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RESEARCH ARTICLE

A randomised, double-blind, placebo-controlled trial of metformin on myocardial efficiency in insulin-resistant chronic heart failure patients without diabetes

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Aims The present study tested the hypothesis that metformin treatment may increase myocardial efficiency (stroke work/myocardial oxygen consumption) in insulin-resistant patients with heart failure and reduced ejection fraction (HFrEF) without diabetes.

Methods and results Thirty-six HFrEF patients (ejection fraction 37 ± 8%; median age 66 years) were randomised to metformin ($n = 19$) or placebo ($n = 17$) for 3 months in addition to standard heart failure therapy. The primary endpoint was change in myocardial efficiency expressed as the work metabolic index (WMI), assessed by ^{11}C-acetate positron emission tomography and transthoracic echocardiography. Compared with placebo, metformin treatment (1450 ± 550 mg/day) increased WMI [absolute mean difference, 1.0 mmHg·mL·m^{-2}·10^6; 95% confidence interval (CI) 0.1 to 1.8; $P = 0.03$], equivalent to a 20% relative efficiency increase. Patients with above-median plasma metformin levels displayed greater WMI increase (25% vs. −4%; $P = 0.02$). Metformin reduced myocardial oxygen consumption (−1.6 mL O_2·100 g^{-1}·min^{-1}; $P = 0.014$). Cardiac stroke work was preserved (−2 J; 95% CI −11 to 7; $P = 0.69$). Metformin reduced body weight (−2.2 kg; 95% CI −3.6 to −0.8; $P = 0.003$) and glycated haemoglobin levels (−0.2%; 95% CI −0.3 to 0.0; $P = 0.02$). Changes in resting and exercise ejection fraction, global longitudinal strain, and exercise capacity did not differ between groups.

Conclusion Metformin treatment in non-diabetic HFrEF patients improved myocardial efficiency by reducing myocardial oxygen consumption. Measurement of circulating metformin levels differentiated responders from non-responders. These energy-sparing effects of metformin encourage further large-scale investigations in heart failure patients without diabetes.

Keywords Metformin • Heart failure • Myocardial efficiency • Myocardial oxygen consumption • Insulin resistance • Mitochondrial function

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Introduction

Insulin resistance, diabetes, abnormal whole-body and myocardial metabolism combined with mitochondrial dysfunction are characteristic features in patients with heart failure (HF).[1,2] These metabolic alterations contribute to disease progression and they are associated with a poor prognosis[2,3] and therefore constitute a potential target for metabolic therapy in HF.

Metformin is currently the preferred oral antihyperglycaemic agent in type 2 diabetes mellitus (T2DM), based on a purportedly favourable profile on cardiovascular morbidity and mortality.[4] These cardioprotective effects appear independent of glycaemic control, suggestive of pleiotropic effects of metformin.[4,5] In patients with T2DM, observational studies suggest that metformin use is associated with a lower risk of new-onset HF.[6] In T2DM patients with pre-existing HF, metformin treatment predicts reduced mortality and hospitalisation.[6,7] However, randomised data of metformin in chronic HF patients are scarce,[8] likely due to previous concerns about lactic acidosis and only recent approval of its use in HF by the US Food and Drug Administration.[9] Experimental non-diabetic HF models have demonstrated beneficial effects of metformin on cardiac mechanical function, i.e. increased contractile reserve[10,11] and attenuated remodelling,[11–13] and on cardiac metabolism, i.e. reduced insulin resistance.[13] Metformin has recently been shown to exert a direct effect on myocardial mitochondrial enzymatic activity in rodents[14,15] and may improve mitochondrial respiration and energy synthesis in HF.[11]

We hypothesised that in chronic HF patients without diabetes metformin treatment would have beneficial effects on myocardial efficiency, myocardial mitochondrial function and cardiac function. In a double-blind randomised design, we studied the effects of metformin vs. placebo treatment on myocardial efficiency and myocardial oxygen consumption (MVO_2) (i.e. mitochondrial function) as determined by ^{11}C-acetate positron emission tomography (PET) and transthoracic echocardiography. Myocardial efficiency is a powerful prognostic marker in HF[16] that measures the coupling between myocardial energy consumption and function.[17] In addition, we studied the treatment effects of metformin on cardiac function, contractile reserve, and exercise capacity.

