Effects of Acute GLP-1 Infusion on Pulmonary and Systemic Hemodynamics in Patients With Heart Failure: A Pilot Study

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ABSTRACT

Purpose: Cardiovascular-safety studies assessing glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase 4 inhibitors have provided inconsistent data on the risk for developing heart failure. Animal studies have shown that GLP-1 is a vasodilator; if confirmed in humans, this may ameliorate heart failure symptoms.

Methods: In a single-center, observational pilot study, we recruited 10 patients with advanced heart failure undergoing right heart catheterization, and we recorded pulmonary hemodynamic measures, including cardiac output calculated by thermodilution and the indirect Fick method before and after a 15-minute continuous infusion of native GLP-1 (7-36) NH_2.

Findings: There was a neutral effect of GLP-1 on all pressure and hemodynamics indices as derived by cardiac output calculated by thermodilution. However, there was a small but consistent reduction in cardiac output as calculated by the indirect Fick method after GLP-1 infusion (baseline, 4.0 [1.1] L/min vs GLP-1, 3.6 [0.9] L/min; $P = 0.003$), driven by a consistent reduction in mixed venous oxygen saturation after GLP-1 infusion (baseline, 62.2% [7.0%] vs GLP-1, 59.3% [6.8%]; $P < 0.001$), whereas arterial saturation remained constant (baseline, 96.8% [3.3%] vs GLP-1, 97.0% [3.2%]; $P = 0.34$). This resulted in an increase in systemic vascular resistance by Fick (baseline, 1285 [228] dyn · s/cm^5 vs GLP-1, 1562 [247] dyn · s/cm^5; $P = 0.001$).

Implications: Acute infusion of GLP-1 has a neutral hemodynamic effect, when assessed by thermodilution, in patients with heart failure. However, GLP-1 reduces mixed venous oxygen saturation. ClinicalTrials.gov identifier: NCT02129179. (*Clin Ther*. 2019;41:118–127)

Key words: GLP-1, heart failure, hemodynamics, right heart catheterization.

INTRODUCTION

An increasing proportion of patients survive an acute myocardial infarction due to timely and effective reperfusion, but many subsequently develop left ventricular (LV) dysfunction and congestive heart failure (CHF).[1] Ischemia reperfusion injury contributes significantly to the final infarct size.[2] Therapies that protect the heart against ischemia reperfusion injury and optimize ventricular myocardial performance and contractility may ameliorate the clinical effects of CHF.[3]

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The incretin hormone glucagon-like peptide (GLP)-1 and its analogues have been reported to protect the heart from ischemia reperfusion injury during experimentally induced acute myocardial infarction in animal models[4] and have been shown to prevent deterioration in LV performance during both demand and supply ischemia in humans.[5–10] However, data on the effects of inhibitors of dipeptidyl peptidase 4—the enzyme involved in GLP-1 breakdown—and GLP-1 receptor agonists versus placebo on the risk of developing CHF were inconsistent in large-scale, randomized, controlled cardiovascular-safety studies in patients with diabetes.[11,12]

The mechanism of GLP-1 cardioprotection also remains elusive; in humans, GLP-1 does not appear to act via mitochondrial ATP-sensitive K^+ channel–dependent intracellular conditioning pathways,[13] and GLP-1 receptors are not expressed on human ventricular myocytes.[14] Peripheral vasodilatation after both active GLP-1 (7-36) NH_2 and metabolite (9-36) NH_2 infusions have been reported in animal models.[15–17] This vasodilatory effect may be beneficial in patients with heart failure, although it has not been extensively studied in humans.[18–22] If confirmed, the observed improvements in ventricular function previously reported could simply reflect reductions in afterload and systemic vascular resistance (SVR) rather than a direct ventricular myocardial effect. We sought to establish whether GLP-1 has any hemodynamic and, in particular, peripheral vasodilatory effects in patients with stable chronic heart failure undergoing right heart catheterization during cardiac transplantation assessment.

Patients and Methods

Patients with stable chronic heart failure referred for transplant assessment and on the waiting list for right heart catheterization to determine transplant eligibility at Royal Papworth Hospital (Cambridge, United Kingdom), were consecutively approached over a period of 12 months. Eligible patients were aged over 18 years and able to give informed consent.

