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The effect of metformin on insulin resistance and exercise parameters in patients with heart failure

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Aims Chronic heart failure (CHF) is an insulin-resistant state. The degree of insulin resistance (IR) correlates with disease severity and is associated with reduced exercise capacity. In this proof of concept study, we have examined the effect of metformin on IR and exercise capacity in non-diabetic CHF patients identified to have IR.

Methods and results In a double-blind, placebo-controlled study, 62 non-diabetic IR CHF patients (mean age, 65.2 $\pm$ 8.0 years; male, 90%; left ventricular ejection fraction, 32.6 $\pm$ 8.3%; New York Heart Association class I/II/III/IV, 11/45/6/0) were randomized to receive either 4 months of metformin ($n = 39$, 2 g/day) or matching placebo ($n = 23$). IR was defined by a fasting insulin resistance index (FIRI) $\geq$2.7. Cardiopulmonary exercise testing and FIRI were assessed at baseline and after 4 months of intervention. Compared with placebo, metformin decreased FIRI (from 5.8 $\pm$ 3.8 to 4.0 $\pm$ 2.5, $P < 0.001$) and resulted in a weight loss of 1.9 kg ($P < 0.001$). The primary endpoint of the study, peak oxygen uptake (VO_2), did not differ between treatment groups. However, metformin improved the secondary endpoint of the slope of the ratio of minute ventilation to carbon dioxide production (VE/VCO_2 slope), from 32.9 $\pm$ 15.9 to 28.1 $\pm$ 8.8 ($P = 0.034$). In the metformin-treated group, FIRI was significantly related to the reduction of the VE/VCO_2 slope ($R = 0.41$, $P = 0.036$).

Conclusion Metformin treatment significantly improved IR but had no effect on peak VO_2, the primary endpoint of our study. However, metformin treatment did result in a significant improvement in VE/VCO_2 slope.
Trial registration: NCT00473876.

Keywords Diabetes • Chronic heart failure • Metformin

Introduction

Chronic heart failure (CHF) is an insulin-resistant state.[1] Insulin resistance (IR) is highly prevalent among non-diabetic patients with CHF and is associated with disease severity and outcome.[2–5] It is unclear whether IR is a bystander reflecting disease severity or whether it is a culprit contributing to the pathophysiology of CHF. Therefore, a proof of concept study is required to test the hypothesis that IR is a culprit and that reversing IR will lead to clinical improvement in CHF. However, the insulin sensitizers that are suitable to be tested are limited. Thiazolidinediones have the potential to exacerbate CHF in patients with reduced cardiac reserve. Although metformin is a widely prescribed drug in type 2 diabetes mellitus (T2DM), its use in patients with CHF had been discouraged due to concerns over the risk of lactic acidosis originating from earlier experience with phenformin. However, clinical experience suggests that the risk of metformin-associated lactic acidosis is low.[6] Indeed, observational data suggest that metformin may actually be beneficial for CHF.[7,8] As CHF patients with IR have reduced exercise capacity,[2,3] we have conducted a proof of concept study to evaluate the impact of metformin on IR and its effects on exercise capacity in non-diabetic patients with CHF.

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Research design and methods

This is a randomized placebo-controlled study designed to evaluate the impact of metformin on IR and its effects on exercise capacity in non-diabetic patients with CHF. The primary endpoint of the study was peak oxygen uptake (peak VO_2). However, many patients with CHF are unable to perform maximal exercise, and oxygen requirements for daily activities rarely approach maximal levels.[9] Therefore, we have included the submaximal derived exercise variable of the slope of the ratio of minute ventilation (VE) to carbon dioxide production (VCO_2) (VE/VCO_2 slope) as a secondary endpoint of this study. VE/VCO_2 slope is an index of ventilatory response to exercise and, unlike peak VO_2, VE/VCO_2 is not influenced by the mechanical work done during exercise testing but reflects peripheral alterations in CHF that contribute to the progression and symptomatology of CHF.[10] The VE/VCO_2 slope had been reported to be a more accurate prognostic index for cardiac-related mortality and hospitalization than peak VO_2,[11] and the ventilatory classification system has been proposed to guide therapy in patients with CHF.[12] Possible mechanisms of improvement of exercise capacity were explored by measurement of left ventricular ejection fraction (LVEF) by echocardiography, and endothelial and related biomarkers.

