynamic actions of GLP-1 (7–36) amide are mediated through its own receptors [11].

Another study [12] showed that the recombinant GLP-1 (rGLP-1) has antihypertensive and cardiac and renoprotective effects in Dahl salt-sensitive (Dahl S) rats fed a high salt diet for 2 weeks. Dahl S rats are salt-sensitive, insulin-resistant and hyperlipidemic. They also develop endothelial dysfunction, cardiac injury and glomerulosclerosis. The authors showed that chronic treatment with rGLP-1 administered at 1 μg/kg/min attenuates the development of hypertension, reduces renal and cardiac end organ damage and improves endothelial function in Dahl S rats fed a high salt diet. The antihypertensive effect of rGLP-1 in Dahl S rats was attributed mainly to the natriuretic effects of the rGLP-1 and not to improvement in insulin-resistance [12].

A recent study [13] examined the response to exenatide in rats under normotensive conditions and in a model of hypertension/metabolic syndrome induced by corticosterone. After 21 days of treatment with corticosterone the rats developed hypertriglyceridemia, visceral fat deposition, hyperglycemia, insulin resistance, and an elevation of the mean arterial blood pressure (MAP) by 14±1 mmHg. Exenatide given at a 1 μg/kg per day reversed significantly the corticosterone-induced increase in blood pressure and this normalization occurred independently from change in body weight. Additionally, exenatide reduced MAP by 5±3 mmHg in normotensive control rats. The above results confirmed an antihypertensive effect of exenatide in an experimental model with metabolic syndrome [13].

Hirata *et al.* examined the anti-hypertensive effect of 20 mg exendin-4 in salt-sensitive obese db/db mice after a salt load and after infusion of angiotensin II (ang-II). The study showed that in db/db mice, the urinary sodium excretion was delayed, arterial blood pressure was elevated and intra-renal ang-II concentration was increased in response to a high-salt load. However, treatment for 12 weeks with exendin-4 inhibited the development of hypertension in the mice. Furthermore, exendin-4 prevented ang-II-induced hypertension in non-diabetic mice and inhibited ang-II-induced phosphorylation in cultured renal cells. The authors concluded that treatment with exendin-4 exerts anti-hypertensive effects through attenuation of ang-II-induced high-salt sensitivity [14].

The mechanisms involved in the action of GLP-1 to the cardiovascular system were examined in another study [15]. They showed that the intracerebroventricular administration of the peptide produced an increase in arterial blood pressure and heart rate, which was blocked by previous intracerebroventricular administration of exendin (9–39), but not when it was intravenously injected. Intravenous administration of GLP-1 (7–36) amide produced a significant increase in arterial blood pressure and heart rate, which was blocked by previous intracerebroventricular or intravenous administration of exendin (9-39). Bilateral vagotomy blocked the stimulating effect of intracerebroventricular GLP-1 on arterial blood pressure and heart rate. Also, bilateral vagotomy prevented the blocking effect of intracerebroventricular but not of intravenous exendin (9–39) on the hemodynamic parameters after intravenous administration of GLP-1 (7–36) amide. They concluded that the action of GLP-1 (7–36) amide on cardiovascular system is under a dual control from both the central nervous system and peripheral structures and that the neural information emerging in the brain is transmitted to the periphery through the vagus nerve [15].

In accordance with the above findings, another study by Yamamoto *et al.* showed that the action of GLP-1 is controlled in part by the central nervous system [16]. They reported that centrally and peripherally administered exendin-4, increased dose-dependently blood pressure and heart rate. GLP-1R activation induced c-fos expression in the adrenal medulla and in neurons located at autonomic control sites in the rat brain, including medullary catecholamine neurons providing input to sympathetic preganglionic neurons. Furthermore, GLP-1R agonists rapidly activated tyrosine hydroxylase transcription in the catecholamine neurons of the brainstem. The above findings suggest that the central GLP-1 system represents a regulator of sympathetic outflow leading to downstream activation of cardiovascular responses *in vivo* [16].

