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ARTICLE

Effects of intravenous exenatide in type 2 diabetic patients with congestive heart failure: a double-blind, randomised controlled clinical trial of efficacy and safety

D. Nathanson · B. Ullman · U. Löfström · A. Hedman · M. Frick · Å. Sjöholm · T. Nyström

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Abstract
Aims/hypothesis The aim of this study was to determine whether exenatide improves haemodynamic function in patients with type 2 diabetes with congestive heart failure (CHF).
Methods The main eligibility criteria for inclusion were: male/female (18–80 years) with type 2 diabetes and CHF (ejection fraction ≤35%, and New York Heart Association functional class III or IV). Out of 237 patients screened, 20 male type 2 diabetic patients participated in this crossover trial design and were allocated (sequentially numbered) to i. v. infusions during two consecutive days with (1) exenatide (0.12 pmol/kg/min); and (2) placebo for 6 h followed by a washout period for 18 h, at Stockholm South Hospital, Sweden. Patients and researchers were blinded to the assignment. Cardiac haemodynamic variables were determined by right heart catheterisation. The primary endpoint was defined as an increase in cardiac index (CI) or a decrease in pulmonary capillary wedge pressure (PCWP) of ≥20%. Secondary endpoints were tolerability and safety of exenatide infusion.
Results CI increased at 3 and 6 h by 0.4±0.1 (23%) and 0.33±0.1 (17%) l min^{-1} m^{-2}, during exenatide infusion vs −0.02±0.1 (−1%) and −0.08±0.1 (−5%) l min^{-1} m^{-2} during placebo (p=0.003); and heart rate (HR) increased at 1, 3 and 6 h by 8±3 (11%), 15±4 (21%) and 21±5 (29%) beats per min (bpm), during exenatide infusion vs −1±2 (−2%), 1±1 (2%) and 6±2 (8%) bpm, during placebo (p=0.006); and PCWP decreased at 1, 3 and 6 h by −1.3±0.8 (−8%), −1.2±1 (−8%) and −2.2±0.9 (−15%) mmHg, during exenatide infusion vs 0.3±0.5 (2%), 1±0.6 (6%) and 1.4±0.7 (8%) mmHg, during placebo (p=0.001). No serious adverse event was observed. Adverse events were reported in nine patients (six, nausea; two, increased HR; one, increased systolic blood pressure).
Conclusions/interpretation Infusion of exenatide in male type 2 diabetic patients with CHF increased the CI as a result of chronotropy, with concomitant favourable effects on PCWP and reasonable tolerability of the drug. The clinical implications of using exenatide in patients with CHF are still not clear and further studies are warranted.

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Keywords Congestive heart failure · Double-blind randomised trial · Exenatide · GLP-1 · Heart catheterisation · Type 2 diabetes

Abbreviations

AF	Atrial fibrillation
CABG	Coronary artery bypass graft
CAD	Coronary artery disease

D. Nathanson · Å. Sjöholm · T. Nyström (✉)
Division of Internal Medicine, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset AB,
SE-118 83 Stockholm, Sweden
e-mail: thomas.nystrom@sodersjukhuset.se

B. Ullman · U. Löfström · A. Hedman · M. Frick
Division of Cardiology, Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden

CHF	Congestive heart failure
CI	Cardiac index
CO	Cardiac output
CVD	Cardiovascular disease
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated GFR
GLP-1	Glucagon-like peptide-1
HR	Heart rate
LV	Left ventricular
MAP	Mean arterial blood pressure
MI	Myocardial infarction
NYHA	New York Heart Association classification
PADP	Pulmonary arterial diastolic pressure
PAP	Pulmonary artery pressure
PASP	Pulmonary arterial systolic pressure
PCWP	Pulmonary capillary wedge pressure
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
SV	Stroke volume
SVR	Systemic vascular resistance

Introduction

There is a growing body of evidence that the intestinally produced peptide hormone, glucagon-like peptide-1 (GLP-1), might have a beneficial role in cardiovascular function in addition to its antihyperglycaemic action [1]. It was recently shown that GLP-1 improves left ventricular (LV) haemodynamics in a canine model with advanced dilated cardiomyopathy [2]. The observation that these effects were accompanied by an increase in myocardial uptake of glucose, without any change in levels of insulin, suggests that GLP-1 exerts insulinomimetic effects in the myocardium [2]. Furthermore, some human studies demonstrate beneficial effects of GLP-1 on the heart. Short term infusion of GLP-1 in patients with acute myocardial infarction (MI) improves LV systolic function following successful reperfusion [3], as does chronic infusion in patients with congestive heart failure (CHF) [4]. However, not all studies have arrived at the same conclusion [5].