Patient population

Every patient provided written informed consent prior to participation in this study, which was approved by the East of Scotland Research Ethics Service (www.clinicaltrials.gov: NCT00473876). Patients with symptomatic CHF were recruited from outpatient cardiology clinics and a local echocardiography database. Eligible patients with a history of CHF and left ventricular systolic dysfunction on echocardiography were approached to have a fasting blood test to determine their fasting insulin resistance index (FIRI), consisting of the product of plasma insulin and glucose divided by 25. CHF patients with a FIRI $\geq$ 2.7 were considered to have IR[2] and were invited to participate in the study. Exclusion criteria included: patients with a history of T2DM or fasting glucose of $>$ 7 mmol/L; patients aged $>$80 years; patients with New York Heart Association (NYHA) functional class IV and decompensated CHF; patients with renal dysfunction (serum creatinine $>$160 μmol/L); and patients who were unable to exercise. Patients had to be on a stable dose of CHF medications at least 1 month prior to screening. Treatment allocation was masked for patients and investigators until after database lock. Tablet counting assessed compliance.

Study protocol

The study consisted of six visits. At Visit 1, patients underwent physical examination, fasting blood tests, cardiopulmonary exercise testing (CPET), two-dimensional echocardiography (2-D echo), endothelial function assessments, 6 min unencouraged walk test (6MWT), and Minnesota Living with Heart Failure (MLHF) questionnaires. CPET was repeated at a separate visit (Visit 2) within a week in order to achieve consistent exercise parameters with a variation of exercise duration of $<$ 15% prior to randomization. Following this visit, patients were randomized to receive either 4 months of metformin (1000 mg b.d.) or matching placebo using a pre-established computer-generated sequence from our study drug provider (Western Infirmary, Glasgow, UK). The dose and duration of metformin therapy was based on a previous study in patients with impaired glucose tolerance, which showed that this dose regimen was well tolerated and had a beneficial effect on endothelial function.[13] The metformin study drug was commenced at 500 mg b.d for 2 weeks and was up-titrated if well tolerated based on symptoms and measurement of plasma lactate and renal function. At subsequent visits, patients were reassessed and doses of study drug altered according to tolerability. All measurements of interests were repeated after 4 months of intervention.

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed in the fasting state as previously described.[14] Prior to exercise, the patient was instructed on the re-breathing technique. An incremental symptom-limited bicycle exercise testing was performed using an upright, braked cycle ergometer. After 3 min rest, exercise was begun at 0 W and increased every 3 min by 25 W until symptom-limited maximal exercise was achieved. Expired gas analysis was performed continuously with the Innocor system (Innovision A/S, Odense, Denmark). Peak VO_2 was defined as the highest value of VO_2 achieved in the final 20 s of exercise. The VE/VCO_2 slope was calculated from the start of incremental exercise to the anaerobic threshold, by least squares linear regression. The Innocor system allowed measurement of cardiac output (CO), by the inert gas re-breathing method, at the end of the rest period and at peak exercise.[14] The inert gas re-breathing method is a validated, reliable, and safe method for non-invasive measurements of pulmonary blood flow, which is equivalent to CO in the absence of shunts.[14] VO_2 (mL/kg/min), VCO_2 (L/min), and VE (L/min) were measured on a breath-by-breath basis. CPET was performed at Visit 1 and Visit 2 to achieve a variation of exercise duration of $<$ 15% prior to randomization to minimize the 'learning effect'. If variation was $>$ 15%, further CPET was repeated and the highest value of peak VO_2 was chosen to be the baseline. The intrasubject and intersubject variability in our cardiopulmonary exercise laboratory for peak VO_2 were 1.06% and 7.14%, respectively, and for VE/VCO_2 slope, they were 5% and 34%, respectively.