Isbil-Buyukcoskun *et al.* investigated the effects of intracerebroventricularly injected GLP-1 on blood pressure and heart rate, and the role of the central cholinergic system and vasopressinergic system using male Wistar albino rats [17]. They showed that intracerebroventricularly GLP-1 increases arterial blood pressure and heart rate, and that stimulation of the central nicotinic and partially muscarinic receptors as well as vasopressinergic system, mediate the intracerebroventricularly GLP-1 effects on arterial blood pressure. The authors concluded that the effect of GLP-1 on heart rate and arterial blood might be partially due to stimulation of central nicotinic receptors [17].

In another study [18], exendin-4 was infused in awake, free-moving mice into the lateral ventricle of the brain in the basal state and during a hyperinsulinemic euglycemic clamp. Arterial femoral blood flow, whole-body insulin-stimulated glucose utilization and heart rate were continuously recorded. A continuous 3-h brain infusion of exendin-4 resulted in a decrease in femoral arterial blood flow and in whole-body glucose utilization, demonstrating that this effect was glucose dependent. However, the heart rate remained unchanged. The metabolic and vascular effects of exendin-4 were markedly attenuated by central infusion of the GLP-1R antagonist exendin-9 and totally abolished in GLP-1R knockout mice. The above data demonstrated that central GLP-1 signaling is an essential component of circuits integrating cardiovascular and metabolic responses to hyperglycemia [18].

It is known that GLP-1 exerts cAMP/protein kinase A-mediated insulinotropic actions in target endocrine tissues [9]. Vila Petroff *et al.* using rat cardiac myocytes showed that GLP-1 increased cAMP but failed to augment contraction, suggesting the existence of functionally distinct cAMP/protein kinase A compartments [19]. Furthermore,

they showed that GLP-1 elicited a cAMP-dependent modest negative inotropic effect produced by a decrease in myofilament-Ca^{2+} responsiveness, probably resulting from intracellular acidification [19].

Nyström *et al.* investigated the direct vascular effects of GLP-1 in a rat organ bath model. They found that GLP-1 induced relaxation of isolated rings of the femoral artery in a dose-response manner, an effect which was inhibited completely by the GLP-1R antagonist exendin (9–39). Neither the specific nitric oxide (NO) synthase inhibitor N-nitro-l-arginine nor removal of endothelium affected the GLP-1 relaxant effect. These findings suggest that there is a direct vasodilatory effect of GLP-1 on conduit vessels which is independent of NO production and of endothelium. This direct vasodilatory effect of GLP-1 may be of clinical relevance in subjects with T2DM who manifest endothelial dysfunction [20].

In another study it was showed that mice with genetic deletion of the GLP-1R (GLP-$1R^{-/-}$) exhibited lower resting heart rate, increased left ventricular (LV) dimensions and end-diastolic pressure compared with wild-type controls [21]. Although baseline hemodynamic parameters of GLP-$1R^{-/-}$ did not differ significantly from those of wild type, GLP-$1R^{-/-}$ mice displayed impaired LV contractility and diastolic function after insulin administration. These findings provided new evidence implicating an essential role for GLP-1R in the control of cardiac structure and function *in vivo* [21].

The effect of rGLP-1 infusion on hemodynamic parameters, myocardial metabolism, and infarct size during normoxic conditions as well as during ischemia and reperfusion was investigated using an open-chest porcine heart model. In the presence of rGLP-1, interstitial levels of pyruvate and lactate decreased during ischemia and reperfusion both in ischemic and non-ischemic tissue. Moreover, rGLP-1 infusion resulted in increased plasma insulin levels and decreased blood glucose levels. Neither hemodynamic variables nor the consequent infarct size were influenced by rGLP-1 infusion. They concluded that rGLP-1 altered myocardial glucose utilization during ischemia and reperfusion. These changes were associated with increased plasma insulin levels. rGLP-1 infusion in the current setting did not result in any hemodynamic effects [22].