To date, studies evaluating cardiac filling pressure evoked by GLP-1 treatment in humans by the gold standard method (heart catheterisation) are sparse. GLP-1 infusion before and after coronary artery bypass graft (CABG) was found to reduce the need for inotropic agents to achieve optimal haemodynamic results [6], and short term infusion of GLP-1 protects the heart against ischaemic LV dysfunction after balloon occlusion within the coronary artery in humans [7]. GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) to the split product GLP-1 (9-36), which does not interact with the GLP-1 receptor [8]. Because of the rapid degradation of GLP-1, different GLP-1 receptor agonists, for example exenatide and liraglutide, which are resistant to DPP-4, have been developed and are currently approved for the treatment of type 2 diabetes. These agonists exert their effects via the GLP-1 receptor and mimic the actions evoked by native GLP-1 [1]. Chronic treatment with exenatide in mice with dilated cardiomyopathy [9] and rats with CHF [10] delays the progression of heart failure and prolongs the animals' survival, probably as a result of changes in glucose metabolism. Whether exenatide can directly improve cardiac output (CO) remains elusive and has not been studied in humans.

The aims of the present study were to investigate whether exenatide improves haemodynamic function in type 2 diabetic patients with CHF independent of glycaemia, and the safety/tolerability of this drug, in an acute setting.

Methods

Participants Patients were recruited from Stockholm South Hospital, Sweden. Inclusion criteria were: male and female participants, 18–80 years of age, known type 2 diabetes, hospitalisation owing to CHF according to the New York Heart Association classification (NYHA) III-IV, LV systolic dysfunction with a documented LV ejection fraction of ≤35% (assessed by echocardiography), and a clinically stable period of 24 h using established therapy (diuretics, ACE/A-II inhibitors and β-blockers). Exclusion criteria were: type 1 diabetes, ongoing treatment with inotropic agents, acute coronary syndrome or documented acute MI within the previous 8 weeks, active myocarditis, significant aortic stenosis or mitral/tricuspid regurgitation, symptomatic primary pulmonary disease, ventricular arrhythmias, second- or third-degree atrioventricular block, implanted cardioverter defibrillator or biventricular pacemaker, supine systolic blood pressure <85 or >200 mmHg, primary renal or hepatic impairment (estimated GFR [eGFR] <30 ml/min, aspartate aminotransferase/alanine aminotransferase >2 times upper limit of normal), hypokalaemia (<3.5 mmol/l) or hyperkalaemia (>5.5 mmol/l), significant anaemia (Hb <100 g/l), pregnancy, or present or previous treatment with a GLP-1 receptor agonist or a DPP-4 inhibitor. Participants were screened for diabetic retinopathy by mydriatic fundal retinal photography. The protocol was approved by the Swedish Central Ethical Review Board and the Medical Products Agency and conducted according to the principles of the Declaration of Helsinki 1975. Written informed consent was obtained from all participants.

Study design This was a single-centre, randomised, two-period crossover, double-blind study. The primary endpoint was defined as an increase in cardiac index (CI) or a decrease in pulmonary capillary wedge pressure (PCWP) of ≥20%. Secondary endpoints were changes in mean arterial blood

pressure (MAP) and mean pulmonary arterial pressure (PAP), and tolerability of exenatide in this acute setting. Potential adverse events were monitored continuously and reported annually to the Medical Products Agency. The criterion to break the blinding and stop the study was deterioration of heart function in more than three patients or one serious adverse event.

The study protocol was performed in two sessions over two consecutive days. After an overnight fast, all participants underwent i.v. infusion with glucose (50 mg/ml; 50 ml/h) and insulin (Actrapid, Novo Nordisk, Bagsværd, Denmark, 1-6 U/h to maintain normoglycaemia [4–6 mmol/l]), and exenatide (0.12 pmol kg^{-1} min^{-1}) or placebo (solvent used in the exenatide infusion) provided by Eli Lilly Amylin Alliance (Indianapolis, IN, USA) in a syringe pump device (IVAC, Medical Systems, Basingstoke, UK) for 6 h, followed by a washout period for 18 h. The dose of exenatide was estimated from an earlier human study [11] avoiding plasma levels of exenatide exceeding 3 nmol/l, as suggested by earlier experimental data [12]. In the two session block-randomisation procedure, group A received exenatide during day 1 followed by placebo on day 2 and group B received placebo on day 1 followed by exenatide on day 2 (Fig. 1). Participants were given their regular medication in the morning (07:00 hours) and in the evening (19:00 hours), except for prandial insulin, metformin and sulfonylurea, which were withheld during the study protocol. NPH insulin was given at bed time (22:00–23:00 hours). Participants were confined to the intensive care unit during the whole study period, including 6 h in a supine position during measurements. The main haemodynamic measurements (heart rate [HR], right atrial pressure [RAP], PAP, PCWP, MAP, CO, CI, stroke volume [SV], pulmonary vascular resistance [PVR], and systemic vascular resistance [SVR]) were recorded at baseline (before the start of the infusions) and thereafter at 1, 3 and 6 h after the start of infusion. All patients remained fasted during the study protocol.

Concomitant medications Details of all medications used by the patients studied are given in Table 1. All patients were on stable doses of angiotensin-converting enzyme or angiotensin-II receptor antagonists, β-blockers (except one patient) and diuretics. All patients but three received pharmacological glucose-lowering therapy.