Patients receiving treatment with a dipeptidyl peptidase 4 inhibitor or a GLP-1 receptor agonist were excluded, and those who were using insulin were excluded to minimize the risk for hypoglycemia during the study. Glibenclamide treatment was also an exclusion criterion to minimize hypoglycemia, and as it has the potential to block cardioprotective pathways. Those taking conditioning-mimetic medication (eg, nicorandil) were also excluded.

Ethics and Permissions

The protocol was approved by the local ethics committee (NRES Committee East of England, Cambridge East, United Kingdom; REC reference no. 14/EE/0017) and written informed consent was obtained from all participants before they were enrolled into the study. The study was carried out according to institutional guidelines, was registered with ClinicalTrials.gov (NCT02129179), and was performed in accordance with the principles set forth in the Declaration of Helsinki.

Protocol

Patients acted as their own controls, and initially a right heart catheterization was undertaken, as per usual standard of care, by a consultant cardiologist, to record baseline hemodynamic measures. Each patient was studied in a supine position and a 7 Fr sheath was placed in the right internal jugular vein for access using ultrasound guidance. After 5-minute steady state, baseline systemic blood pressure and heart rate were recorded using an automated sphygmomanometer attached to the upper arm, and blood was drawn from the jugular vein for measurements of glucose, GLP-1 (7-36) NH_2, insulin, and free fatty acid. A 7 Fr thermodilution pulmonary artery catheter (Edwards Lifesciences, Irvine, California) was zeroed at the phlebostatic axis, advanced to the right atrium under fluoroscopic guidance, and then floated through the right heart and into the pulmonary circulation. Baseline right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure were recorded in end-expiration. "Over-wedging" was avoided by floating the catheter into the pulmonary circulation with the balloon inflated. In the event of uncertainty about the adequacy of wedging, this was confirmed by ensuring complete oxygen saturation of blood aspirated through the distal lumen of the pulmonary artery catheter. Cardiac output was estimated using the thermodilution method; the mean of four 10-mL room-temperature saline injections from the proximal port of the thermodilution catheter was calculated, and measurements were deemed accurate

Table I. Patients' demographic and clinical characteristics at baseline (N = 10).

Characteristic	Value
Age, mean (SD), y	54.1 (10.2)
Male, n	8
Weight, mean (SD), kg	87.8 (20.2)
Height, mean (SD), m	1.78 (0.13)
Body mass index, mean (SD), kg/m^2	27.5 (4.0)
Body surface area, mean (SD), m^2	2.07 (0.31)
NYHA class II/III, n	3/7
Comorbidities, n	
CKD stage 1/2/3	2/4/4
Atrial fibrillation	4
Stroke	1
Hypothyroidism	5
Etiology, n	
DCM	5
ARVC	2
ICM	1
HCM	1
RCM	1
Medications, n	
Loop diuretic	10
ACEI/ARB	8
MRA	9
Beta-blocker	7
Digoxin	5
Amiodarone	3
Warfarin	7
Device therapy, n	
CRT-D	5
ICD	2
CRT-P	1
PPM	1
Blood chemistry, mean (SD)	
Cr, μmol/L	113.3 (32.6)
eGFR, mL/min	63.6 (19.1)
Hb, g/L	135.4 (21.9)
Echocardiography, mean (SD)	
EF, %	27.2 (11.2)
LVEDd, cm	6.5 (1.2)
LVESd, cm	5.6 (1.4)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARVC = arrhythmogenic right ventricular cardiomyopathy; CKD = chronic kidney disease; Cr = creatinine; CRT-D = cardiac resynchronization therapy–defibrillator; DCM = dilated cardiomyopathy; eGFR = estimated glomerular filtration rate; EF = ejection fraction; Hb = hemoglobin; HCM = hypertrophic cardiomyopathy; ICD = implantable cardiac defibrillator; ICM = ischemic cardiomyopathy; LVEDd = left ventricular end diastolic dimension; LVESd = left ventricular end systolic dimension; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; -P = pacemaker; PPM = permanent pacemaker; RCM = restrictive cardiomyopathy.

Table II. Jugular venous plasma biochemistry at baseline and following glucagon-like peptide (GLP)-1 administration for 15 minutes (N = 10). Data are given as mean (SD).

