Cardiovascular and metabolic effects of 48-h glucagon-like peptide-1 infusion in compensated chronic patients with heart failure

Mads Halbirk,1,2 Helene Nørrelund,4 Niels Møller,2 Jens Juul Holst,5 Ole Schmitz,2 Roni Nielsen,1,2 Jens Erik Nielsen-Kudsk,1 Søren Steen Nielsen,3 Torsten Toftegaard Nielsen,1 Hans Eiskjær,1 Hans Erik Botker,1 and Henrik Wiggers1

Departments of 1Cardiology, 2Endocrinology, and 3Nuclear Medicine, Aarhus University Hospital, Skejby, Aarhus; 4Department of Medicine, Viborg Hospital, Viborg; and 5Department of Biomedical Sciences, the Panum Institute, University of Copenhagen, Copenhagen, Denmark

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PATIENTS WITH HEART FAILURE (HF) display a variety of metabolic abnormalities ranging from abnormal glucose tolerance to overt diabetes. The prevalence of insulin resistance and glucose abnormalities in this population is ~40% (26, 27) and even in patients with HF and without diabetes whole body metabolism is deranged and characterized by decreased glucose oxidation and muscle uptake and increased levels and muscle utilization of free fatty acids (FFA) (18). Left ventricular function is inversely correlated with myocardial FFA oxidation in patients with HF (12). In experimental HF models, increased cardiac FFA uptake causes myocardial accumulation of triglycerides and ceramide and contractile dysfunction, but this finding has not been confirmed in clinically relevant animal models of HF (25). Hence compromised whole body and cardiac metabolism has been suggested to promote progression of HF. However, the effects of substrate uptake on cardiac function are still uncertain (30, 33) and the potential hemodynamic effect of treatments targeting myocardial metabolism is controversial (28).

The optimal strategy for the treatment of diabetes in patients with HF is debated (8, 22). Recently, new types of antidiabetic treatments [glucagon-like peptide-1 (GLP-1) analogs and dipeptidyl-peptidase-4 inhibitors] targeting the incretin system have emerged. During a meal the incretin system mediates insulin release even before blood glucose increases. GLP-1 regulates gastric emptying, amplifies nutrient-induced insulin response, and suppresses the glucagon response. It reduces appetite, and long-term treatment with GLP-1 mimetics lowers body weight (32, 36). GLP-1 lowers glucose levels by increasing insulin levels, inhibiting pancreatic glucagon release (6), and enhances (albeit presumably indirectly) the effects of insulin on peripheral tissues (10).

The hypothesis is that GLP-1 improves cardiac function and exercise capacity. The value of GLP-1 treatment is not yet established in HF, but preliminary nonrandomized human (17, 24) and animal (16, 21) studies have shown beneficial effect in HF. The aims of the present study were to assess safety and to investigate the cardiovascular and metabolic effects of 48-h GLP-1 infusion in patients without diabetes but with chronic HF in a randomized double-blinded study.

METHODS

Patients. We included 20 patients with HF due to ischemic heart disease who were in New York Heart Association class II and III, had left ventricular ejection fraction (LVEF) <40%, were between 30 and 80 years of age, and stable on oral optimized medication. We excluded patients with reduced renal function (serum creatinine >200 μmol/l or renal creatinine clearance <60 ml·min⁻¹·1.73 m⁻²), acute myocardial infarction within the last 3 mo, significant cardiac valve disease, disability, or prior malignant disease. Patients with diabetes were excluded from the study by patient history and by a diabetic response to an oral glucose tolerance test performed before inclusion. Patients who had biochemical or anamnestic signs of impaired liver function were not considered eligible to this study.