Thermodilution The thermodilution catheters were inserted via the internal jugular veins. The tip of the catheter was advanced into the pulmonary artery to reach a position adequate for monitoring of the wedge pressure. Pulmonary artery thermodilution catheters (7.5 F; AH-05050, Arrow International, Bernville, PA, USA) and the Siemens Sirecust SC 9000XL computer (Siemens, Denver, CO, USA) were used to calculate CO from the modified Steward–Hamilton equation. The injections were made by hand, 10 ml of ice-

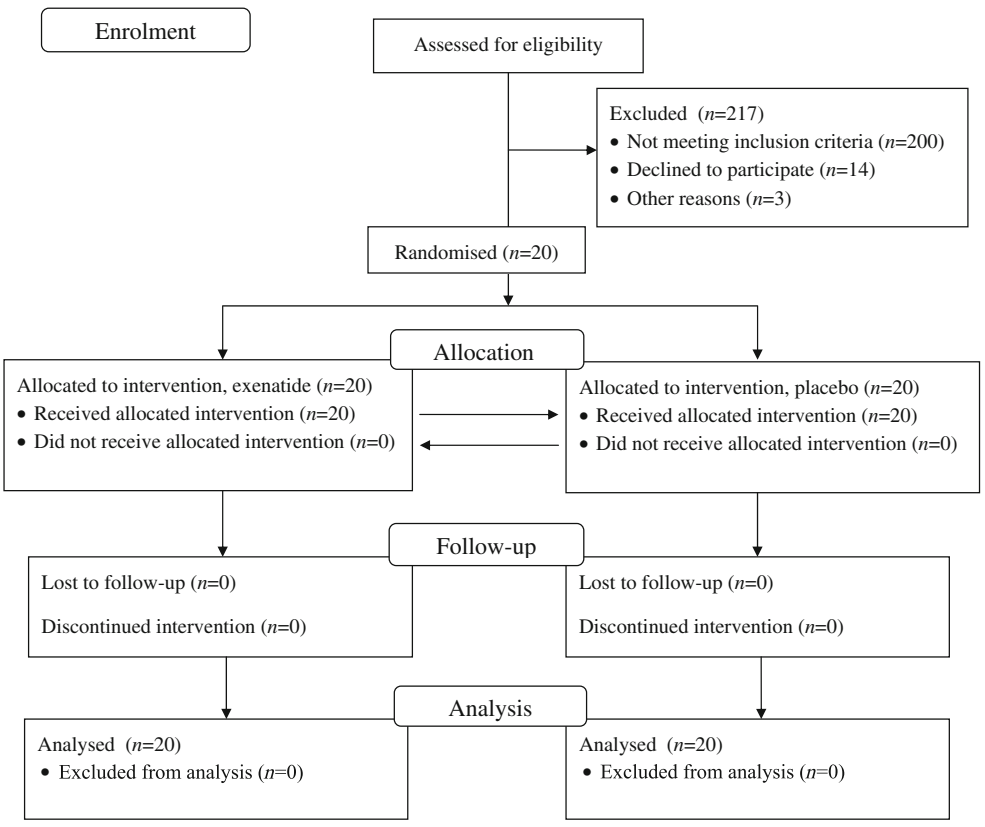

Fig. 1 Design of the double-blind randomised crossover clinical trial. Patients were allocated in a two-period crossover double-blind manner receiving a 6 h infusion protocol followed by a washout period for 18 h. Group A received exenatide during day 1 followed by re-allocation to placebo on day 2. Group B received placebo on day 1 followed by re-allocation to exenatide on day 2, i.e. patients were their own controls

Table 1 Participants' characteristics

Variable	Value
Patients (*n*)	20
Male/female	20/0
Age (years)	66±1
BMI (kg/m^2)	31±1
Diabetes duration (years)	13±2
Microalbuminuria (20–200 μg/min)	7/20
Mean (μg/min)	36±18
Macroalbuminuria (>200 μg/min)	5/20
Mean (μg/min)	368±63
Diabetic retinopathy	16/20
None	4
Mild non-proliferative	7
Moderate non-proliferative	7
Severe non-proliferative	2
HbA_{1c} (%)	8.1±0.4
HbA_{1c} (mmol/mol)	65±4
Cholesterol (mmol/l)	4.1±0.3
HDL-cholesterol (mmol/l)	1.0±0.1
LDL-cholesterol (mmol/l)	2.4±0.2
Triacylglycerol (mmol/l)	1.4±0.1
eGFR(ml min^{-1} [1.73 m]$^{-2}$)	64±7
NYHA functional class (%)	
III	55
IV	45
LV ejection fraction (%)	26±2
Risk factors for heart failure (%)	
CAD	60
Hypertension	80
DCM	10
Smoking (%)	
Former smoker	60
Current smoker	40
AF (%)	55
Concomitant medication (%)	
ACE inhibitors/A-II receptor antagonists	100
β-Blocker	95
Loop diuretic	100
Spironolactone	40
ASA/clopidogrel	55
Warfarin	55
Diabetes treatment (%)	
Insulin	60
Metformin	25
Sulfonylurea	5
Combination therapy	5
Diet only	15

Values are means ± SEM

A-II receptor antagonists, angiotensin-II receptor antagonists; DCM, dilated cardiomyopathy

chilled (10°C) glucose (50 mg/ml), and always completed within 3 s. The mean of five consecutive CO measurements were used in all time points.