Nikolaidis *et al.* examined the effect of rGLP-1 administration on LV function, hemodynamic parameters and myocardial substrate utilization in conscious dogs with advanced dilated cardiomyopathy (DCM). They showed that infusion of rGLP-1 at 1.5 pmol/kg/min for 48 hours resulted in improvement in LV function and in peripheral vasodilatation in dogs with DCM. This improvement was associated with increased myocardial glucose uptake and decreased plasma norepinephrine and glucagon levels. On the contrary, no significant changes were seen in normal dogs after infusion of rGLP-1. These findings suggest that GLP-1 may be of benefit in patients with heart failure [23]. The same team compared the effects of GLP-1 (7–36) amide and its metabolite GLP-1 (9–36) amide administered at 1.5 pmol/kg/min, which is a pharmacological dose resulting in an increase in plasma GLP-1 levels by 10-fold, on LV function and myocardial glucose uptake in dogs with DCM. Both treatments improved significantly LV pressures, contractility and performance, while no significant effect was seen in the control group. These data suggested that GLP-1 (9–36) amide is an active peptide and mimics the effects of GLP-1 (7–36) in stimulating myocardial glucose uptake and improving LV performance through insulinomimetic effects [24].

In another study GLP-1 was administered at a pharmacological dose (1.5 pmol/kg/min) to six dogs undergoing occlusion of the left circumflex coronary artery for 10 min followed by reperfusion after 24 hours. They compared the responses of coronary blood flow and regional thickening of the posterior wall with a group of eight vehicle-treated dogs undergoing the same occlusion-reperfusion protocol. Although the recovery of coronary blood flow was identical, regional wall motion recovery occurred earlier and was complete in the GLP-1-treated dogs, whereas residual contractile dysfunction persisted in the control group. Also, isovolumic left ventricular relaxation improved significantly in GLP-1-treated dogs. They concluded that GLP-1 enhanced recovery from ischemic myocardial stunning after successful reperfusion [25].

Bose *et al.* using the isolated perfused rat heart model and whole animal models of ischemia/reperfusion injury showed that administration of 0.3 nmol of GLP-1 before ischemia resulted in a significant reduction in the infarction size in comparison with the control group. Furthermore, this protection was abolished in the *in vitro* hearts by the GLP-1R antagonist exendin (9-39). The results of this study showed that GLP-1 protects the heart against injury *via* prosurvival signaling pathways [26]. Another study by the same team demonstrated that 0.3 nmol of GLP-1 exerts a significant protective effect against myocardial infarction, when given either prior to ischemia or during reperfusion due to its ability to activate prosurvival kinases, independent of its incretin properties [27]. They further confirmed that the intact GLP-1 (7-36) is capable of attenuating myocardial ischaemic-reperfusion injury in the isolated perfused rat heart model. GLP-1 was not effective in the absence of an inhibitor of GLP-1 breakdown, suggesting that the protective actions of GLP-1 against myocardial infarction were mediated by intact GLP-1 [28].

Another study in isolated rat hearts demonstrated that 500 pmol/l of GLP-1 enhanced functional recovery of the postischemic myocardium in contrast to its negative inotropic effects on the normally perfused heart. The effects of GLP-1 to stimulate myocardial glucose uptake were not mediated through the classic insulin-signaling cascade involving Akt-1 activation and GLUT-4 translocation but rather through increased myocardial nitric oxide production, p38 MAP kinase activity, and GLUT-1 translocation [29].

Sonne *et al.* tested the possible protective effects of exendin-4 and GLP-1 (9–36) amide against ischemia–reperfusion injury in an isolated rat heart preparation. They showed that 5 nmol of exendin-4, administered at the point of reperfusion, reduced the infarct size and improved the performance of the isolated rat heart. These results suggest that beyond its glucose lowering properties, exendin-4 may be a suitable candidate post-conditioning agent in the man-

agement of acute myocardial infarction (thrombolysis or angioplasty) or coronary artery bypass grafting. In addition, these results suggest that GLP-1 (9–36) amide is capable of a post-ischemic myocardial performance-enhancing action in the heart. This action of GLP-1 (9–36) amide was not related with infarct size, and may be mediated by receptors distinct from the classic GLP-1R [30].

A recent study examined whether exenatide is capable of reducing myocardial infarct size. In this study pigs were randomized to receive either exenatide at a pharmacological dose (10 μg subcutaneously and 10 μg intravenously) 5 min before the onset of reperfusion or phosphate-buffered saline after 75 min of coronary artery ligation and subsequent reperfusion. Cardiac function was measured with epicardial ultrasound and conductance catheter-based pressure-volume loops. In addition, they studied markers of apoptosis/survival and oxidative stress. This study showed that exenatide reduced myocardial infarct size and prevented deterioration of systolic and diastolic cardiac function. After exenatide treatment, myocardial phosphorylated Akt and Bcl-2 expression levels were higher compared with those after phosphate-buffered saline treatment. In addition, nuclear oxidative stress was reduced in the exenatide treatment arm, while superoxide dismutase activity and catalase activity were increased. These data identified exenatide as a potentially effective compound to reduce infarct size in adjunction to reperfusion therapy in patients with acute myocardial infarction [31].