Design. In a double-blinded placebo-controlled crossover design, patients were hospitalized and received GLP-1 infusion and placebo...
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infusion for 48 h. We studied the patients in random order on two separate occasions at least 14 days apart. The pharmacy at Aarhus University Hospital performed the randomization and kept the randomization list until data analysis was completed. We used a randomized crossover design. It was predetermined that half of the patients should receive placebo first and the other half GLP-1. The patients were studied in random order as determined by the randomization. The patients were studied on their usual medication. Examinations were started at 8 AM after an overnight fast. Infusion was started when baseline testing was completed. Initially, the patients received infusion of native GLP-1 at a rate of 1.0 pmol·kg⁻¹·min⁻¹ (∼3.3 ng·kg⁻¹·min⁻¹) and placebo infusion with concentrations of NaCl and albumin equivalent to the GLP-1 solution and at a similar rate. After three patients completed both treatments it was decided to reduce infusion rate to 0.7 pmol·kg⁻¹·min⁻¹ in all subsequent patients owing to repeated blood glucose levels <3.5 mmol/l. This decision was made without unblinding patients. Patients had standard hospital meals during the study. Tests at baseline and 24 and 48 h were performed after an overnight fast. At baseline and after 48 h the patients were studied by echocardiography, 6-min hall walk tests, cardiopulmonary exercise testing, and cardiac output measurement, and we obtained brain natriuretic peptide (BNP) and metabolic profiles. The study protocol was approved by the local Ethics Committee. Informed written consent was obtained from all patients. The study is registered at http://clinicaltrials.gov. Identifier NCT00264199.

Safety measures. Patients were admitted to hospital during infusions. Pulse, blood pressure, and capillary blood glucose was recorded at baseline, after 1 h of infusions, and scheduled measurements were made approximately every 5 h during the rest of the experiment. To maintain blinding, scheduled measurements were recorded by the nursing staff and records were kept apart. Measurements were repeated if an adverse reaction was suspected.

Echocardiography. Two-dimensional echocardiographic imaging and analysis were obtained at rest and after maximal exercise by one observer as previously described (33). We assessed left ventricular diastolic function from mitral inflow components E-wave, A-wave, E/A-ratio, E-deceleration time, and isovolumetric relaxation time, which were recorded. Parameters were estimated as averages of three consecutive heart beats. Tissue Doppler imaging was performed as previously described (33). We measured peak systolic velocities (Vmax) during ejection time.

Cardiopulmonary exercise testing and cardiac output measurement. Before the experiments, the patients underwent exercise testing to become familiarized with the experimental setting. Patients performed a staged bicycle exercise test with stages lasting 1 min and in increments of 10 watts·min⁻¹. At rest and at peak exercise oxygen uptake, saturation, cardiac index (CI), stroke volume, and pulse were recorded using the Innocor rebreathing system (Innovation A/S, Odense, Denmark). This device derives cardiac output by the Fick principle using an inert soluble and an insoluble gas. ECG, blood pressure, and heart rate are registered simultaneously (1).

6-min hall walk test. Patients performed a 6-min hall walk test at baseline and at 48 h. The test was carried out on a straight 50-meter indoor course. The patients carried a mobile infusion pump in a backpack allowing maximal mobility during the test.

Metabolic parameters and BNP. Fasting venous plasma glucose, insulin and FFA, and BNP were measured at baseline and 24 and 48 h. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) and calculated as follows: fasting insulin (µU/ml) × fasting glucose (mmol/l)/22.5 (14). Individuals having a HOMA-IR above 2.77 are considered insulin resistant (5). Blood samples were immediately cooled and spun and stored at −80°C until analysis (18). Fasting plasma glucose was analyzed on VITROS 5.1 FS Chemistry System (Ortho-Clinical Diagnostics, Raritan, NJ). Insulin was determined by a commercial enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark). FFA was determined by a colorimetric method employing a commercial kit (Wako Chemicals, Neuss, Germany). BNP was analyzed using a commercially available kit (Triage BNP Test; Biosite, San Diego, CA). Plasma samples were assayed for total GLP-1 immunoreactivity using a radioimmunoassay (antiserum no. 89390), as previously described (20). Intact GLP-1 was measured using an enzyme-linked immunosorbent assay, as previously described (31, 34). For both assays detection limits were below 1 pmol/l, and intra-assay coefficients of variation were below 5% at 20 pmol/l.