Invasive arterial blood pressure and heart rate measurements A catheter with an arterial line primed with NaCl (0.9%) was positioned in the radial artery in the right wrist of all patients. Calculation of HR was based on the average R-R interval over the final 10 s (Siemens Sirecust SC 9000XL).

Biochemical analyses Serum insulin and C-peptide levels were measured by an immunometric method with monoclonal antibodies (Modular E 170, Roche Diagnostics Scandinavia, Stockholm, Sweden). NEFA levels were determined using a NEFA-HR kit (Wako Chemicals, Neuss, Germany) on a Thermo T20xti instrument (Kone, Espoo, Finland). Plasma glucagon concentrations were measured using a glucagon radioimmunoassay kit (Euria-Glucagon, Euro-Diagnostica, Dieren, the Netherlands) in a multigamma counter. Plasma lactate levels were measured using an ABL800 FLEX blood gas analyser (Labcompare, San Francisco, CA, USA). Plasma exenatide levels were measured by ELISA (Tandem Labs, San Diego, CA, USA). Other routine laboratory variables were measured by the local clinical chemistry laboratory (Stockholm South Hospital).

Statistical analyses All analyses were defined in the statistical analysis plan, before un-blinding. A cardiologist, blinded to the allocated treatment, scrutinised all haemodynamic data (from every time point) from print-outs from the Sirecust monitor to certify that all data were correctly reported in the data file. Values are presented as means ± SEM or *n* for categorical variables. A general linear mixed model with participant and time as repeated factors and treatment as a fixed factor was used to test the effect of treatment on continuous variables. The baseline value for the outcome variables was included in the model (unstructured covariance matrix) as covariates. This model assumes that pair-wise correlations are not constrained by the data, that is, no assumptions are made about the relative magnitude of the correlation between any of the pairs of observations. If an overall significant difference between exenatide vs placebo was present, pair-wise comparisons with Tukey's least significant difference test were performed to determine differences between active treatment and placebo at each time point. McNemar's and sign tests were used for dichotomous variables, i.e. proportions. Paired *t* tests were used to compare the infused amount of insulin between exenatide and placebo infusions. To detect any potential carry-over effects, tests for the interaction of treatment and period (treatment × period) were performed, separate figures for each variable for Group A vs Group B were compared and

finally, paired *t* tests between haemodynamic baseline levels for days 1 and 2 in Group A were performed. All variables for primary and secondary endpoints were normally distributed as tested by Shapiro–Wilk's test.

Power calculation The calculation was carried out according to previous studies [3, 13]. The primary endpoint was defined as a clinically meaningful improvement, i.e. a relative increase in CI of ≥20%. This was assumed by an absolute change of CI from 2.0 to 2.4 l min^{-1} m^{-2} with an SD of 1.0 l min^{-1} m^{-2}, between exenatide and placebo treatment. With an α error of 0.05, two sided testing, and a power of 0.80, we needed 17 patients in the study. However, as dropouts were estimated to be ~20%, we estimated at least 20 patients would be required to show differences in the primary endpoint between treatments.

Results

Baseline characteristics Baseline characteristics of the study population are shown in Table 1. Despite considerable efforts to include both female and male study participants, the majority of patients screened for the study were male; only three women matched the criteria and all declined to participate (Fig. 1). Baseline haemodynamic variables were consistent with CHF with a depression of CI and an elevation of PCWP (Table 2). We found no significant carry-over effects in any of the primary endpoint variables.