Endothelial function

Endothelial function was assessed by both reactive hyperaemia peripheral arterial tonometry, (RH-PAT; Itamar Medical Ltd, Caesarea, Israel) and by flow-mediated dilatation (FMD).[2,15] The intrasubject coefficients of variation for RH-PAT and FMD in our laboratory were 18.9% and 5.2%, respectively, and the repeatability coefficient for FMD was 0.3 $\pm$ 1.4%.

Echocardiography

Standard 2-D echo was performed in all patients. Biplane LVEF was calculated using the Simpson's method.

Six minute walk test

The 6MWT was performed using a standardized approach over a 25 m course.

Minnesota Living with Heart Failure Questionnaire

The MLHF questionnaire is a 21-item questionnaire which assesses physical activity, subjective symptoms, and psychosocial issues.

Biomarkers

Venous blood samples were obtained following a 20 min semi-recumbent rest at baseline and at the end of study for measurement of full blood count, renal function, glycated haemoglobin (HbA_{1c}), glucose, lipids, lactate, insulin (INSIK-5, DiaSorin, UK), brain natriuretic peptide (BNP), adiponectin (Quantikine, R&D System, UK), leptin (Quantikine, R&D System, UK), and resistin.

Safety assessments

Safety was assessed via monitoring for adverse events (AEs), clinical examination, standard laboratory testing, electrocardiogram (ECG) recordings, and measurements of vital signs. Lactate levels were measured 2 weeks after initiation of study treatment, and at the end of the study visits.

Power calculation and statistical method

We targeted 66 subjects and the power calculations were based on our previous observational study of CHF with IR,[2] with a mean peak VO_2 of 11 mL/min/kg and standard deviation (SD) of 1.8 mL/min/kg which would provide 80% power to detect a 13.5% change in peak VO_2 in the two groups of patients with CHF (alpha = 0.05) allowing for a 10% drop-out rate. Statistical analysis was performed using SPSS for Windows version 16 (SPSS Inc., Chicago, IL, USA). Numeric values were expressed as the mean $\pm$ SD. An intention to treat analysis was used. The significant of differences between the two treatment groups of changes from baseline was analysed using independent *t*-tests and chi-square[2] tests. Correlations were made using Pearson product–moment correlation coefficients. A *P*-value of < 0.05 was considered statistically significant.

Results

A total of 127 patients were invited for screening, and 53 patients were excluded based on our exclusion criteria (*Figure 1*). A total of 62 patients were randomized; 39 were allocated to metformin treatment and 23 to placebo. In the metformin group, three patients were lost to follow-up and were therefore excluded from analysis. Five patients were discontinued on medications due to side effects; however, they were included in our intention to treat analysis. In the placebo group, one patient was lost to follow-up and was excluded from analysis.

Baseline characteristics and measurements of interests are shown in *Tables 1* and *2*. Patients in the placebo group were somewhat older, had CHF that was more likely to be ischaemic in aetiology, and had a lower FMD, although these differences were not statistically significant. Additionally, patients in the metformin group had higher baseline levels of serum glucose (5.6 vs. 5.3 mmol/L) and serum total cholesterol (4.3 vs. 3.8 mmol/L).

Changes in weight, fasting insulin resistance index, and biomarkers

Compared with placebo, metformin resulted in a significant reduction in weight and body mass index (BMI) ($P < 0.001$, $P = 0.037$, respectively). Metformin significantly decreased FIRI ($P < 0.001$) and serum HbA_{1c} ($P = 0.002$). Serum leptin levels were significant reduced with metformin (metformin, -4.56 ± 11.0 ng/mL vs, placebo, 0.58 ± 3.5 ng/mL, $P = 0.038$). There was no significant

