Efficacy of GLP-1 Infusion in Congestive Heart Failure Patients on Myocardial Function

Romilla Yogesh Bijlani

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Efficacy of GLP-1 Infusion in Congestive Heart Failure Patients on Myocardial Function

Abstract

Background: Congestive heart failure (CHF) and diabetes mellitus are serious and chronic complex diseases that commonly coexist together. The pathophysiology of the link between congestive heart failure and diabetes is impaired glucose homeostasis that affects the myocardium at both the cellular and structural level that eventually affects its intrinsic biochemical pathway leading to progression of the failing heart. The aim of this study was to attempt to clarify whether glucagon-like peptide (GLP-1) infusions improve cardiac function in congestive heart failure patients.

Methods: An exhaustive search of Medline-OVID, CINAHL, Medline-PubMed and Google Scholar using the keywords: congestive heart failure, insulin resistance, diabetes, metabolism, GLP-1, exenatide, liraglutide, and left ventricular function.

Relevant articles were assessed for quality using GRADE.

Results: Three studies met inclusion criteria and were included in this systematic review. A non-randomized pilot study of 21 CHF patients with and without diabetes with 5 weeks of GLP-1 infusion that demonstrated improved left ventricular ejection fraction (LVEF) and quality of life (QOL). A double-blind, randomized, two-period cross-over trial of 20 CHF patients with diabetes with 6 hours of GLP-1 infusion followed by a wash out period illustrated improved cardiac function (cardiac index, PCWP, RAP). The final study was a non-randomized pilot study of 6 patients with diabetes with 3 days of GLP-1 infusion that showed improved global systolic and diastolic function.

Conclusion: The above clinical studies have provided a promising impact in the improvement of cardiac function in a failing heart. However, these studies lack randomization and are of a small sample size. Therefore, further intense research studies are necessary to confirm these initial observations and to investigate the underlying mechanisms and explore possible interactions with the current heart failure therapies. At this point, the role of GLP-1 in reversing the cardiac function in the failing heart are still at its infancy, thus more clinical trials with stronger patient important outcomes in regards to cardiovascular morbidity and mortality as needed.

Keywords: congestive heart failure, insulin resistance, diabetes, metabolism, GLP-1, exenatide, liraglutide and left ventricular function

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Degree Name
Master of Science in Physician Assistant Studies

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Anjanette Sommers, PA-C, MS

Keywords
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Efficacy of GLP-1 Infusion in Congestive Heart Failure Patients on Myocardial Function

Romilla Y. Bijlani

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 10th 2013

Faculty Advisor: Davis-Risen Saje, PA
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Romilla Bijlani was born in India and was brought up in Hong Kong. She received a Bachelor of Science degree from Willamette University, Oregon in Biology in 1996. As she moved in 2007 to the United States permanently and started her own family with a supportive husband, she started volunteering at the Old Town Clinic in Portland, Oregon. This provided her an opportunity to learn firsthand about the impact that PAs can have to the health care system while serving underserved communities. One of the most exciting things about the PA program is that she can look forward to being with a very diverse range of individuals with varied experiences and backgrounds. She sees herself as adding another rich facet to the PA profession and perspective borne from interacting with patients and hospital staff from urban and rural hospitals around the globe.
Abstract

**Background:** Congestive heart failure (CHF) and diabetes mellitus are serious and chronic complex diseases that commonly coexist together. The pathophysiology of the link between congestive heart failure and diabetes is impaired glucose homeostasis that affects the myocardium at both the cellular and structural level that eventually affects its intrinsic biochemical pathway leading to progression of the failing heart. The aim of this study was to attempt to clarify whether glucagon-like peptide (GLP-1) infusions improve cardiac function in congestive heart failure patients.