Haemodynamic effects There were no missing data in the primary endpoint variables. The exenatide infusion rate was 0.12 pmol kg^{-1} min^{-1} during the 6 h of infusion for all patients, except for a dose reduction of 8% over 3 h in one patient, due to nausea. All haemodynamic data are given in Table 2. Relative changes of the primary endpoints CI and PCWP from baseline and during the protocol are given in Fig. 2a and b. The proportion of participants, during exenatide vs placebo infusions, that reached the endpoints by an increase of 20% in CI were; at 1 h 5/20 vs 3/20 (p=0.7), at 3 h 13/20 vs 2/20 (p=0.003), and at 6 h 12/20 vs 3/20 (p=0.004), and at any time point during the protocol, 15/20 vs 4/20 (p=0.001); and by a decrease of 20% in PCWP were; at 1 h 6/20 vs 2/20 (p=0.2), at 3 h 6/20 vs 0/20 (p=0.03) and at 6 h 10/20 vs 1/20 (p=0.004), and at any time point during the protocol, 10/20 vs 2/20 (p=0.008). CI increased significantly from baseline during exenatide vs placebo infusion at 3 h, by 0.4±0.1 vs −0.02±0.01 l min^{-1} m^{-2} (21% vs −1%); and at 6 h by 0.33±0.1 vs −0.08±0.1 l min^{-1} m^{-2} (18% vs −5%). HR increased significantly from baseline during exenatide vs placebo infusion at 1 h by 8±3 vs −1±2 bpm (11% vs −2%), 3 h 15±4 vs 1±0.6 bpm (21% vs 2%) and at 6 h 21±5 vs 6±2 bpm (29% vs 8%). SV did not change significantly over time during exenatide vs placebo infusion. PCWP decreased significantly from baseline during exenatide vs placebo infusion at 1 h −1.3±0.8 vs 0.3±0.5 mmHg (−8% vs 2%), at 3 h −1.2±1 vs 1±0.6 mmHg (−8% vs 6%) and at 6 h −2.2±0.9 vs 1.4±0.7 mmHg (−15% vs 8%). The decrease in PCWP remained significant (p=0.02, overall) after adjustment for HR. RAP slightly decreased from baseline during exenatide vs placebo infusion at 3 h by −1.4±0.7 vs 0.3±0.7 mmHg (−17% vs 3.4%). Neither MAP nor PAP differed between exenatide and placebo infusions. Furthermore, there were no overall significant differences between the effects of exenatide vs placebo on PVR. However, a slight (albeit statistically significant) decrease in SVR during exenatide vs placebo infusion was observed at 3 h −160±79 vs 70±49 dyne s^{-1} cm^{-5} [1 dyne=10^{-5} N] (−9% vs 4%), although not over time. Fifty-five per cent and 60% of the study participants suffered from atrial fibrillation (AF) and coronary artery disease (CAD), respectively. No interaction was observed between AF or non-AF patients on treatment-induced changes in HR (p=0.3), CI (p=0.9) and PCWP (p=0.2). However, an interaction was observed between participants with and without CAD on exenatide treatment for changes in CI (p=0.009), but not for HR (p=0.3) or PCWP (p=0.7). This interaction was reflected by a slight increase in changes in CI for each time point; baseline (1.8±0.1 vs 1.9±0.2 lmin^{-1} m^{-2}), 0 h (1.8±0.1 vs 1.8±0.2 l min^{-1} m^{-2}), 1 h (2.1±0.1 vs 2.0±0.2 l min^{-1} m^{-2}), 3 h (2.4±0.1 vs 1.9±0.1 l min^{-1} m^{-2}) and 6 h (2.3±0.1 vs 2.0±0.2 l min^{-1} m^{-2}) in participants with CAD vs non-CAD.

Metabolic effects All metabolic data are given in Table 2. Normoglycaemia was achieved by adjustments of insulin infusion rate during exenatide and placebo infusions. Participants required somewhat less exogenous insulin during exenatide vs placebo infusion (9 vs 13 U/patient, p=0.002). There were no significant differences in glucagon, insulin or lactate levels between exenatide and placebo infusions. C-peptide levels increased significantly during exenatide infusion vs placebo infusion at 1, 3 and 6 h. Serum concentrations of NEFAs increased significantly during exenatide and placebo infusions at 6 h compared with baseline, and were higher at 6 h after exenatide vs placebo infusions.

Adverse events No serious adverse event was observed. Adverse events were reported in 45% of the exenatide infusions and 0% of the placebo infusions. Six patients suffered adverse events in the form of nausea/vomiting, but three patients experienced cardiovascular adverse events: two patients with AF experienced an increase in heart rate to an extent (from 83 to 161 bpm and 116 to 124 bpm, respectively) that necessitated the use of digoxin (0.25 mg i.v.) during (at 3 h) and directly after (at 6 h) the exenatide infusion; one patient had an increase in systolic