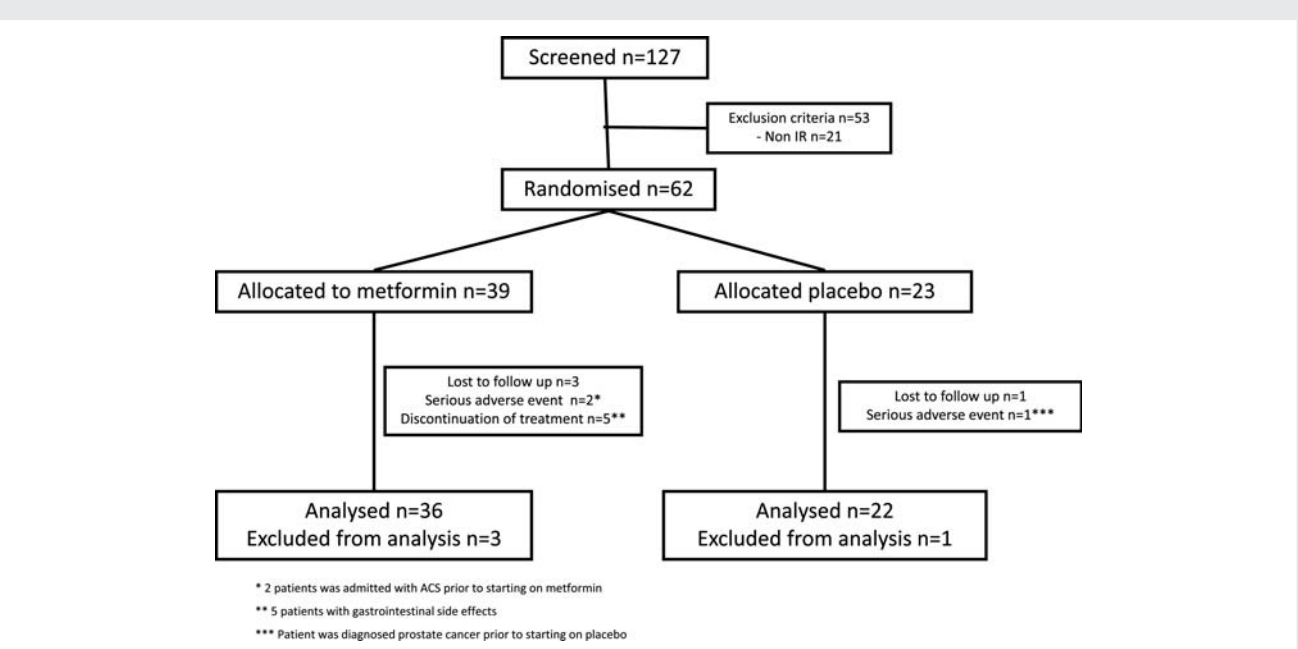

Figure 1 The CONSORT (Consolidated Standards of Reporting Trial) diagram describing outcomes of all patients within the study.

Table 1 Baseline characteristics

	Metformin ($n = 39$)	Placebo ($n = 23$)	All patients ($n = 62$)	*P*-value
Age	64 ± 8	68 ± 7	65 ± 8	0.063
Sex (male/female)	35/4	22/1	57/5	0.409
Systolic blood pressure (mmHg)	113 ± 16	114 ± 17	113 ± 16	0.761
Diastolic blood pressure (mmHg)	71 ± 9	73 ± 10	72 ± 9	0.563
Mean heart rate (b.p.m.)	74 ± 16	71 ± 19	73 ± 16	0.597
Body mass index	30 ± 5	29 ± 4	29.7 ± 4.6	0.224
LV ejection fraction (%)	34 ± 8	30 ± 8	33 ± 8	0.083
NYHA (I/II/III/IV)	7/29/3/0	3/17/3/0	10/46/6/0	0.725
Aetiology of heart failure				
Ischaemic	28	21	49	0.068
Non-ischaemic	11	2	13	
Past medical history (%)				
Ischaemic heart disease	80	91	63	0.036
Atrial fibrillation	31	17	26	0.245
Revascularization	33	35	34	0.944
Peripheral vascular disease	3	9	5	0.277
Hypertension	41	43	55	0.850
Chronic obstructive pulmonary disease	3	13	7	0.105
Medications (%)				
Diuretics	51	52	53	0.946
Angiotension-converting enzyme inhibitors	74	82	74	0.473
Angiotensin receptor blockers	21	14	18	0.474
Beta-blockers	82	91	82	0.329
Aldosterone antagonist	37	14	27	0.055
Digoxin	8	14	10	0.475
Calcium channel blocker	11	18	13	0.401
HMG Co-A reductase inhibitors (statins)	82	100	91	0.031
Isosorbide mononitrate	18	36	12	0.122

LV, left ventricular; NYHA, New York Heart Association.

change in serum adiponectin ($P = 0.168$) and resistin levels ($P = 0.094$). The change in plasma BNP was not statistically significant (metformin, −20.2 ± 78.7 pg/mL vs. placebo, 7.5 ± 131.2 pg/mL).