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Table of Contents

Biography ................................................................. 2
Abstract ......................................................................... 3
Table of Contents .............................................................. 4
List of Abbreviations .......................................................... 5
Background ........................................................................ 6
Methods ........................................................................... 8
Results .............................................................................. 8
Discussion ......................................................................... 13
Conclusion .......................................................................... 16
References .......................................................................... 17
Table 1 Grade table .............................................................. 20
Table 2 Summary of Findings: Sokos study .................................. 21
Table 3 Summary of Findings: Nathanson study ................................ 21
Table 4 Summary of Findings: Thrainsottir study ............................ 21

List of Tables

Table 1: Grade Quality Assessment
Table 2: Sokos et al Summary of Findings
Table 3: Nathanson et al Summary of Findings
Table 4: Thrainsottir et al Summary of Findings
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic Adenosine Phosphate</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>CI</td>
<td>Cardiac Index</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac Output</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DM II</td>
<td>Diabetes Mellitus Type II</td>
</tr>
<tr>
<td>DPP-4</td>
<td>Dipeptidyl Peptidase-4</td>
</tr>
<tr>
<td>FFA</td>
<td>Free Fatty Acids</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-Like-Peptide-1</td>
</tr>
<tr>
<td>rGLP-1</td>
<td>Recombinant Glucagon-like-Peptide</td>
</tr>
<tr>
<td>HD</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>HF</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>HgbA1c</td>
<td>Hemoglobin A1c</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricle Ejection Fraction</td>
</tr>
<tr>
<td>LVEDV</td>
<td>Left Ventricular End Diastolic Volume</td>
</tr>
<tr>
<td>LVESV</td>
<td>Left Ventricular End Systolic Volume</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>NEFAs</td>
<td>Non-esterified fatty acids</td>
</tr>
<tr>
<td>MNQOL</td>
<td>Minnesota Quality of Life score</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>PCWP</td>
<td>Pulmonary Capillary Wedge Pressure</td>
</tr>
<tr>
<td>RAP</td>
<td>Right Atrial Pressure</td>
</tr>
<tr>
<td>RPP</td>
<td>Rate Product Pressure</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke Volume</td>
</tr>
<tr>
<td>VO₂</td>
<td>Ventilation oxygen consumption</td>
</tr>
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</table>
Efficacy of GLP-1 Infusion in Congestive Heart Failure Patients on Myocardial Function

BACKGROUND

Congestive heart failure (CHF) and diabetes mellitus are a serious and chronic complex disease that commonly coexists together. Despite the use of many current pharmacological interventions in the treatment of congestive heart failure, there has not been an improvement in morbidity and mortality rates. It is estimated that 5.7 million people in the United States have CHF with about half of them dying within 5 years of diagnosis.\(^1\) Heart failure has costs to the nation $34.4 billion each year, which includes the cost of health care services, medications, and lost productivity.\(^2\) Several factors have been linked to congestive heart failure, but diabetes mellitus has been the major cornerstone in the progression of the failing heart. The Framingham study\(^3\) was the first to show an increased risk of CHF in patient with diabetes mellitus, with an incidence of CHF that showed a 4-fold and 8-fold increase in men and women with diabetes mellitus, respectively, compared with those without diabetes mellitus. In the National Health and Nutritional Examination Survey (NHANES), diabetes mellitus was independently associated with an increased risk of CHF (RR 1.85; 95% CI=1.51, 2.28; p<0.01).\(^3\)

The pathophysiology behind the failing heart is the underlying impaired glucose homeostasis that eventually affects the myocardium at the cellular, structural and molecular level and various biological pathways regulating to these changes. Patients with CHF display a variety of metabolic abnormalities ranging from abnormal glucose intolerance to overt diabetes.\(^4\) Moreover, studies\(^5,6\) on patients with diabetes have demonstrated that there are several structural and cellular changes within the heart that is
related to glucose intolerance. In fact, the impaired glucose uptake caused by diabetes mellitus may be particularly deleterious in patients with concomitant coronary artery disease (CAD). Having these disease together is associated with a shift in the myocardial metabolism from free fatty acids (FFA) to glucose and glycolysis.\textsuperscript{7,8} Furthermore, left ventricular functions are inversely correlated with myocardial FFA oxidation in patients with heart failure (HF). Based on the pathophysiology of the impact of diabetes mellitus in the progression of the failing heart, it clearly suggests that by preventing diabetes or incorporating diabetes mellitus (DMII) treatment should help to reduce both the morbidity and mortality of patient in CHF.