Other authors showed that GLP-1 can act directly on cardiac myocytes and protect them from hypoxia-reoxygenation injury, mainly by inhibiting their apoptosis probably through the phosphatidylinositol-3-phophate kinase pathway [32]. Another study by Huisamen *et al.* examined the insulinomimetic effects of GLP-1 administered at a dose of 10^{-11}-10^{-8} mol/l on the heart using isolated perfused rat hearts and adult cardiac ventricular myocytes. During normoxic perfusion, no effect of increased concentrations of GLP-1 on either heart rate or left ventricular pressures was found. The study showed that during global low-flow ischaemia, GLP-1 protected the heart against low-flow ischaemia by enhancing glycolysis, probably *via* activation of AMP kinase and by modulating the profile of activation of the survival kinase PKB/Akt. In addition, GLP-1 had an infarct-sparing effect when supported by co-administration of a DPP-IV inhibitor [33].

A recent study proposed a novel two-pathway schema for cardiovascular actions of GLP-1, one that depends on the GLP-1R for its inotropic action, glucose uptake, ischemic preconditioning, and mild vasodilatory actions and the second that depends on rapid metabolism of GLP-1 to GLP-1 (9-36), the latter having GLP-1R–independent effects on postischemic recovery of cardiac function and vasodilation. They also suggested that GLP-1 (9-36) is not an inotrope agent, it has at best modest effects on myocardial glucose uptake *in vitro*, and causes vasodilatation through an NO/cGMP-dependent mechanism, thus offering cardioprotective effects in the setting of insulin resistance injury [34].

The outcome of coronary artery occlusion in normal and diabetic mice pre-treated with the GLP-1R agonist liraglutide administered at 200 μg/kg was also examined. The study showed that survival rates were higher in the liraglutide-treated mice. Furthermore, liraglutide reduced cardiac rupture and infarct size and improved cardiac output. Moreover, liraglutide conferred cardioprotection and survival advantages over metformin, despite equivalent glycemic control in diabetic mice with experimental myocardial infraction. These findings demonstrate that GLP-1R activation engages pro-survival pathways in the normal and diabetic mouse heart, leading to improved outcomes and enhanced survival following myocardial infraction *in vivo* [35]. A summary of the main results on the effect of GLP-1 on the cardiovascular system in experimental models is shown in Table **1**.

STUDIES IN HUMANS

There are few studies regarding the effects of GLP-1 on human cardiovascular system. Nyström *et al.* investigated the effect of GLP-1 administered at the pharmacological dose of 2 pmol/kg/min on endothelial function and insulin sensitivity in two groups: 12 T2DM patients with stable coronary artery disease and 10 healthy subjects with normal endothelial function and insulin sensitivity by determination of the post-ischemic flow mediated vasodilatation (FMD) of the brachial artery and the hyperinsulinemic isoglycemic clamp. They concluded that GLP-1 improves endothelial dysfunction but not insulin resistance in T2DM patients with established coronary artery disease, without affecting whole body glucose uptake [36].

It is well established that diabetes is an independent risk factor for congestive heart failure (CHF), probably in part due to disturbances in fuel uptake and utilization by myocardial cells. In another study the feasibility and safety of three days infusion of rGLP-1 at the pharmacological dose of 4 pmol/kg/min was examined in an open observational study in six patients with T2DM and CHF. The authors found that the treatment was safe and well tolerated and all patients completed the study. They showed that rGLP-1 has a modest effect on glycaemic control and in improvement of myocardial function. However, the observed changes were non significant and more studies are needed in large number of patients to confirm a potential beneficial effect on cardiac function in patients with T2DM who have CHF [37].