Maximal and submaximal exercise parameters and 6 min walk test

Peak exercise parameters did not differ between treatment groups (*Table 3*). Compared with placebo, metformin decreased the VE/VCO_2 slope (from 32.9 ± 15.9 to 28.1 ± 8.8, $P = 0.034$) and ventilatory class (χ^2 test, $P = 0.008$). There was no difference in 6MWT.

Correlations between the VE/VCO_2 slope, weight, and fasting insulin resistance index

Pearson correlations and a linear regression model showed that weight reduction on its own was not correlated with the reduction of the VE/VCO_2 slope ($P = 0.801$). In the metformin-treated group, change in FIRI and serum leptin levels was significantly related to the reduction of the VE/VCO_2 slope ($R = 0.41$; difference in FIRI, $\beta = -14.07$, $P = 0.036$; difference in leptin, $\beta = 0.29$, $P = 0.023$).

Symptoms

There was no significant change in NYHA functional class between the treatment groups (χ^2 test, $P = 0.124$) The MLHF questionnaire scores did not differ between the groups. Heart failure medications including diuretic dosage remained unchanged throughout the study.

Echocardiography and endothelial function

There was no significant change in LVEF. Changes in RH-PAT (metformin, 0.12 ± 0.4 vs. placebo, 0.06 ± 0.70) and in FMD (metformin, −0.38 ± 4.46 vs. placebo, −1.74 ± 2.71) were not statistically significant.

Tolerability and safety of metformin

There were no reported cases of lactic acidosis in either treatment group, and lactate levels did not differ between groups. AEs were

Table 2 Baseline measurements

	Metformin ($n = 39$)	Placebo ($n = 23$)	*P*-value
Exercise parameters			
Peak VO_2 (mL/kg/min)	19.5 ± 4.9	18.5 ± 5.1	0.312
Peak vardiac output (L/min)	8.3 ± 2.9	7.8 ± 2.6	0.631
VE/VCO_2 slope	32.9 ± 15.9	32 ± 5.9	0.821
Ventilatory class I/II/III/IV	13/12/7/1	8/7/5/0	0.845
Respiratory gas exchange ratio (R)	0.9 ± 0.1	0.8 ± 0.1	0.088
Total exercise duration (s)	1049 ± 207	940 ± 288	0.091
6 min walk test (m)	438 ± 76	414 ± 86	0.280
Endothelial function			
Reactive hyperaemic index	1.8 ± 0.3	1.9 ± 0.6	0.264
Flow-mediated dilatation (%)	7.1 ± 3.7	5.4 ± 3.7	0.119
Laboratory parameters			
Haemoglobin (g/dL)	14.8 ± 1.4	14.5 ± 1.3	0.361
Creatinine (μmol/L)	87.8 ± 16.3	88.3 ± 19.5	0.912
Glucose (mmol/L)	5.6 ± 0.6	5.3 ± 0.4	0.029
Insulin (mU/L)	26.8 ± 14.3	23.2 ± 10.5	0.198
Fasting insulin resistance index	6.6 ± 3.9	6.5 ± 4.6	0.116
Total cholesterol (mmol/L)	4.3 ± 1.0	3.8 ± 0.6	0.023
Adiponectin (mg/mL)	8.4 ± 6.7	8.7 ± 5.5	0.879
Leptin (ng/mL)	16.6 ± 23.2	10.9 ± 6.4	0.265
BNP (pg/mL)	131.7 ± 158.5	187.1 ± 251.3	0.362
Resistin (ng/mL)	5.1 ± 2.3	4.0 ± 1.1	0.054