Biochemistry	Baseline	GLP-1	*P*
Blood glucose, mmol/L	6.26 (2.06)	6.189 (6.63)	0.14
Free fatty acid, μmol/L	260.1 (181.1)	309.9 (206.3)	0.3
Insulin, pmol/L	246.4 (232.5)	282 (297.3)	0.43
GLP-1 (7-36), pmol/L	3.8 (4.2)	19.1 (21.8)	0.05
GLP-1 (9-36), pmol/L	13.0 (5.9)	30.8 (26.8)	0.05

if there was <10% variation.[23] Cardiac output was also estimated by the indirect Fick method,[24] using peripheral arterial oxygen saturation (measured by noninvasive finger pulse oximetry), mixed venous oxygen saturation (measured invasively from the main pulmonary artery), and tabulated estimated oxygen consumption based on calculated body surface area.[25]

Jugular venous blood and right heart catheter measurements were repeated again after a 15-minute

Table III. Mean hemodynamic measurements at baseline and following glucagon-like peptide (GLP)-1 administration for 15 minutes (N = 10). Data are given as mean (SD).

Parameter	Baseline	GLP-1	*P*
Heart rate, bpm	70.9 (11.99)	64.5 (24.34)	0.34
Systolic BP, mm Hg	99.9 (14.01)	101.7 (15.1)	0.75
Diastolic BP, mm Hg	59.8 (8.3)	64.3 (14.1)	0.48
MAP, mm Hg	73.2 (8.95)	76.8 (13.77)	0.22
Mean RA pressure, mm Hg	11.8 (4.8)	9.8 (5.35)	0.12
RV end diastolic pressure, mm Hg	11.2 (4.42)	11.9 (4.51)	0.21
PA pressure, mm Hg	29.0 (14.41)	30.4 (13.49)	0.68
PCW pressure, mm Hg	20.0 (7.89)	22.1 (8.95)	0.09
TPG	9.0 (2.75)	8.3 (2.58)	0.50
CO_{TD}, L/min	4.1 (1.0)	4.1 (0.8)	0.50
CI_{TD}, L/min/m^2	2.0 (0.5)	2.0 (0.4)	0.51
PVR_{TD}, dyn · s/cm^5	187 (68)	163 (42)	0.22
SVR_{TD}, dyn · s/cm^5	1266 (252)	1375 (299)	0.12
CO_F, L/min	4.0 (1.1)	3.6 (0.9)	0.003
CI_F, L/min/m^2	1.9 (0.4)	1.7 (0.3)	0.001
PVR_F, dyn · s/cm^5	188 (60)	188 (55)	1.00
SVR_F, dyn · s/cm^5	1285 (228)	1562 (247)	0.001
Arterial oxygen saturation %	96.8 (3.3)	97.0 (3.2)	0.34
Mixed venous oxygen saturation, %	62.2 (7.0)	59.3 (6.8)	<0.001

BP = blood pressure; CI = cardiac index; CO = cardiac output; F = Fick; MAP = mean arterial pressure; PA = pulmonary artery; PCW = pulmonary capillary wedge; PVR = pulmonary vascular resistance; RA = right atrial; RV = right ventricular; SVR = systemic vascular resistance; TD = thermodilution; TPG = transpulmonary gradient.