Sokos *et al.* investigated the safety and efficacy of a 5-week infusion of GLP-1 at a pharmacological dose of 2.5 pmol/kg/min, in addition to their standard therapy in 12 patients with New York Heart Association class III/IV heart failure with and without diabetes and compared the results with those of 9 patients with heart failure on standard therapy. Echocardiograms, maximum myocardial ventilation oxygen consumption (VO2 max), 6-minute walk test, and the Minnesota Living with Heart Failure quality of life score were assessed. The authors showed that prolonged infusion of GLP-1 improved LV function, functional status and quality of life in patients with severe heart failure while no such effect was seen in the control group. The improvement in LV function in the GLP-1-treated patients was not related to changes in blood pressure and they were observed in patients with and without diabetes [38].

The same team conducted a study in order to examine whether perioperative treatment with GLP-1 at a pharmacol-

Table 1. Cardiovascular Effects of GLP-1 in Animal Models

Reference	Author	Year	Animal model	Substance	Result
[10]	Barragan *et al.*	1994	Rats	GLP-1	↑ SBP/DBP, ↑ HR
[12]	Yu *et al.*	2003	Dahl salt-sensitive rats	GLP-1	Antihypertensive and cardioprotective effects
[13]	Laugero *et al.*	2009	Rats with hypertension/metabolic syndrome	Exenatide	↓ Hypertension
[14]	Hirata *et al.*	2009	Salt-sensitive mice	Exendin-4	↓ Hypertension
[16]	Yamamoto *et al.*	2002	Rats	Exendin-4	↑ BP & HR
[18]	Cabou *et al.*	2008	Mice	Exendin-4	↓ Femoral arterial blood flow
[20]	Nystrom *et al.*	2005	Rats	GLP-1	Relax femoral artery
[22]	Kavianipour *et al.*	2003	Porcine	rGLP-1	Altered myocardial glucose utilization during ischemia and reperfusion
[23]	Nikolaidis *et al.*	2004	Dogs with dilated cardiomyopathy	rGLP-1	Improve LV and systemic hemodynamics
[26]	Bose *et al.*	2005	Rats	GLP-1	↓ MI size
[29]	Zhao *et al.*	2006	Rats	GLP-1	↓ MI size
[30]	Sone *et al.*	2008	Rats	GLP-1/ Exendin-4	↓ MI size
[31]	Timmers *et al.*	2009	Pigs	Exenatide	↓ MI size
[35]	Noyan-Ashraf *et al.*	2009	Mice	Liraglutide	↓ MI size

SBP; Systolic blood pressure, DPB; Diastolic blood pressure, HR; Heart rate, BP; Blood pressure, LV; left ventricular, MI; myocardial infraction.

ogical dose of 1.5 pmol/kg/min affects hemodynamic recovery after coronary artery bypass grafting (CABG). Twenty patients with coronary heart disease and preserved left ventricular function who were scheduled to undergo CABG were randomized to receive standard therapy at the discretion of the surgeon or treatment with GLP-1 as a continuous infusion beginning 12 hours before CABG and continuing for 48 hours after surgery. Peri-operative hemodynamics, the LV ejection fraction (LVEF), plasma glucose, and requirements for insulin and inotropic support were monitored. The authors found that GLP-1 infusion was associated with reduced pre- and perioperative plasma glucose levels and reduced requirements for insulin infusion to achieve euglycemia in the postoperative period compared with standard treatment. The authors did not find significant differences in postoperative hemodynamic parameters or LVEF in the two groups; however, treatment with GLP-1 was associated with less need for pharmacologic and mechanical support to achieve hemodynamic outcomes. Similarly, GLP-1-treated patients had fewer arrhythmias requiring treatment compared with those who received the standard treatment and these benefits were achieved without significant side effects [39].

Another study investigated the safety and efficacy of a 72-hour infusion of GLP-1 at a pharmacological dose of 1.5 pmol/kg/min added to background therapy in 10 patients with acute myocardial infraction and LVEF < 40% after successful angioplasty compared with 11 control patients. They showed that the addition of GLP-1 to standard therapy improved significantly LVEF and global as well as regional wall motion score indexes in patients with acute myocardial infraction and systolic dysfunction after successful angioplasty. The beneficial effects of GLP-1 were independent of the location of the myocardial infraction or diabetes mellitus status [40].