New pharmaceutical agents in the management of DMII, glucagon-like peptide 1 (GLP-1) agonists (such as liraglutide and exenatide) have been studied in animals which demonstrated the possibility of a significant impact in the improvement of cardiac function in the setting of CHF patients.\textsuperscript{9} Glucagon-like peptide 1 (GLP-1) is an incretin that is released when blood glucose levels are above fasting levels.\textsuperscript{9} GLP-1 receptor agonists favors glycemic control by decreasing postprandial sugars. This is important to note as multiple studies\textsuperscript{10,11-14} have shown hyperglycemia to be an independent risk factor associated with poor outcomes in the setting of CHF. Furthermore, GLP-1 receptor agonists have extra-glycemic effects, including promoting beta cell proliferation, slowing gastric emptying, increasing satiety, and promoting weight loss. This results in the reduction of postprandial glycemic levels, improvement of endothelial function, a decrease in systolic blood pressure (BP), and improvement in the lipid profile.

By taking into consideration, the characteristics of GLP-1 receptor agonists along with its cardio protective role proven in the animal models, has allowed one to consider
these drugs as an alternative use in the setting of CHF patients with diabetes. The purpose of this review was to attempt to clarify whether GLP-1 agonist infusions improve cardiac markers in setting of CHF in the humans.

**METHODS**

An exhaustive search of Medline-OVID, CINAHL, Medline-PubMed and Google Scholar using the keywords: GLP-1, exenatide, liraglutide, diabetes, metabolism, heart failure, insulin resistance, ejection fraction, cardiac output, cardiac index, mortality, right atrial pressure, and pulmonary capillary wedge pressure. The articles that were obtained through this search were screened for additional relevant articles pertaining to the graduate project title. The inclusion criteria was comprised of studies investigating the improvement of myocardial function of GLP-1 in diabetic and non-diabetic patients in the setting of CHF using left ventricular ejection fraction (LVEF), cardiac index (CI), cardiac output (CO), Pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and quality of life (QOL). Excluded were animal studies and studies evaluating GLP-1 receptor agonists in the setting of myocardial infarction and ischemia. All the relevant articles were assessed for quality using GRADE.\(^\text{15}\)

**RESULTS**

The initial result of the search yielded 14 articles for review. From this search, three articles met inclusion articles.\(^\text{16-18}\) See Table 1. A search on the NIH clinical trials website revealed there is one current on-going trial.\(^\text{19}\) involving liraglutide (GLP-1 agonist drug) and heart failure in type 2 diabetes.
This small (n=21), single center, randomized, pilot study was designed to evaluate the efficacy of a 5-week infusion of a GLP-1 receptor agonist (at 2.5 pmol/kg/min) along with current therapy in CHF patients. The first 12 patients to complete the consent form and be screened for inclusion and exclusion criteria were given a GLP-1 receptor agonist (7-36 amide, Restoragen, Inc., Lincoln NE) and the following nine individuals were placed on placebo.

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 3.5mg/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. In the study, all the patients were on a standard stable heart failure medication regime. The study was to test the efficacy of a 5-week infusion of GLP-1 agonist (2.5 pmol/kg/min) along with added therapy in CHF patients.

The primary outcome was to evaluate the left ventricular (LV) function at rest assessed by 2-dimensional ECHO and exertion by VO2 max measured by cardiopulmonary exercised treadmill test. The secondary outcome was to measure the
QOL by a 6-minute walk distance and Minnesota Living and Heart Failure Questionnaire.\textsuperscript{16}

Evaluation of the LVEF thru Simpson’s method on standard 2-dimenional images was analyzed by qualified echocardiographer that was blinded in the study. The authors reported that \textsuperscript{16} LVEF was (21 ± 3\% to 27 ± 3\%; p<0.001) in the GLP-1 agonist treated patients vs. unchanged in the control group (21 ± 4\% to 22 ± 4\%).

Evaluation of the secondary outcomes were as follows: 6-minute walk distance improved in the treatment group (232 ± 15m to 286 ± 12m; p<0.001) vs. was unchanged in the control group (233 ± 21 to 258 ± 21m), VO2 max improved from 10.8 ± 0.9 to 13.9 ± 0.6 ml/kg/min (p<0.001) in the treatment group vs. was unchanged in the control group (13.3 ± 0.9 to 13 ± 1.0ml/kg/min), and QOL improved in the treatment group (64 ± to 44 ± 5, p<0.01) vs. was unchanged in the control group (52 ± 12 to 46 ± 12).\textsuperscript{16} See Table 2.