Myocardial SPECT/PET. 99mTc-Sestamibi and FDG-γ camera PET was performed as previously described (33). We aligned the images with the 16 echocardiographic regions and scored the regional myocardial tracer uptake of Sestamibi and FDG semiquantitatively as follows: 0 for normal, 1 for mildly reduced, 2 for moderately reduced, 3 for severely reduced, and 4 for none. Regions with a normal Sestamibi and FDG uptake (Sestamibi ≤ 1 and FDG ≤ 1) were classified as control if echocardiographic wall motion score was normal and as stunned if wall motion was dysfunctional. Regions with impaired tracer uptake were classified as either hibernating (Sestamibi = 2 and FDG = 0) or Sestamibi = 3 and FDG = 1) or infarcted (Sestamibi ≥ 2 and FDG ≥ 2).

Statistics. Data were analyzed using Stata 9 software (StataCorp, College Station, TX). Δ values (48-h, baseline) were obtained for LVEF, max Vo2, CI, maximal workload, and BNP and compared using a Student’s paired t-test. Baseline and 48-h values were compared using a two-way ANOVA model (time and intervention). Tissue Doppler Images were analyzed using a three-way ANOVA model (intervention, patient, and region). Area under curve was calculated for pulse, blood pressures, capillary blood glucose, and hormones and compared using a Student’s t-test. Data are reported as means ± SE.

RESULTS

The study population comprised 17 males and 3 females, of whom 15 completed the protocol (Fig. 1). The patients were 61 ± 3 yr of age (range, 40–77 yr), and mean LVEF was 30 ± 2%. Further baseline characteristics are listed in Table 1. All 15 patients had suffered myocardial infarctions, none had exercise limiting chest pains, and only one had ST-segment depressions during exercise. Intravenous volume load during infusions was dependent on body weight and averaged 4.7 ± 0.2 ml·h⁻¹ in both study arms in the 15 patients who completed the protocol. Body weight did not change significantly in either study arm and changes did not differ [GLP-1 vs. placebo (day 2–day 0; in kg): 0.1 ± 0.2 and −0.2 ± 0.2; P = 0.66]. The average HOMA-IR was 2.5 ± 0.5, signifying a degree of insulin resistance in the study population.

Safety. Fifteen patients (13 males) completed the protocol (Fig. 1). Five patients were excluded from analysis due to failure to complete the protocol. The reasons for drop out were severe nausea and vomiting during GLP-1 infusion (discontinued infusion), a diagnosis of lung cancer during the washout period, development of severe thrombocytopenia 4 wk after the first intervention (GLP-1) in a patient with known thrombocytopenia, failure to comply with examinations, and withdrawal of consent. During GLP-1-infusions, eight patients experienced nine episodes of hypoglycemia (capillary glucose < 3.5 mmol/l) versus none during placebo. In two of these episodes glucose levels were below 3 mmol/l (2.2 and 2.8 mmol/l, respectively). Four episodes occurred within 1 h after starting GLP-1 and two further episodes within 4 h. All episodes except one were asymptomatic. One patient with blood glucose below 3 mmol/l had hypoglycemic symptoms within 1 h after starting GLP-1 infusion but symptoms ceased after drinking juice. Other side effects were limited. One patient suffered from severe nausea during GLP-1 infusion and...
was excluded as mentioned earlier. Two patients complained of mild self-limiting nausea on day one during GLP-1 infusions (none during placebo). No cardiovascular side effects were noted in any patients. Blinding remained intact in all patients.