Gutzwiller *et al.* examined the effects of GLP-1 at a pharmacological dose of 1.5 pmol/kg·min on water and sodium excretion in healthy lean and obese men. In particularly, 15 healthy lean and 16 obese men were examined in a double-blind, placebo-controlled, crossover study to examine the effect of a 3-h infusion of GLP-1 on urinary sodium excretion, urinary output, and the glomerular filtration rate after a salt load. The authors showed that infusion of GLP-1 evoked a dose-dependent increase in urinary sodium excretion in the lean subjects. Additionally, in the obese men there was a significant increase in urinary sodium excretion, a decrease in urinary H^+ secretion and in the glomerular filtration rate. These findings suggest an action at the proximal renal tubule and a potential renoprotective effect [41].

It is known that GLP-1 inhibits vagal activity and activates nitrergic pathways in experimental animals [15, 16]. In rats, GLP-1 increase sympathetic activity, heart rate, and blood pressure [15, 16]. However, the effects of GLP-1 on sympathetic activity in humans are unknown. A recent study assessed the effects of a GLP-1 agonist on autonomic nervous functions in 48 healthy volunteers using spectral analysis of heart rate. They showed that GLP-1 administered at a dose of 2.4 pmol/kg/min for 10 min followed by 1.2 pmol/kg/min increases skeletal muscle sympathetic nerve activity but did not affect cardiac sympathetic or parasympathetic activity

[42]. Noteworthy, these doses were pharmacological and were decided to achieve normal blood glucose levels.

In addition, it was demonstrated that in healthy volunteers GLP-1 given at a pharmacologicala dose of 1.2 pmol/kg/min, increases vasodilatation as assessed by venous occlusion plethysmography with graded intra-arterial infusion of acetylcholine [43]. This effect was independent of alterations in glucose or insulin concentrations and could be abolished by glyburide (glibenclamide) but not with glimepiride. No alteration in endothelium independent vasodilatation was seen.

Another interesting study published recently in nondiabetic patients with chronic compensated CHF showed that a 48-h infusion of 0.7 pmol/kg/min of GLP-1 resulted in minor increase in heart rate and diastolic blood pressure, while LVEF, cardiac index, tissue Doppler indexes and brain natriuretic peptide did not change during the experiment [44]. In addition, low blood glucose values were frequently seen. These results emphasize the need for further research in this area and the need for frequent blood glucose monitoring during GLP-1 infusion. The results of the cardiovascular effects of GLP-1 in humans are summarized in Table **2**. The proposed action of GLP-1 on the cardiovascular system is depicted in Fig. (**1**).

LIMITATIONS AND FUTURE RESEARCH PRIORITIES

In vitro, GLP-1 exerts a negative inotropic effect in rat cardiomyocytes despite increases in cAMP [19]. However, of specific interest is the fact that GLP-1 has also been shown to promote the activity of phosphoinositide 3-kinase in both β-cells and myocardium [45]. Activation of this kinase has been associated with myocardial protection in the setting of ischemic/reperfusion injury [46] as well as myocardial preconditioning [47, 48]. GLP-1 protects myocardium by reducing infarct size [26] in both *in vitro* and *in vivo* rat heart model, when the agent was given in pharmacological doses throughout ischemia and reperfusion. However, in a porcine model of myocardial ischemia, rGLP-1 prevented the accumulation of pyruvate and lactate but failed to decrease the infarction size [22]. These data from animal studies suggest that GLP-1 may be used with promising results in patients with acute myocardial infarction in addition to the standard therapy and during coronary artery reperfusion procedures. However, data from human studies are missing and there is need for research in this area.

The findings regarding the effects of GLP-1 on arterial blood pressure and heart rate showed differences between animal models and humans. It has been shown that the infusion of either GLP-1 or exendin-4, a long acting GLP-1 receptor agonist, increased blood pressure and heart rate in animal models [10, 16]. However, a study using pigs, failed to demonstrate significant hemodynamic changes [49]. Also, it has been found that prolonged GLP-1 treatment had antihypertensive effects in a rat model [12]. In a study in T2DM patients, both systolic and diastolic pressures were not altered with continuous infusion of GLP-1 [50]. However, reduction in blood pressure was constantly seen during treatment with either exenatide [51] or liraglutide [52] in long-term prospective studies without any change in heart rate. This effect, although moderate, is clinically meaningful as such reductions have been associated with significant improvement in cardiovascular outcomes. Therefore, it seems that in humans prolonged treatment with GLP-1 analogues