BNP, brain natriuretic peptide.

more frequent with metformin treatment although the majority of these AEs were transient, and were mild to moderate in severity. The main AEs were abdominal discomfort (16% metformin, 4% placebo, $P = 0.18$), diarrhoea (47% metformin, 13% placebo, $P = 0.008$), nausea (29% metformin, 0% placebo, $P = 0.005$), and anorexia (21% metformin, 0% placebo, $P = 0.021$). AEs led to premature discontinuation for five metformin-treated patients. The average tolerable dose of metformin was 1675 mg daily.

Discussion

This study had two main findings. First, metformin significantly reduced FIRI and resulted in a weight loss of 1.9 kg in patients identified to have IR and CHF. Secondly, although metformin had no effect on peak exercise parameters including peak VO_2, metformin did result in a significant improvement in the VE/VCO_2 slope, a pre-specified endpoint of this proof of concept study.

To the best of our knowledge, this is the first proof of concept study to examine the impact of metformin on IR and exercise parameters in patients with CHF identified to have IR. IR is highly prevalent in CHF[2,16] and is associated with decreased exercise capacity, endothelial dysfunction,[2] and worse prognosis.[2,3,5] The prognostic impact of IR is independent of other variables, including peak VO_2 and LVEF, which may imply that IR may be pathogenic rather than a marker for worsened CHF.[3] In this study, we have chosen metformin as the insulin sensitizer to be tested although the precise mechanisms of metformin's action are not entirely understood.[17] Indeed, several lines of evidence suggest that metformin may have cardioprotective effects in the setting of CHF that are not attributed to the glucose-lowering effects alone. First, in animal models of CHF, metformin has been shown to confer cardioprotective effects via the 5′-AMP-activated protein kinase (AMPK) pathway, which is activated by metformin.[1,18,19] Secondly, observational studies of patients with CHF and T2DM taking metformin suggest a morbidity and mortality benefit.[7,8] However, observational studies have the potential for selection bias imposed by different therapies. What is needed is a prospective placebo-controlled study with metformin in patients with CHF. Given the pathophysiological role of IR in CHF patients, the target population in these proposed trials should be those identified to have IR rather than patients with co-existing T2DM and CHF. This is because a trial of metformin in patients with T2DM and CHF may not be feasible as such a trial was attempted but failed to recruit because of metformin's widespread use in these patients.[20] In a study of metformin in CHF patients with IR, IR may be identified by an elevated FIRI or another measure of dysglycaemia such as by oral glucose tolerance testing.[16]

In this study, we were interested in determining if reversing IR with metformin would result in an improvement in exercise capacity. We did not observe an effect of metformin on peak VO_2, the primary endpoint of our study. However, metformin treatment did reduce the pre-specified secondary endpoint of VE/VCO_2, which improved from 32.9 to 28.1. The finding of a lack of change in peak VO_2 despite a significant improvement in the VE/