**Metabolic effects.** Neither circulating total GLP-1 (Fig. 2) nor active GLP-1 [GLP-1 vs. placebo (in pmol/l): 0.5 ± 0.2 and 0.5 ± 0.3; \( P = 0.97 \)] differed at baseline. After 48 h GLP-1 infusion, circulating total GLP-1 (Fig. 2) and active GLP-1 [GLP-1 vs. placebo (in pmol/l): 11.7 ± 3.0 and 1.4 ± 0.9; \( P < 0.01 \)] were increased. At baseline, neither fasting venous plasma glucose [GLP-1 vs. placebo (in mmol/l): 5.6 ± 0.1 and 5.8 ± 0.2; \( P = 0.14 \)] nor fasting serum insulin [GLP-1 vs. placebo (in pmol/l): 69 ± 13 and 66 ± 13; \( P = 0.80 \)] differed between study arms. GLP-1 treatment increased 48-h average insulin [GLP-1 vs. placebo (in pmol/l): 90 ± 17 and 69 ± 12; \( P = 0.01 \); Fig. 3] and decreased 48-h average plasma glucose [GLP-1 vs. placebo (in mmol/l): 5.0 ± 0.1 and 5.7 ± 0.53; \( P < 0.01 \); Fig. 3] and 48-h average capillary blood glucose [GLP-1 vs. placebo (in mmol/l): 5.2 ± 0.1 and 5.6 ± 0.1; \( P < 0.01 \); Fig. 3] and 48-h average capillary blood glucose [GLP-1 vs. placebo (in mmol/l): 5.0 ± 0.1 and 5.7 ± 0.53; \( P < 0.01 \)]. HOMA-IR did not differ at baseline (GLP-1 vs. placebo: 2.54 ± 0.53 and 2.49 ± 0.48; \( P = 0.88 \)) but 48-h GLP-1 infusions

![Fig. 2. Circulating total glucagon-like peptide-1 (GLP-1). Fasting levels of total GLP-1 before infusion (0 h) and after 24 and 48 h are shown. *\( P < 0.05 \).](image1)

![Fig. 3. Glucose and insulin levels. Fasting P-insulin (bottom, open markers) and fasting P-glucose (top, closed markers) values are shown. *\( P < 0.05 \) (area under curve).](image2)

**Table 1.** Baseline characteristics and medication

| Baseline |  
| --- | --- |
| Age, yr | 61 ± 3 |
| Male/female | 13/2 |
| Body mass index, kg·m\(^{-2}\) | 26 ± 3 |
| LVEF, % | 30 ± 2 |
| New York Heart Association, II/III | 11/4 |
| Previous myocardial infarction, n | 15 |
| Exercise limiting angina | 0 |
| Baseline medication, % |  
| ACE-inhibitor/ARB | 100 |
| β-Blocker | 94 |
| Loop diuretic | 67 |
| Spironolactone | 60 |
| Statin | 100 |

Values are means ± SE; \( n = 15 \) for baseline. LVEF, left ventricular ejection fraction.
revealed a strong trend toward a higher index (GLP-1 vs.
placebo: 3.41 ± 0.76 and 2.19 ± 0.33; P = 0.06). Forty-eight-
hour average FFA did not differ significantly after GLP-1
treatment [GLP-1 vs. placebo (in mmol/l): 0.32 ± 0.02 and
0.37 ± 0.02; P = 0.16].

BNP. BNP did not differ at baseline [GLP-1 vs. placebo (in
pg/ml): 284 ± 175 and 219 ± 83; P = 0.33]. There was a
significant decrease in BNP levels during infusions in both
groups, but effects of infusions did not differ [day 2–day 0;
GLP-1 vs. placebo (in pg/ml): −112 ± 54 and −65 ± 44; P = 0.17].

Blood pressure and heart rate. At baseline, pulse and blood
pressure did not differ (data not shown). During GLP-1 treat-
ment mean heart rate was increased [GLP-1 and placebo (in
beats/min): 67 ± 2 vs. 65 ± 2; P = 0.016] and mean diastolic
blood pressure was higher in the GLP-1 arm [GLP-1 and
placebo (in mmHg): 71 ± 2 and 68 ± 2; P = 0.008]. Mean
systolic blood pressure remained unaffected [GLP-1 vs. pla-
cebo (in mmHg): 113 ± 5 and 113 ± 4; P = 0.95].

SPECT/PET. In 14 patients, data from Myocardial SPECT
and 99mTc-sestamibi and FDG-γ camera PET examinations
were available. The 15th patient declined to undergo the study.
Five regions could not be classified due to poor image quality.
The remaining 219 regions were classified as infarcted (106
regions, 48%), hibernating (18 regions, 8%), stunned (48
regions, 22%), and control (47 regions, 21%).