Table 2. Cardiovascular Effects of GLP-1 in Humans

Reference	Author	Year	Subjects	Substance	Result
[36]	Nystrom *et al.*	2004	T2D with CAD vs. healthy subjects	GLP-1	Improved endothelial function
[37]	Thrainsdottir *et al.*	2004	T2D with CHF subjects	rGLP-1	Improved myocardial function
[38]	Sokos *et al.*	2006	Subjects with CHF	GLP-1 vs. standard therapy	Improved LV function
[39]	Sokos *et al.*	2007	Subjects undergoing CABG	GLP-1 vs. standard therapy	↓ Arrhythmias/ no difference in LVEF
[40]	Nikolaidis *et al.*	2004	Subjects with acute MI after angioplasty vs. healthy subjects	GLP-1 vs. standard therapy	Improved LVEF
[41]	Gutzwiller *et al.*	2004	Healthy vs. obese men	GLP-1	↑ Natriuresis
[44]	Halbirk *et al.*	2010	Subjects with compensated CHF	GLP-1	↑ heart rate ↑ diastolic blood pressure No change in LVEF, cardiac index, tissue Doppler indexes and BNP

T2D; type 2 diabetes, CAD; coronary artery disease, CHF; chronic heart failure, CABG; coronary artery bypass grafting, MI; myocardial infraction, LV; left ventricular, LVEF; left ventricular ejection fraction; BNP; brain natriuretic peptide.

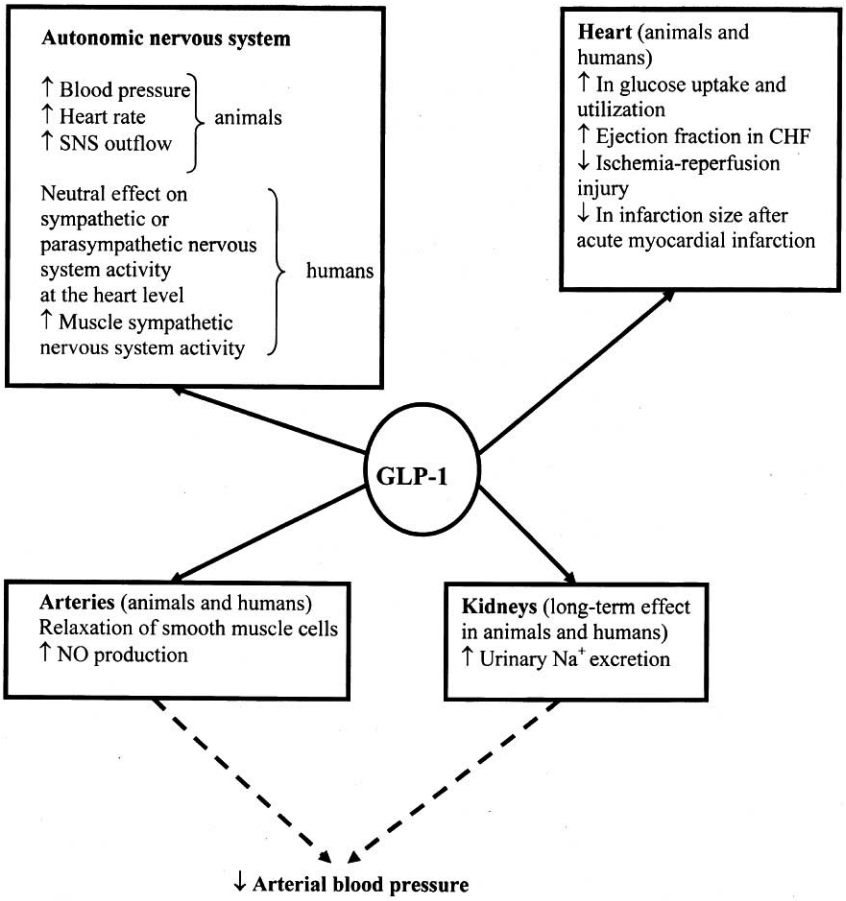

Fig. (1).

and agonists is required in order blood pressure reduction to be documented. The reduction in blood pressure is attributed to the vasorelaxant and natriuretic properties of GLP-1.