Adverse events were also reported. After 17 days of continuous infusion of GLP-1 receptor agonist in a patient with class IV heart failure secondary to severe aortic stenosis, died on the 18\textsuperscript{th} day of this study.\textsuperscript{16} In addition, there were two hospitalizations in each group with non-sustained ventricular tachycardia and one episode of atrial fibrillation in the GLP-1 receptor agonist treated group.\textsuperscript{16} The most common adverse effects in the treatment group was nausea and constipation which occurred (eight episodes) in five patients. Additionally, nine episodes of hypoglycemia (glucose 50-70 mg/dl) in 4 GLP-1 treated patients and four episodes of hypoglycemia in two control patients.\textsuperscript{16}
The purpose of this study determines whether exenatide improves hemodynamic function in patients with type 2 diabetic patients with congestive heart failure. Within 237 patients screened, 20 male type 2 diabetic patients participated in this double-blind, randomized crossover trial and were allocated (sequentially numbered) to intravenous infusions during two consecutive days with 1) exenatide (at 0.12 pmol/kg/min) and (2) placebo provided by Eli Lilly Amylin Alliance Indianapolis, IN, USA for 6 hours followed by a washout period for 18 hours at Stockholm South Hospital, Sweden.

Furthermore, the study populations were given their regular heart failure medication such as angiotensin-converting enzyme or angiotensin-II receptor antagonist, beta blockers (except one patient) and diuretics along in the morning (07:00 hours) and evening (19:00 hours), except for prandial insulin, metformin, and sulfonylurea that were withheld during the study protocol. Participants were confined to the intensive care unit during the whole study period, including 6 hours in a supine position during measurements. Both operator and patients were blinded to the assignment.

Patients were excluded from the study if they had: 1) type 1 diabetes, 2) ongoing treatment with inotropic agents, 3) acute coronary syndrome or documented acute MI within the previous 8 weeks, 4) active myocarditis, 5) significant aortic stenosis or mitral/tricuspid regurgitation, 6) symptomatic primary pulmonary disease, 7) ventricular arrhythmias, 8) second- or third-degree atrioventricular block, 9) implanted cardioverter defibrillator or biventricular pacemaker, 10) supine systolic blood pressure <85 or >200 mmHg, 11) primary renal or hepatic impairment (estimated GFR [eGFR] <30 ml/min, aspartate aminotransferase/alanine aminotransferase >2 times upper limit of normal), 12)
hypokalemia (<3.5 mmol/l) or hyperkalemia (>5.5 mmol/l), 13) significant anemia (Hb < 100 g/l), 14) pregnancy, and 15) previous treatment with GLP-1 receptor agonist or a DPP-4 inhibitor.\textsuperscript{17}

The primary endpoints were defined as an increase in cardiac index (CI) or a decrease in pulmonary capillary wedge pressure (PCWP) of ≥ 20% that were determined by cardiac catheterization (pulmonary artery thermodilution catheters 7.5 F; AH-05050, Arrow International, Bernville, PA, USA) and were used to calculate CO from the modified Steward-Hamilton equation.\textsuperscript{17}

The authors reported statistically significant improvements in all cardiac measures in the participants. See Table 3. Specifically, cardiac index increased at 3 and 6 hours by 23% and 17% during exenatide infusion vs. -1% and -5% during placebo (p = 0.003); and heart rate (HR) increased at 3, and 6 hours by 21% and 29% beats per min (bpm), during exenatide infusion vs. 2% and 8% bpm, during placebo (p = 0.006); and PCWP decreased at 3 and 6 h by -8% and -15% mmHg, during exenatide infusion vs. 6% and 8% mmHg, during placebo (p = 0.001). There were nine patients that had adverse side effects of the drug (six, nausea; two, increased HR; one, increased systolic blood pressure).\textsuperscript{17}

\textbf{Thrainsottir et al}

The purpose of this study\textsuperscript{18} was to assess the viability and safety of three days' infusion of recombinant GLP-1 receptor agonist (at 4 pmol/kg/min, or in the case of nausea during the infusion at 3 pmol/kg/min) in an open observational study in six hospitalized male patients with type 2 diabetes and CHF. The authors\textsuperscript{18} included
assessment of metabolic control (by measuring plasma concentration of free fatty acids, glucagon, insulin, C-peptide) and myocardial function (by measuring rate pressure, PCWP, RAP, and heart rate). See Table 4. The rate pressure is a measure of the stress put on the cardiac muscle based on the number of times it needs to beat per minute (HR) and the arterial blood pressure that it is pumping against (SBP). These measures were recorded at rest upon awaking in the morning and at stress post exercising. There were no major complications of the infusion, and all patients completed the study protocol.