Table 2 Haemodynamic and metabolic variables during the study protocol

Treatment	Baseline[a]	Time point								*p* overall[b]
		0 h		1 h		3 h		6 h		
		Exenatide	Placebo	Exenatide	Placebo	Exenatide	Placebo	Exenatide	Placebo	
Haemodynamic										
HR (bpm)	73±4	73±4	74±4	81±5[c]	72±4	88±4[d]	75±4	94±5[c]	79±4	0.006
SBP (mmHg)	140±5	137±6	138±5	141±7	129±4	144±7	140±5	148±6	145±5	0.13
DBP (mmHg)	67±4	65±4	69±3	68±4	66±2	71±4	70±3	74±4	72±3	0.38
RAP (mmHg)	9.0±1	7.5±1	8.5±1	6.8±1	8.4±1	6.1±1[b]	8.8±1	6.6±1	7.9±1	0.03
PASP (mmHg)	47±3	44±4	45±3	43±4	47±3	42±4	48±3	42±4	48±3	0.065
PADP (mmHg)	18±2	17±2	20±2	17±2	19±2	17±2[b]	21±2	18±2	20±2	0.11
PAP (mmHg)	28±2	26±2	28±2	26±3	28±2	25±3	30±2	26±3	29±2	0.08
PCWP (mmHg)	17±2	14.8±2	16.0±2	13.5±1[c]	16.3±2	13.6±2[b]	17.0±1	12.6±2[e]	17.4±2	0.001
MAP (mmHg)	92±4	89±3	92±3	93±4	87±3	95±5	93±3	99±4	96±3	0.2
CO (l/min)	4.0±0.2	4.0±0.2	4.0±0.2	4.5±0.3	4.1±0.2	4.8±0.3[c]	4.0±0.2	4.7±0.3[c]	4.2±0.3	0.001
CI (l min^{-1} m^{-2})	1.8±0.1	1.8±0.1	1.8±0.1	2.1±0.1	1.8±0.1	2.2±0.1[c]	1.8±0.1	2.1±0.1[b]	1.9±0.1	0.003
SV (ml/beats)	57±4	57±4	56±4	58±4	60±5	57±4	56±4	52±4	55±4	0.5
PVR (Wu)	3.0±0.4	3.0±0.5	3.0±0.3	3.0±0.5	3.0±0.4	3.0±0.5	4.0±0.6	3.0±0.5	3.0±0.6	0.2
SVR (dyne s^{-1} cm^{-5})[f]	1,750±120	1,730±110	1,750±110	1,630±120	1,650±100	1,570±130[b]	1,820±130	1,650±110	1,770±120	0.2
Metabolic										
Glucose (mmol/l)	6.6±0.3	6.8±0.3	7.0±0.3	6.3±0.2	6.4±0.3	5.9±0.2	5.9±0.3	6.0±0.3	6.0±0.2	0.2
C-peptide (nmol/l)	1.2±0.2	1.0±0.2	1.3±0.2	1.5±0.3[b]	1.1±0.2	1.4±0.3[c]	0.9±0.2	1.3±0.3[c]	0.7±0.1	0.004
Insulin (pmol/l)	440±120	410±100	440±120	550±160	510±250	290±50	300±80	270±40	190±30	0.7
Glucagon (pmol/l)	40±3	39±3	42±3	38±2	42±3	42±4	44±3	42±3	45±3	0.9
NEFA (mmol/l)	0.3±0.06	0.3±0.1	0.3±0.1	–	–	–	–	0.6±0.1[b]	0.5±0.05	0.03
Lactate (mmol/l)	1.0±0.09	1.0±0.1	1.0±0.1	1.0±0.1	1.0±0.1	0.9±0.1	0.8±0.1	0.8±0.1	0.8±0.05	0.2
Exenatide (pmol/l)	0.6±0.5	3.5±3	1.9±1	54.5±4[d]	1.0±0.5	105±8[d]	1.0±0.5	132±11[d]	1.0±0.5	0.001

Values are means ± SEM

[a] Haemodynamic and metabolic variables prior to the protocol (before any infusions); [b] *p* overall: *p* value for exenatide treatment vs placebo over all time points, for every variable, included in the model; [c] $p<0.05$; [d] $p<0.01$; [e] $p<0.001$ for exenatide vs placebo adjusted for baseline

SBP, systolic BP; DBP, diastolic BP.