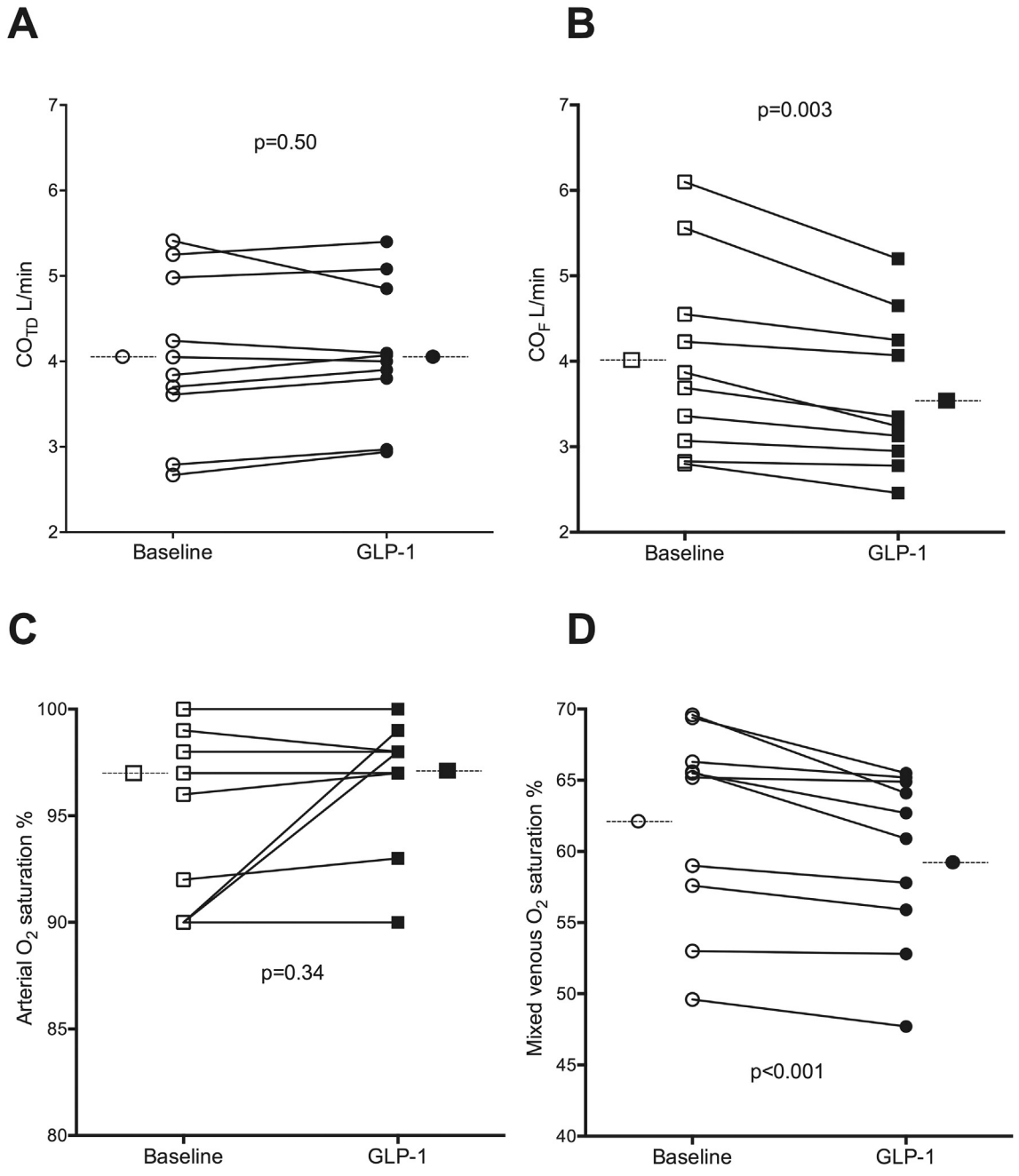

Figure. Cardiac output, as measured by thermodilution (CO_{TD}; A) and indirect Fick (CO_F; B). Although CO_{TD} remained constant, CO_F fell in every patient following the administration of glucagon-like peptide (GLP)-1. Saturation of arterial oxygen (C) and mixed venous oxygen (D), at baseline and following the administration of GLP-1. There was a consistent reduction in mixed venous oxygen saturation following the administration of GLP-1.

antecubital venous continuous infusion of GLP-1 (7-36) NH_2 (Bachem, Bubendorf, Switzerland) was administered at a rate of 1.2 pmol/kg/min. The GLP-1 infusion was discontinued after completion of the study and the patients resumed their normal care. The venous sheath was removed and hemostasis was achieved using manual pressure. Chest radiography was performed after the procedure to exclude pneumothorax.

Calculations

Pulmonary vascular resistance (PVR) and SVR cardiac index were calculated using both the thermodilution and Fick estimates of cardiac output, according to the following equations:

$$\text{PVR (dyn/cm}^5) = 80 \cdot (\text{mean PAP} - \text{mean PCWP})/\text{CO}; \quad (1)$$

$$\text{SVR (dyn/cm}^5) = 80 \cdot (\text{MAP} - \text{mean RAP})/\text{CO}; \text{ and} \quad (2)$$

$$\text{CI} = \text{CO}/\text{BSA}, \quad (3)$$

where *CO* is cardiac output, *CI* is cardiac index, *PAP* is pulmonary artery pressure, *PCWP* is pulmonary capillary wedge pressure, *MAP* is systemic mean arterial pressure (estimated as: [systolic blood pressure + 2 · diastolic blood pressure]/3), *RA* is right arterial pressure, and *BSA* is body surface area (estimated by the Mosteller formula[26]: square root of [height (cm) · weight (kg)/3600]).