The authors reported an overall reduction in the rate pressure during the study period both at rest from 9225 bpm*mmHg on day 1 to 8658 bpm*mmHg on day 4. Similarly, at stress the rate pressure reduced from 17136 bpm*mmHg on day 1 to 16170 bpm*mmHg on day 4. Furthermore, there was a significant reduction in resting heart rate at day 2 and 3, but was minimal at day 4. Similarly, there was a slight trend towards decreasing systolic pressure and increase diastolic pressure.

Briefly, individuals in this study not only benefited from short-term GLP-1 receptor agonist infusion on the myocardial parameters but the average fasting blood glucose decreased significantly on day two but increased somewhat after that. The plasma concentrations of free fatty acids were decreased in four of the two patients. The average plasma concentrations (mg/dl) on day 1 vs. day 4 were as follows: for glucagon were 20 vs. 22.2, insulin 10.5 vs. 6.3, C-peptide 1.53 vs. 1.22 and free fatty acids 0.63 vs. 0.28.
DISCUSSION

Hence for patients with heart failure and diabetes, GLP-1 receptor agonist could be considered as an alternative when other glucose lowering drugs such as insulin and thiazolidinediones are associated with fluid retention, and metformin is contraindicated in patients with significant renal insufficiency. (CITE) In the setting of CHF patients, Sokos et al\textsuperscript{16} demonstrated that long term GLP-1 receptor agonist treatment (5 weeks) in both diabetic and normoglycemic chronic heart failure patients (New York Heart Association class III and IV) to significantly improve LV ejection fraction, myocardial oxygen consumption, and functional status, whereas no effect from GLP-1 receptor agonist was observed in patients with normal cardiac function.\textsuperscript{16} Additionally, this study \textsuperscript{16} showed improvement in glycemic control and less use of inotropic and vasoactive infusions with few arrhythmias in GLP-1 receptor agonist treated patients and reduction of B-type natriuretic peptide (BNP) in the GLP-1 treated (289 ± 129; 5 weeks: 218 ± 102pg/ml) vs. control group (296 ± 129; 5 weeks: 285 ± 152 pg/ml). Despite the fact that Sokos et al \textsuperscript{16} showed promising results in the improvement of the hemodynamic parameters and no side effects of hypoglycemia were reported, the study was limited to its non-randomized small sample size with no control groups methodology. Furthermore, individuals were obese (BMI>30) thus, the results may not be applicable to heart failure patients with cachexia.

Furthermore, the other study that evaluated GLP-1 receptor agonist use in long term, Thrainsottir et al\textsuperscript{18} showed improvement in a different set of cardiac parameters in the setting of diabetic patients with CHF. The rate pressure is a crucial hemodynamics parameter in the management of CHF patients where it is a measure that rates the fluid
overload when the heart is trying to utilize its energy to pump against this high resistance pressure to pump blood out of the ventricles to be distributed to the entire body. The rate pressure was improved both at rest and stress along with moderate improvement in heart rate and systolic and diastolic function.\textsuperscript{18}

In contrast, in a short-term study by Nathanson et al study\textsuperscript{17} improvements were observed using different hemodynamic cardiac parameters, specifically the cardiac index and pulmonary capillary wedge pressure. In this study,\textsuperscript{17} there was an increase in the cardiac index that was directly linked with an increase in heart rate without any change in SV, suggestion of a positive chronotropic effect of exenatide.\textsuperscript{17} One way to minimize the work load on the heart is to increase cardiac index through elevations of inotropy and chronotropy effect.\textsuperscript{17} This is in contrast to rodent studies, in which exenatide dose-dependently induced chronotropic effects paralleled by pressor action.\textsuperscript{21} The increase in heart rate noted prior to fasting and with the infusion of exanatide, was contributed because of the increase levels of non-esterified fatty acids (NEFA) levels (measured by using NEFA-HR kit Wako Chemicals Neuss, Germany on a Thermo T20xti instrument Kone, Espoo, Finland) that leads to lipotoxicity and insulin resistance and this effect is more pronounced on the myocardial metabolism in female than male.\textsuperscript{17} Despite, the increase in HR, which can be detrimental in the setting CHF patients there were no symptoms of worsening of heart failure or other serious adverse events observed in the study. Furthermore, in this study\textsuperscript{17}, there was a substantial decreased in PCWP and right atrial pressure (RAP) following exenatide infusion having a direct vasodilatory effect in the vessel beds.
Although, these clinical studies\textsuperscript{16-18} have encourage the potential use of GLP-1 receptor agonists in the treatment of heart failure, they lack randomization and were of a small sample size. Moreover, Trainsdottir et al\textsuperscript{18} lacked a control group. Overall, these flaws result in an overall GRADE of very low quality of evidence. See Table 1. It is clear that significant further research is required to confirm these initial observations, investigating the underlying mechanisms and exploring possible interactions with current heart failure therapies. Currently, in progress is a study\textsuperscript{19} to determine whether GLP-1 receptor analogue liraglutide improves heart function after 18 weeks of liraglutide + metformin, compared with glimepride + metformin, using tissue Doppler echocardiography. This study and hopefully many more in the future may provide answers to many of the previous questions and investigations on the role of GLP-1 receptor agonists in the setting of CHF on myocardial function.