Echocardiography. After 48 h infusions resting and postex-
ercise LVEF did not differ between study arms (Table 2). Peak
E-, peak A-wave, E-deceleration time, and isovolumetric re-
lation time did not differ between study arms (Table 2).
Using Doppler tissue velocity imaging, we found no impact of
infusions on V_{max} [GLP-1 vs. placebo (48 h; cm·s^{-1}): 1.6 ±
0.1 and 1.7 ± 0.1; P = 0.43]. V_{max} was highest in control
regions, intermediate in hibernating/stunned regions, and low-
est in scarred regions, but GLP-1 did not affect V_{max} in either
region (data not shown).

Exercise. CI and stroke volume increased at maximal work-
load, and systemic vascular resistance was lower when com-
pared with at rest. GLP-1 infusion did not affect exercise
capacity, CI, heart rate, stroke volume, max V_{O2}, and systemic
vascular resistance during exercise (Table 3).

6-min hall walk test. At baseline, distance covered was
similar. At 48 h patients performed equally well independent
of infusions [GLP-1 vs. placebo (in meters): 499 ± 18 and 502 ±
13; P = 0.78].

DISCUSSION

We studied the metabolic and hemodynamic effects of 48-h
GLP-1 infusions in a double-blinded placebo-controlled cross-
over design in patients without diabetes but with stable chronic
HF. GLP-1 infusion increased circulating insulin levels and
reduced plasma glucose levels and resulted in hypoglycemia in
eight patients. Some in vitro (13) and animal (9) studies
indicate an immediate insulin sensitizing effect, but we could
not confirm this effect in these patients. On the contrary,
HOMA-IR tended to increase during GLP-1. A long-term
effect on insulin sensitivity through GLP-1-mediated weight
loss is a possibility, but was beyond the scope of this study.
The observed decrease in blood glucose levels was probably
due to the increased insulin levels and perhaps to the glu-
cagonostatic effects of GLP-1 demonstrated by others (6, 15).
We found no effect of GLP-1 on LVEF, diastolic function,
exercise capacity, regional myocardial contractile function, or
BNP. We observed a small but significant increase in heart rate
and diastolic blood pressure during GLP-1 infusion.

Prior studies of GLP-1 in HF. Our findings are in contrast
with some of the prior patient and animal studies on treatment

<p>| Table 2. Echocardiography at rest at baseline and after 48 h |
|-----------------|-----------------|-----------------|-----------------|
|                 | Day 0           | Day 2           |                 |</p>
<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>28 ± 2</td>
<td>30 ± 2</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Diastolic diameter, cm</td>
<td>6.2 ± 0.3</td>
<td>6.5 ± 0.3</td>
<td>6.4 ± 0.3</td>
</tr>
<tr>
<td>E-wave, m/s</td>
<td>0.55 ± 0.05</td>
<td>0.45 ± 0.03</td>
<td>0.58 ± 0.03</td>
</tr>
<tr>
<td>A-wave, m/s</td>
<td>0.56 ± 0.05</td>
<td>0.56 ± 0.04</td>
<td>0.63 ± 0.04</td>
</tr>
<tr>
<td>E-deceleration time, ms</td>
<td>250 ± 20</td>
<td>260 ± 20</td>
<td>260 ± 20</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>127 ± 6</td>
<td>129 ± 7</td>
<td>119 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SE. GLP-1, glucagon-like peptide-1; IVRT, isovolumetric relaxation time.