Table 3 Changes after 4 months of metformin treatment

	Metformin ($n = 36$)	Placebo ($n = 22$)	*P*-value
Peak exercise parameters			
Peak VO_2 (mL/kg/min)	−0.38 ± 1.40	3.60 ± 3.90	0.08
Peak CO (L/min)	0.03 ± 3.10	−0.35 ± 2.10	0.682
Submaximal exercise parameters			
VE/VCO_2 slope	-4.45 ± 10.72	−0.23 ± 3.54	0.034
Ventilatory class I/II/III/IV	21/8/2/2	8/6/7/1	0.008
NYHA functional class I/II/III/IV	10/25/1/0	3/15/4/0	0.124
Heart failure questionnaires	1.58 ± 14.78	0.45 ± 8.57	0.746
6 min walk test (m)	6 ± 40	6 ± 32	0.988
Biomarkers and laboratory parameters			
HbA_{1c} (%)	−0.12 ± 0.19	0.08 ± 0.17	0.035
Glucose (mmol/L)	−0.36 ± 0.45	0.09 ± 0.71	0.005
Insulin (mU/L)	−6.60 ± 8.80	4.10 ± 13.10	0.000
FIRI (log)	−1.44 ± 0.16	0.05 ± 0.18	0.000
Leptin (ng/mL)	−4.56 ± 11.0	0.58 ± 3.50	0.038
Adiponectin (mg/mL)	−0.44 ± 2.16	0.43 ± 2.54	0.168
Resistin (ng/mL)	0.01 ± 0.08	0.04 ± 0.06	0.094
BNP (pg/mL)	−20.2 ± 78.7	17.5 ± 131.2	0.184
Creatinine (μmol/L)	0.50 ± 12.46	1.41 ± 7.39	0.758
Lactate (mmol/L)	0.09 ± 0.63	0.00 ± 0.42	0.562
Cholesterol (mmol/L)	−0.32 ± 0.54	−0.01 ± 0.65	0.055
Triglyceride (mmol/L)	−0.17 ± 0.60	−0.04 ± 0.80	0.467
Weight (kg)	−1.9 ± 2.3	1.1 ± 2.5	0.000
Body mass index	−2.03 ± 6.07	0.39 ± 0.89	0.037
Waist–hip ratio	−0.08 ± 0.03	−0.49 ± 2.02	0.341
Ejection fraction (%)	0.35 ± 5.50	−1.10 ± 4.20	0.356
Endothelial function			
Reactive hyperaemic index (endo-PAT)	0.12 ± 0.54	0.06 ± 0.70	0.743
Flow-mediated dilatation (%)	−0.38 ± 4.36	−1.74 ± 2.71	0.201

BNP, brain natriuretic peptide; CO, cardiac output; FIRI, fasting insulin resistance index; HbA_{1c}, glycated haemoglobin; NYHA, New York Heart Association; PAT, peripheral arterial tonometry.

VCO_2 slope deserves some consideration. In our study, many patients did not often achieve the anaerobic threshold, which is not unexpected in CHF patients undergoing CPET.[10,21] Peak VO_2 is only an indirect measure of cardiac output at anaerobic threshold[22] and, at submaximal exercise, VO_2 is merely a consequence of the amount of mechanical work done and loses it prognostic value at submaximal exercise.[10,21] Consequently, submaximal measurements such VE/VCO_2 that are not influenced by mechanical work done at submaximal exercise may have more prognostic value in these patients that can only carry out submaximal exercise.[10] Another consideration is that it is possible that metformin may have differential effects on peak VO_2 and VE/VCO_2. In this respect, metformin has been shown to have an inhibitory effect on the activity of complex I (transfer of electrons from NADPH to coenzyme Q10) of the mitochondrial electron transport system.[23] Inhibition of complex I may slow the transfer of reducing equivalents from the tricarboxylic acid cycle and potentially limit the capacity for oxidative metabolism. If the inhibition of complex I exceeds that extra capacity, this would lead to a lowering of maximal cardiorespiratory capacity but not at submaximal workloads, which has indeed been shown in a study of metformin in healthy individuals.[24]

What are the possible explanations for our findings of metformin's impact on VE/VCO_2 and functional capacity? One possible explanation might be the weight loss of 1.9 kg associated with metformin therapy. Both diet- and drug-induced weight loss have been shown to improve functional status in CHF patients.[25] However, in our study, weight reduction did not correlate with the reduction in the VE/VCO_2 slope. Another consideration is that the insulin-sensitizing properties of metformin might confer some beneficial effects on exercise capacity. IR has been associated with decreased exercise capacity in CHF[2,3] and in other chronic disease states.[26] Improving insulin sensitivity has been shown to improve exercise capacity in diabetic individuals.[27] In our study, the improvement in FIRI with metformin correlated with the improvement in VE/VCO_2, which may support the notion that improving insulin sensitivity may improve exercise capacity in patients with CHF, although the precise mechanism(s) for this cannot be determined from this study.