Some studies have suggested a role for the GLP-1 in the control of cardiac structure and function. Mice with a targeted gene deletion of the GLP-1R have enlarged hearts [21]. In addition, infusion of GLP-1 was associated with improvements in myocardial glucose uptake and LV systolic function in conscious dogs with dilated cardiomyopathy but not in normal dogs [23]. Beyond improving myocardial performance in animal models of CHF, recent data suggest that GLP-1R signaling protects against ischemic damage. In a dog model of acute occlusive ischemia, intravenous administration of GLP-1 reduced contractile dysfunction and improved ventricular relaxation [25]. In patients with diabetes and established coronary artery disease, intravenous GLP-1 increased significantly endothelial function assessed by FMD [36].

The prolonged infusion of GLP-1 improved LVEF and exercise performance in patients with heart failure [38]. In patients with myocardial infarction, GLP-1 infusion improved regional and global function and LV systolic dysfunction after angioplasty [40]. However, neither hemodynamics nor consequent infarct size was altered by GLP-1 infusion in an open chest, anesthetized porcine model of ischemia [22]. By contrast, GLP-1 infusion reduced infarct size in an isolated isovolumic rodent model of regional ischemia, but ventricular function was unaffected and glucose uptake was not measured [27].

All data suggest that the cardiovascular effects of GLP-1 analogies are independent of the effect on blood glucose levels. However, GLP-1 administration results in increase in plasma insulin concentrations [44], which is known that it exerts central sympathoexcitatory and direct vasodilatory effects in acute experiments. The studies published so far do not discriminate between the effects of insulin and GLP-1 per se. However, data from animal models suggest that the cardiovascular effects of GLP-1 was independent from changes in plasma insulin concentrations because they have been observed during intracerebroventricular GLP-1 administration [15-18] and in isolated heart [22, 26] and rings of femoral artery [20]. In addition, knockout mice lacking GLP-1R exhibit lower heart rate, increased LV dimensions and impaired LV contractility [21]. Therefore, it seems that the effects of GLP-1 on vasculature are mediated through specific GLP-1R independently from blood glucose or insulin concentrations.

It should be noted that the acute or short term effects of GLP-1 analogues cannot necessarily be translated to long-term clinically meaningful effects on the vasculature. Actually, no studies exist regarding the long-term effects of the GLP-1 analogues on cardiovascular system and outcomes. Given the beneficial effects observed so far, prospective studies are required to prove the potential effect of this new

class of medications on cardiovascular outcomes in humans. In addition, the magnitude of the effects of GLP-1 on cardiac performance can be viewed as mild and/or moderate. Moreover, no data exist to show any effect of GLP-1 to patients with cardiogenic shock or shock of any cause. Therefore, these agents do not seem to be of benefit in such patients.

CONCLUSION

The results of the studies on the cardiovascular effects of GLP-1 in animal models and in humans suggest that GLP-1 may be used with promising results in patients with heart failure, during coronary artery reperfusion procedures and in acute myocardial infarction in addition to the standard therapy. However, the long-term cardiovascular effects of GLP-1 have not been examined so far in studies designed for this purpose. Clearly there is urgent need for more research in this field with prospective studies.

ACKNOWLEDGEMENTS

This work was supported by a research grand (NKUA/SARG 70/4/8615) from the National and Kapodistrian University of Athens, Greece.

ABBREVIATIONS

GLP-1	=	Glucagon-like peptide-1
DPP-IV	=	Dipeptidyl peptidase-IV
GLP-1R	=	Glucagon-like peptide-1receptor
rGLP-1	=	Recombinant glucagon-like peptide-1
MAP	=	Mean arterial blood pressure
Ang-II	=	Angiotensin II
T2DM	=	Type 2 diabetes mellitus
LV	=	Left ventricle
DCM	=	Dilated cardiomyopathy
GLUT	=	Glucose transporters
NO	=	Nitric oxide
FMD	=	Flow mediated vasodilatation
CHF	=	Congestive heart failure
CABG	=	Coronary artery bypass grafting
LVEF	=	Left ventricular ejection fraction

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Received: July 08, 2010 Revised: September 11, 2010 Accepted: September 15, 2010