Statistical Analysis

The primary end point was change from baseline in SVR after GLP-1 infusion. A previous study investigating the vasodilatory effect of GLP-1 in animal models reported a 10% increase in vessel diameter.[27] In the present study, as mentioned, patients acted as their own controls. We estimated that the number of patients required to detect a difference of 10% in SVR between baseline and post−GLP-1 was 8. Taking into account possible technical failures and incomplete datasets, we planned to recruit 10 patients (power, 80%; $\alpha = 0.05$; $\beta = 0.2$).

Statistical analysis was performed using IBM SPSS Statistics version 21.0 (IBM, Armonk, NY). Continuous data are presented as means (SD) and were analyzed using the *t* test or Wilcoxon rank test as appropriate. Categorical data are presented as counts or frequencies (%) and were analyzed by the χ^2 or Fisher exact test as appropriate. All calculations were 2-tailed, and a *P* value of <0.05 was deemed statistically significant.

RESULTS

Eleven patients were recruited from the cardiac transplant−assessment waiting list from July 2015 to July 2016. One patient was excluded due to new-onset atrial fibrillation with rapid ventricular response at the time of right heart catheterization. The remaining 10 patients' demographic details are summarized in Table I. The majority were male, with New York Heart Association class II/III symptoms secondary to dilated cardiomyopathy. None of the patients had diabetes mellitus. Mean LV ejection fraction was 27.2%, and there was evidence of end-organ failure with chronic kidney disease stage 2 or 3 seen in 8 of the cohort. The majority were on evidence-based medical therapy for CHF and had also received device therapy with a cardiac resynchronization therapy−defibrillator or an implantable cardiac defibrillator. All patients underwent serial blood sampling and right heart catheterization before and after GLP-1 infusion, without complications or adverse events.

Biochemical data are summarized in Table II. We confirmed that GLP-1 (7-36) NH_2 and its metabolite (9-36) were increased as expected after a 15-minute infusion but that a short infusion of GLP-1 had no effect on blood glucose, free fatty acid, or insulin concentrations.

Comparisons of baseline and post−GLP-1 right heart data are summarized in Table III. There was no effect of GLP-1 on heart rate or on noninvasively derived systolic, diastolic, or mean blood pressures, nor did we observe any effect of GLP-1 on any invasive pressure measurement obtained from the pulmonary artery catheterization. Cardiac output calculated by thermodilution was not significantly different between baseline and post−GLP-1 (Figure, part A and Table III), and as a result the derived PVR and SVR calculations remained constant after GLP-1 administration. However, cardiac output calculated by the indirect Fick method gave different results. We observed lower cardiac outputs after GLP-1 administration in all patients (baseline, 4.0 [1.1] L/min vs GLP-1, 3.6 [0.9] L/min; $P = 0.003$) (Figure, part B), driven by a consistent reduction in mixed venous oxygen saturation after GLP-1 administration (baseline, 62.2% [7.0%] vs GLP-1, 59.3% [6.8%]; $P < 0.001$) (Figure, part C), whereas the arterial saturation remained constant (baseline, 96.8% [3.3%] vs GLP-1, 97.0% [3.2%]; $P = 0.34$) (Figure, part D).

This led to an increase in the indirect Fick–derived SVR (baseline, 1285 [228] dyn · s/cm^5 vs GLP-1, 1562 [247] dyn · s/cm^5; $P = 0.001$), although the PVR was not affected (Table III).

DISCUSSION

We assessed the hemodynamic effects of GLP-1 in a population with stable chronic heart failure and found that a peripheral intravenous infusion of GLP-1 did not have any effect on heart rate, noninvasive systemic blood pressure, invasive right heart and pulmonary pressures, or cardiac output by thermodilution. PVR and SVR when calculated by thermodilution were used to derive that cardiac output was not affected by GLP-1. However, we did observe a small but consistent reduction in mixed venous oxygen saturation, but not systemic arterial saturation, after GLP-1 infusion, which resulted in a small reduction in cardiac output by indirect Fick and increased SVR after GLP-1 administration.