In CHF, IR has been associated with disturbed regulation of adipokines. Leptin, the product of the *ob* gene, can modulate insulin sensitivity[28] and has been shown to be an independent predictor of IR in CHF.[29] This hyperleptinaemia could potentially be implicated in exercise intolerance in CHF as leptin has been shown to have a dose-dependent inhibitory effect on insulin-mediated glucose metabolism of the skeletal muscle.[30] In our study, metformin treatment resulted in a decrease in serum leptin, an effect that has previously been reported with metformin[31] and might be due to a direct effect of metformin on leptin secretion.[32] Besides leptin, adiponectin levels have been reported to be elevated in CHF and associated with poor survival.[33,34] However, adiponectin is associated with improved insulin actions and cardioprotective effects,[35] and it has been suggested that this paradox probably reflects adiponectin resistance in CHF.[36] In our study, metformin had no effect on adiponectin, which is consistent with previous studies of metformin in diabetic individuals.[37] Resistin, a proinflammatory adipokine, is also elevated in CHF[38] and is a potential mediator of IR.[39] Although metformin had previously been reported to decrease resistin levels in diabetic and IR individuals,[40] resistin levels were not altered by metformin in our study.

Another consideration is metformin's ability to activate AMPK, which is expressed in various tissues including the skeletal muscle, myocardium, and the vascular endothelium.[1] In animal models of CHF, metformin has been shown to activate AMPK and improve left ventricular function, and to attenuate oxidative stress-induced cardiomyocyte apoptosis, resulting in improved survival.[19] However, we did not observe an effect of metformin on echo-derived LVEF or CO at rest and during peak exercise. With respect to peripherally mediated mechanisms, an effect of metformin on exercising skeletal muscles could account for the improvement in the VE/VCO_2 slope. Alterations in skeletal muscle energy metabolism have been linked to exercise intolerance in patients with CHF,[41] and therefore a study of the effect of metformin on skeletal muscle enzyme activities in our subjects would be of interest. In our original proposal, we had planned to do this but this invasive procedure was offered as an option and no patient consented to the procedure. We did not see an effect of metformin on endothelial function when assessed by both FMD and RH-PAT, thus providing endothelial function measures in two different vascular beds. Although, metformin had previously been reported to improve endothelial function in some patient groups with glucose abnormalities,[42,43] it is not a consistent finding.[44] To the best of our knowledge, an effect of metformin on endothelial function in patients with CHF has not been studied. Obviously any evidence that metformin improves exercise capacity through central cardiac or peripheral mechanisms in patients with CHF must remain speculative and cannot be inferred directly from this study.

Limitations of the study

There are several limitations of our study. First, in order to comply with our strict inclusion criteria, patients had to be able to perform repeated CPET. These strict inclusion criteria might have resulted in us recruiting a cohort of patients with milder CHF as our patients had a higher peak VO_2 (19 mL/kg/min) than the peak VO_2 (11 mL/kg/min) on which we based our power calculations. Consequently, our study may have been underpowered to observe an effect on peak VO_2. Secondly, although the VE/VCO_2 slope was used as a measure of the ventilation–CO_2 relationship in our patients, there are other measures such as the instantaneous ratio of ventilation to carbon dioxide or the ventilatory equivalent for CO_2 ($VEqCO_2$) which has recently been shown to have prognostic value that was not determined in our study.[45] Thirdly, there were some baseline differences between the treatment groups. Patients in the placebo group were somewhat older, had CHF that was more likely to be ischaemic in aetiology, and had a lower FMD, although these differences were not statistically significant. Additionally, patients in the metformin group had higher baseline levels of serum glucose and total cholesterol. These baseline differences may limit some of the conclusions drawn from our study.

Conclusion

This proof of concept study has shown that in non-diabetic CHF patients identified to have IR, treatment with metformin significantly improved IR and VE/VCO_2 slope, and resulted in significant weight loss, but did not improve peak VO_2, the primary endpoint of the study. Although the improvement of VE/VCO_2 slope was correlated with the improvement of IR, we were not able to ascertain if this was the cause of improvement of submaximal exercise performance owing to the complexity of action of metformin. Our findings are, however, hypothesis generating, and further studies are clearly required to determine the effects of metformin on exercise performance in patients with CHF identified to have IR.

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