**CONCLUSION**

Undoubtedly, GLP-1 receptor agonists in these clinical studies have proved beneficial effects on the metabolic and hemodynamic function in CHF patients. However, there are several important differences between these clinical studies that supported GLP-1 receptor agonist in the role of cardiac function in terms of different cardiac parameters tested, amount of dose and duration with the GLP-1 receptor agonist and methodology. Nevertheless, GLP-1 receptor agonists have also shown improvement in the treatment of hyperglycemia associated with type 2 diabetes mellitus. Since the overall quality of evidence is very low, further research is necessary in order to identify the role that GLP-1 receptor agonists should play in the management of patients with
both diabetes and CHF.
REFERENCES


dpressure_product](http://en.wikipedia.org/wiki/Rate

**Table 1. GRADE Quality Assessment**

<table>
<thead>
<tr>
<th>Design</th>
<th>Number of patients</th>
<th>Infusion time</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sokos et al</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>21</td>
<td>5 weeks of GLP-1 infusion @ 2.5 pmol/kg/min</td>
<td>Very serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>Selection bias (obese individuals)</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Nathanson et al</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>20</td>
<td>6 hr of GLP-1 infusion @ 0.12 pmol/kg/min followed by a washout period of 18 h</td>
<td>Very serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>Study was funded by Eli Lilly Amylin Alliance USA</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Thrainsdottir et al</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>6</td>
<td>3 days of GLP-1 infusion @ 4 pmol/kg/min</td>
<td>Very serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>none</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

<sup>a</sup> Small sample size and lacked randomization. Also, Thrainsdottir et al lacks control group
### Table 2. Sokos et al\textsuperscript{16} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GLP-1 receptor agonist group</th>
<th>Control group</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post treatment</td>
<td>Baseline</td>
</tr>
<tr>
<td>LVEF</td>
<td>21 ± 3%</td>
<td>27 ± 3%</td>
<td>21+/- 4%</td>
</tr>
<tr>
<td>6-minute walk distance (m)</td>
<td>232 ± 15</td>
<td>286 ± 12</td>
<td>233 ± 21</td>
</tr>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>10.8±0.9</td>
<td>13.9±0.6</td>
<td>13.3 ± 0.9</td>
</tr>
</tbody>
</table>

### Table 3. Nathanson et al\textsuperscript{16} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GLP-1 receptor agonist group</th>
<th>Placebo group</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 hours</td>
<td>6 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td>Cardiac index (l/min/m\textsuperscript{2})</td>
<td>2.2 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>13.6 ± 2</td>
<td>12.6 ± 2</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>6.1 ± 1</td>
<td>6.6 ± 1</td>
<td>8.8 ± 1</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>88 ± 4</td>
<td>94 ± 5</td>
<td>75 ± 4</td>
</tr>
</tbody>
</table>

### Table 4. Thrainsottir et al\textsuperscript{17} Summary of Findings

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Day 1</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (b/min)</td>
<td>BP (mmHg)</td>
</tr>
<tr>
<td>Morning, at rest</td>
<td>75</td>
<td>123</td>
</tr>
<tr>
<td>Stress, at exercise</td>
<td>112</td>
<td>153</td>
</tr>
</tbody>
</table>

\textsuperscript{b}RPP = rate pressure product (systolic blood pressure x heart rate)