We and others have observed a consistent effect of GLP-1 on preserving LV function and enhancing contractile recovery after supply ischemia.[5–8,10] The mechanism for this protection remains unclear; however, data from animal studies suggest that a reduction in afterload could be involved. Various groups have identified that GLP-1 is capable of eliciting a vasodilatory effect in animals,[15–17,28–30] and others have reported that GLP-1 and GLP-1 receptor agonists influence both heart rate and blood pressure in rats, potentially mediated both peripherally and centrally via stimulation of the vagus nerve.[31,32] In humans, GLP-1 receptor agonists have shown a modest reduction in systolic blood pressure, particularly with longer-acting molecules.[33] GLP-1 (7-36) NH_2 and GLP-1 receptor agonists have been associated with improvements in endothelial function, whereas the data on vasodilation were inconclusive.[18–22,34] However, our hemodynamic data now suggest that a reduction in SVR and afterload do not explain the observed protection from stunning and ischemic LV dysfunction after GLP-1 infusion.

The mechanism of the GLP-1 cardioprotective effect preventing ischemic LV dysfunction remains elusive. The location of the known GLP-1 receptor in the cardiovascular system remains uncertain but it does not appear to be expressed on human ventricular myocytes. It has been localized to the atria in rat heart, and may be involved in paracrine atrial natriuretic peptide–dependent vasodilatory effects in rats[14] but not in humans.[35–37] Adenosine, another potent endothelium-independent vasodilator, liberated from vascular smooth muscle, has also been implicated as a paracrine secondary messenger liberated after GLP-1 tissue binding in an animal model.[38] GLP-1 receptor expression appears to be abundant in vascular smooth muscle cells,[39] making a vasodilatory mechanism plausible. It is important to determine whether vascular smooth muscle cell expression and GLP-1 binding are ubiquitous or tissue specific to fully understand the mechanism of action of GLP-1.

We had contradictory results when calculating cardiac output by indirect Fick and thermodilution. The "gold standard" way to measure Fick cardiac output is by using a rebreathe Douglas bag technique to determine actual oxygen consumption, but this method was not practical and is rarely performed in clinical practice. The indirect Fick method has the potential to be inaccurate, as it makes assumptions on oxygen consumption derived in a normal population that is unlikely to be representative of the population with severe heart failure that we studied.[40,41] We also used pulse oximetry to measure arterial oxygen saturation, which may be less precise than arterial blood sampling. Cardiac output by thermodilution has been shown to correlate better with direct Fick than with indirect Fick[40] and also allows repeated measurements to be made, minimizing the coefficient of variability. However, it relies on a consistent and accurate injection technique, can have the potential to become less accurate in patients with low cardiac output, and may be less accurate in patients with severe tricuspid regurgitation. Consequently, the correlation between the 2 techniques is not perfect, and thermodilution estimates cardiac output a little higher than Fick within the physiologic range. Thermodilution is believed to be the more accurate method.[42]

Despite these caveats, there was a consistent decrease in mixed venous oxygen saturation after GLP-1 in all patients, and this observation is hard to dismiss. One explanation may be that differential tissue blood flow occurs after GLP-1 infusion.[20] Redistribution of blood through a more metabolically active, high–oxygen-extracting tissue with a relatively small percentage of total cardiac output (4%–5%) (eg, the heart), could reduce mixed oxygen saturation while having minimal effect on global cardiac output. Augmentation of coronary blood flow after GLP-1 could mitigate

postischemic stunning and LV dysfunction by this mechanism, via the Gregg effect. We recently confirmed that resting coronary blood flow velocity is augmented and that basal coronary microvascular resistance is reduced in humans after an acute GLP-1 infusion, in support of this hypothesis.[43]

Limitations

This small-scale, single-center, open-label, observational pilot study assessed the acute hemodynamic effects of GLP-1, and unintentional bias cannot be excluded. We cannot comment on the hemodynamic effects of longer-term administration of GLP-1. Patients acted as their own controls to increase the power of the study and therefore our observations remain valid. Patients were on rate-controlling medication, and all but 1 patient in the cohort had an implantable device that could deliver brady-pacing, and therefore the effects of GLP-1 on heart rate should be interpreted with caution.

CONCLUSIONS

GLP-1 has a neutral hemodynamic effect in patients with heart failure when assessed by thermodilution. Given the results of the present study, the observed improvement in ischemic LV function is unlikely to be explained by peripheral vasodilatation, nor is GLP-1 likely to influence CHF prevalence by altering systemic pressure or vascular resistance. However, further work on the changes in regional blood flow after GLP-1 infusion, particularly in relation to the heart, warrant further exploration.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2018.11.013.

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