| Table 3. Baseline hemodynamics and exercise data after 48 h |
|-----------------|-----------------|-----------------|-----------------|
|                 | GLP-1           | Placebo         |                 |
|                 | Baseline        | 48 h            | Baseline        | 48 h            |
|                 | Rest            | Peak Exercise   | Rest            | Peak Exercise   |
| LVEF, %         | 28 ± 2          | 30 ± 2          | 32 ± 2*         | 30 ± 2          | 33 ± 3*         |
| Heart rate, beats/min | 72 ± 3          | 78 ± 3          | 109 ± 7*        | 72 ± 2          | 109 ± 8*        |
| Exercise capacity, watt | 94 ± 8          | 94 ± 8          | 94 ± 8          | 94 ± 8          |
| vo2, ml·kg^{-1}·min^{-1} | 2.9 ± 0.2       | 3.3 ± 0.5       | 18 ± 2*         | 3.4 ± 0.4       | 3.4 ± 0.6       |
| Stroke volume, ml/heartbeat | 46 ± 4          | 46 ± 4          | 74 ± 12*        | 46 ± 4          | 72 ± 8*         |
| Cardiac index, l/min·m^{-2} | 1.6 ± 0.1       | 1.5 ± 0.1       | 4.0 ± 0.6*      | 1.7 ± 0.1       | 1.7 ± 0.2       |
| Systemic vascular resistance, dyne·s^{-1}·cm^{-5} | 2.142 ± 200     | 2.125 ± 143     | 2.109 ± 153*    | 2.000 ± 188     | 2.079 ± 200     | 1.113 ± 107*    |

Values are means ± SE. *P < 0.05 peak vs. baseline.
with GLP-1 in HF. Seventy-two-hour infusion of GLP-1 improved LVEF when added to standard therapy in 10 patients with acute myocardial infarction and LVEF below 40% (17). In a pilot study, 5 wk GLP-1 treatment in 12 patients with HF improved LVEF and 6-min hall walk test (24). However, none of the studies were randomized and baseline characteristics differed between GLP-1-treated patients and controls. In the study by Sokos et al. (24) diabetes and ischemic heart disease were more common, and fasting glucose and HgbA1c were higher in the GLP-1 group than in the placebo group. In the study by Nikolaidis et al. (17), treated patients were younger and with a higher prevalence of males compared with the control group. It is possible that these differences in baseline characteristics in part account for the differences observed between patients receiving GLP-1 and placebo. We used a double-blind placebo-controlled crossover design to avoid bias due to differences in patient characteristics and to increase the statistical power of the study. The contrasting findings could be explained by the higher prevalence of diabetes and more pronounced metabolic abnormalities in those study populations and more heterogeneous populations consisting of both ischemic and nonischemic cardiomyopathy. Future studies should address in a controlled design whether patients with HF and diabetes benefit from GLP-1 infusion.

**Duration and dosage of GLP-1 infusion.** Whereas Nikolaidis and coworkers (17) tested effects of 72-h infusion on patients with acute myocardial infarction, Sokos and coworkers (24) treated patients with chronic HF for 5 wk. Our study involved a 48-h intervention in patients with chronic HF. GLP-1 infusion exceeding 48 h may be required to achieve any cardiovascular effect. However, in a canine study on rapid pacing-induced dilated cardiomyopathy, Nikolaidis and coworkers (16) demonstrated significant increases in LVEF and cardiac output after 48-h GLP-1 infusion. Experimental studies indicate direct vasodilatory effects by GLP-1 (3), and in contrast with our findings, systemic vascular resistance decreased during infusion in a canine study (16). This difference between patient and animal studies may in part account for the differences in hemodynamic effects of GLP-1.

The dose given to the majority of patients in our study (0.7 pmol/kg per min) was lower than the dose given by Nikolaidis et al. [1.5 pmol/kg per min (17)] and Sokos et al. [2.5 pmol/kg per min (24)] but resulted in supraphysiological circulating GLP-1 levels. In the present study average total fasting GLP-1 levels were ~10 times higher than during placebo and five times higher than the highest average level observed after 75 g oral glucose (data not shown). We observed a metabolic response comparable with prior studies (17, 24) since both fasting plasma glucose levels and 48-h capillary blood glucose were lower and insulin higher during GLP-1 infusion. FFA did not decrease during GLP-1 infusion. The effect of GLP-1 on FFA is inconsistent. Some researchers report decreased FFA levels during treatment (35), whereas others report unchanged levels (29). Lower levels of nonesterified fatty acid levels might mediate some improvement in LVEF, but in the canine study improvement in LVEF correlated with increased myocardial glucose uptake and occurred despite stable circulating insulin and FFA concentrations (16). It can be argued that GLP-1 infusion at a higher rate and of a longer duration could result in cardiovascular effects in the present study population. In the clinical setting, the risk of hypoglycemic events in patients with diabetes argues against this approach, and long-term infusion, although possible, is impractical.