[f] 1 dyne=10^{-5} N

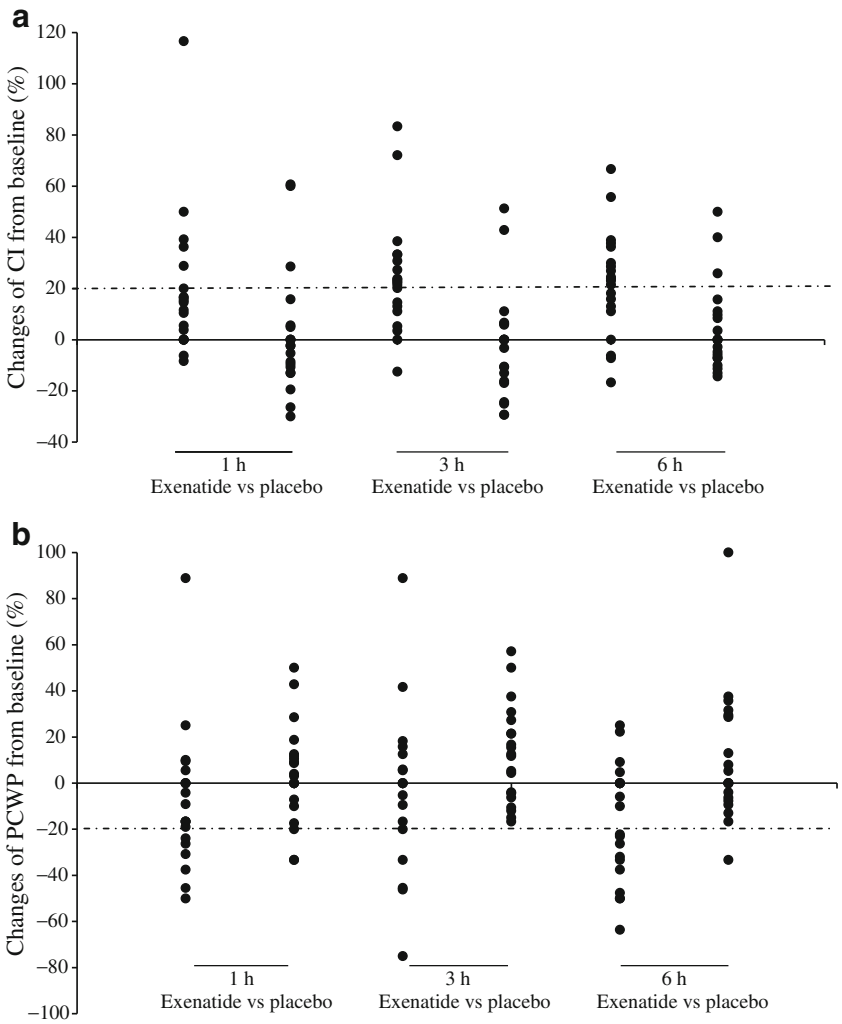

Fig. 2 Relative changes of (**a**) CI and (**b**) PCWP from baseline and during 1, 3 and 6 h infusions of exenatide vs placebo. Dotted lines visualise the calculated endpoint levels i.e. an increase by 20% for CI or a decrease by 20% for PCWP, respectively. For the proportions of patients that reached the endpoint of CI and/or PCWP, see text. **a** 1 h, $p=0.03$; 3 h, $p=0.001$; 6 h, $p=0.002$, exenatide vs placebo. **b** 1 h, $p=0.08$; 3 h, $p=0.03$; 6 h, $p=0.002$, exenatide vs placebo

blood pressure (from 175/85 to 195/105 mmHg) that required 1 h of i.v. nitroglycerine after the exenatide infusion. All analyses of the outcomes were performed both with and without these three patients. As the results for primary and secondary endpoints were almost identical in the intention to treat and the per protocol populations, we have chosen to present the data from the intention to treat population.

Discussion

We demonstrate that exenatide exerts rapid haemodynamic effects in male type 2 diabetic patients with CHF. Previous studies show that short-term infusion of GLP-1 improves LV heart failure in patients with acute MI [3], as does chronic infusion in patients with CHF [4]. In a recent randomised, double-blind, crossover-designed study, 48 h infusion of GLP-1 in patients without diabetes with compensated heart failure had no significant effects on CI or heart filling pressures, although a small but significant increase in HR and diastolic blood pressure was observed [5]. These findings are similar to the present study; however, the settings of the studies differ in terms of drugs, methods, patients and conditions, and therefore are not easily comparable.

The increase in CI was contingent upon an increase in HR without any change in SV, indicative of a positive chronotropic effect of exenatide. This is in contrast to rodent studies, in which exenatide dose-dependently induced chronotropic effects paralleled by pressor action [14]. The GLP-1 receptor is abundantly expressed in areas in the brain known to be involved in the regulation of cardiovascular function [15], in blood vessels [8, 16] and in the heart [8, 17]. In mice, stimulation of central GLP-1 receptors by exenatide modulates parasympathetic outflow, thereby increasing HR [18, 19]. In contrast, GLP-1 increases sympathetic vasoconstrictor neural activity but does not appear to affect cardiac sympathetic or parasympathetic activity in healthy humans [20]. Acute injection of exenatide reportedly increases HR in humans [21], although chronic exenatide treatment produced no clinically meaningful effects on HR

in type 2 diabetic patients [22]. The findings undoubtedly raise questions about the efficacy and safety of exenatide treatment in patients with type 2 diabetes and CHF. Chronically raised HR is a risk factor for adverse outcome in patients with CHF, and drugs lowering HR improve clinical outcome in CHF. Although exenatide treatment was associated with a lower risk of cardiovascular disease (CVD) than other glucose-lowering treatments in a large retrospective LifeLink database [23], there is no robust evidence that treatment with exenatide affects the CVD outcome.