**Heart rate and blood pressure.** Previous reports on the influence of GLP-1 on blood pressure and heart rate have been conflicting (19). In patients with diabetes and without HF, long-term treatment with the GLP-1 analog exenatide did not affect blood pressure or heart rate (11), whereas the GLP-1 analog liraglutide lowered systolic blood pressure (32). We observed small but significant increases in 48-h mean heart rates and diastolic blood pressure. The mechanism behind our observations is not clear since cardiac output and systemic vascular resistance were not affected by GLP-1. It cannot be excluded that our findings relate to subclinical hypoglycemia, but it seems unlikely that these minor changes have clinical significance during short-term treatment in patients with stable chronic HF.

**BNP.** BNP decreased during both treatments, but there were no differences in treatment effects. Patients continued their usual medications during infusions. Prior studies have demonstrated an increase in BNP during exercise (4). The difference between baseline and 48-h values may reflect differences in physical activity between everyday life and hospital life. Our finding of significant decreases in BNP levels during hospitalization, which were similar in both study arms, underlines the importance of a randomized controlled design to eliminate bias due to period effects.

**Safety issues.** Because hypoglycemia in the first three patients was a consistent observation, we reduced the infusion rate from 1.0 pmol·kg\(^{-1}\)·min\(^{-1}\) to 0.7 pmol·kg\(^{-1}\)·min\(^{-1}\) in the subsequent patients. We had no adverse cardiovascular or hemodynamic side effects. Even though infusion rate was reduced we still experienced mild hypoglycemic events in an additional five patients. Sokos et al. (24) reported hypoglycemic events in four out of 12 patients with diabetes, and Nikolaidis et al. (17) reported hypoglycemic events in two of 10 receiving GLP-1. In the present study, eight of nine events occurred within the first 24 h and were managed by the staff, and it is possible that the baseline exercise test made patients more susceptible to the hypoglycemic effects of GLP-1. Hypoglycemia remains a concern in GLP-1 treatment. Despite the reduced infusion rate, we obtained GLP-1 levels comparable with those reported by Sokos et al. (23) in a cohort undergoing coronary artery bypass grafting and higher than those obtained by pharmacologically relevant doses of di-peptidyl peptidase-IV inhibitors in patients with diabetes (2) and in healthy subjects (7). Even at this reduced infusion rate, GLP-1 revealed itself as a potent blood glucose lowering agent in a population without diabetes. Future studies should evaluate the effect of targeting the incretin system in patients with diabetes and HF.

**Limitations.** We used native GLP-1. GLP-1 analogs were not commercially available when this study was commenced and using one of these analogues might alter results. We used a short-term intervention, and it is possible that a longer treatment period is required to achieve any effect of GLP-1 infusion. Due to safety concerns, the infusion rate was reduced, and it can be argued that higher infusion rates mediate stronger responses. However, the GLP-1 levels observed were supraphysiological and the metabolic effects were comparable with prior studies using a higher infusion rate. We investigated stable patients without diabetes with some degree of insulin resistance. It is unknown whether a more metabolically de-
ranged group or patients suffering nonischemic HF could benefit from the treatment. Patients suffered from ischemic heart disease and had large areas of scarred tissue in the myocardium. Whether GLP-1 infusion could improve systolic function in less scarred hearts is unknown, but we consider it unlikely since we could not detect any improvements in either normal or stunned left ventricular myocardium.

The number of patients was low and power calculation was performed using an expected completion rate of 90%, but the actual completion rate was 75%. Although this increases the risk of type II error, the present study excludes any major clinical effect on cardiac contractile function and hemodynamics.

Conclusion

Short-term GLP-1 treatment has no significant cardiovascular effects in patients without diabetes with compensated HF. The impact of minor increases in heart rate and diastolic blood pressure during GLP-1 infusion requires further studies. GLP-1 increased circulating insulin levels and reduced plasma glucose concentration. Hypoglycemia was frequent and calls for caution in patients without diabetes but with HF.

GRANTS

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DISCLOSURES

No conflicts of interest are declared by the author(s).

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