Exenatide significantly decreased PCWP and RAP, but changes in these variables were small compared with other studies [13]. Patients with type 2 diabetes might suffer from heart failure despite having a normal ejection fraction. These patients usually have diastolic dysfunction, suggested to be due to fibrosis [24], or to the inability of the myocardium to switch from fat to carbohydrate as fuel for oxidative energy production [25]. Our study design cannot discriminate between any of these mechanisms. GLP-1 ameliorates cardiac dysfunction in canine [2] and rodent [26, 27] models of heart failure by increasing myocardial glucose use, recently also demonstrated by chronic exenatide treatment in a murine model with dilated cardiomyopathy [9]. Although we carefully matched the metabolic state between treatments, we also cannot rule out the possibility that exenatide might have shifted myocardial substrate metabolism towards a more energetically favourable substrate, improving myocardial performance. Moreover, exenatide might have induced diuresis, explaining the decreased RAP seen in present study, recently shown for GLP-1 that induces diuresis in rats [28] and humans [29] mediated by changes in renal haemodynamics. However, the lack of positive inotropic action of exenatide is consistent with in vitro findings, in which GLP-1 failed to enhance contractility in cardiomyocytes [30]. Even with a fixed low SV, the increase in HR and the improvement of CI noted in the current study might have reduced the diastolic filling pressure. Interestingly, short term infusion of GLP-1 improves ischaemic LV systolic and diastolic dysfunction, mitigating LV stunning in patients awaiting elective percutaneous coronary intervention [7]. In that study, a second cardiac catheter was placed in the LV, which monitored contractile performance in this ventricle. In our study, such information on the pressure–volume loops was regrettably unavailable, but might have given some insight as to why participants with CAD or non-CAD respond differently to exenatide in terms of CI increase. However, it is important to remember that the present study was un-powered for such subgroup analyses. Nevertheless, acute infusion of exenatide seems to be valuable in protecting the ischaemic myocardium [31]. Furthermore, we also cannot entirely exclude the possibility that exenatide might have induced some vasodilatation in the vessel beds, thereby decreasing PCWP and RAP. Exenatide reportedly induces vasodilatation in hind quarters in rodents as a result of activation of β-adrenergic receptors [32]. In the current study, 19 out of 20 participants were on chronic β-blocker treatment, which might have masked a further vasodilatation action by exenatide. A vasodilatory effect is also compatible with the recent finding that exenatide upregulates endothelial nitric oxide synthase (eNOS), promoting release of nitric oxide from human coronary artery endothelial cells [33]. In contrast, exenatide does not directly act as a vasodilator in preconstricted rat conduit artery rings [8, 34]. A dual control of the cardiovascular effects of exenatide has been proposed via the central and peripheral nervous systems, suggested to involve both the autonomic and non-autonomic nervous systems [35]. This might explain some of the discrepant findings in this study.

It has been suggested that CHF associates with a hyperadrenergic state that increases circulating NEFA levels [36]. In type 2 diabetic patients, levels of circulating NEFAs often exceed the normal range, reflecting lipotoxicity and insulin resistance. Lipotoxicity appears to be more important in women, who seem more susceptible to the adverse myocardial metabolic effects of NEFAs compared with men [37]. Despite considerable efforts to include women in this study, all available female participants declined to enter into the study. Sex differences in myocardial metabolism have been suggested inasmuch as sex may modulate the response of therapeutic strategies in heart failure and type 2 diabetes [37]. In the current study, NEFAs increased during both protocols, probably reflecting catabolism during fasting. Interestingly, exenatide increased NEFA levels even further without any changes in plasma lactate levels. There were no differences in glucose, insulin or glucagon levels. C-peptide levels were higher during exenatide infusion, with somewhat less need for insulin, reflecting the known insulinotropic action by exenatide. Without any metabolic changes during the exenatide infusion, the elevated NEFA levels were probably due to the increased HR, reflecting a hyperadrenergic state. This was mirrored by a tendency of increased MAP in both groups, which might have been elicited by β-adrenoreceptor activation [32]. Thus, we cannot exclude the possibility that the tachycardia, concomitant with elevated NEFA levels, evoked by exenatide might be detrimental for a failing heart. Two patients required digoxin in order to terminate a high-frequency AF and a third patient needed temporary nitroglycerine infusion because of increased blood pressure during the exenatide infusion. Furthermore, another six patients suffered from nausea and vomiting. Despite these adverse events, no symptoms of deteriorated heart failure or other serious adverse events were observed in any patient during the protocol.

Strengths and limitations The strengths of our study include the fact that this was a double-blind, placebo-controlled, crossover study. The invasive pulmonary artery catheter

method remains the gold standard for monitoring cardiac filling pressure. There are also limitations of the study. The findings are confined to male patients admitted to the hospital for CHF with type 2 diabetes and therefore it cannot be inferred that such haemodynamic effects will occur in a mixed-sex population. Not using echocardiographic monitoring precluded us from investigating the effects of exenatide on contractility and diastolic function that would have revealed any harmful effects to the heart.

In conclusion, the present study shows that exenatide caused a significant improvement of CI, contingent upon a marked increase in HR, in type 2 diabetic patients with CHF. These effects occurred together with a decrease in PCWP and RAP, and with reasonable tolerability of the drug. Studies of the clinical implications of the use of exenatide in patients with CHF are still in their infancy and further prospective studies with clinically hard endpoints, such as cardiovascular morbidity and mortality, are very much needed.

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Duality of interest D. Nathanson has received consultancy fees from Merck. T. Nyström has received consultancy fees from Eli Lilly, Novo Nordisk, Merck and sanofi-aventis. Å. Sjöholm has received research grants, consultancy fees, lecture honoraria and fees for expert testimony from Eli Lilly, Novo Nordisk, Merck, Boehringer-Ingelheim, AstraZeneca, Novartis and sanofi-aventis and is on the national/Nordic/European/global advisory boards of Eli Lilly, Merck, Boehringer-Ingelheim, AstraZeneca, sanofi-aventis and Novartis.

Contribution statement All authors contributed to the study conception and design. MF and BU conducted the heart catheterisations. DN, BU and TN analysed data. DN and TN wrote the first draft of the paper. All authors commented on and took part in the revision of the paper and approved the final version.

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