Methods

Study design and population

This study was an investigator-initiated, randomised, double-blind, parallel-group trial comparing metformin with placebo added to standard HF therapy for 13 weeks in chronic HF patients with reduced systolic function. Treatment duration was based on previous positive outcome studies of metformin in T2DM patients.[18] The primary endpoint was change in myocardial efficiency, i.e. work metabolic index (WMI), as determined by ^{11}C-acetate PET and transthoracic echocardiography.

Major inclusion criteria were: age >18 years, HF with left ventricular ejection fraction (LVEF) $<45\%$ as determined by two-dimensional echocardiography, insulin resistance defined as glycated haemoglobin (HbA1c) 5.5–6.4%, estimated glomerular filtration rate >30 mL/min/1.73 m^2, and New York Heart Association functional class II–IV. Patients were required to receive maximally tolerated pharmacological HF treatment according to guidelines[19] without changes within the last 3 months. Both ischaemic and non-ischaemic HF patients were included in order to reflect a typical HF population.

Eligible patients were identified by consecutive review of patient lists from the outpatient clinic, Department of Cardiology, Aarhus University Hospital, Denmark, during the period from January 2017 to February 2018. Patients were included after providing informed, written consent according to the principles of the Helsinki Declaration. A total of 36 patients were randomly assigned in a 1:1 ratio to receive either extended-release metformin (Glucophage XR®) or placebo (Merck KGaA, Darmstadt, Germany). The study was conducted according to the standards in Good Clinical Practice. Approvals were obtained from the local scientific ethics committee in the Central Denmark Region, from the Danish Data Protection Agency, and from the Danish Medicines Agency. The trial is registered at ClinicalTrials.gov, NCT02810132. The authors have full access to all the data in the study and take responsibility for its integrity and the data analysis. The data that provide the basis for the findings of the study are available from the corresponding author upon reasonable request.

Study procedures

At baseline and follow-up, all patients were evaluated using ^{11}C-acetate PET followed or preceded by a visit consisting of transthoracic echocardiography at rest and peak exercise, cardiopulmonary exercise testing, 6-min walk test, and body composition assessment within a median period of 3 days (interquartile range 1–6 days) from the PET examination. The procedures were performed in the fasting state in similar sequence and at the same time of day at baseline and follow-up.

^{11}C-acetate positron emission tomography

PET was performed as previously described[20] in all patients to evaluate MVO_2 and blood flow by obtaining quantitative measures of ^{11}C-acetate uptake and clearance rates. We used a Siemens Biograph TruePoint TrueV 64 PET/CT (Siemens Healthcare, Erlangen, Germany), and dynamic data were analysed by single-tissue compartment modelling using the aQuant software package[21] (online supplementary *Methods S1*).

Transthoracic echocardiography and cardiopulmonary exercise testing

Echocardiographic examinations were performed in all patients at rest according to previously described methods[22] and current guidelines.[23] Exercise echocardiography was performed during simultaneous cardiopulmonary exercise testing[22] (online supplementary *Methods S1*).

Myocardial efficiency

The primary endpoint was between-group change in myocardial efficiency, expressed as WMI. WMI was quantified in a dual-imaging approach using ^{11}C-acetate PET and echocardiography, according to the following equation[17,24]:

$$WMI = \frac{SBP \cdot SVI \cdot HR}{k_{mono}} (mmHg \cdot mL \cdot m^{-2})$$

where SBP is systolic blood pressure (mmHg), SVI is echocardiography-derived stroke volume index ($mL \cdot m^{-2}$), HR is heart rate (min^{-1}), and k_{mono} is ^{11}C-acetate clearance rate (min^{-1}). SBP and HR were measured during the echocardiographic assessment.

Myocardial efficiency was also quantified in a single-imaging approach, expressed as myocardial external efficiency (MEE), using ^{11}C-acetate PET and calculated according to[17,21]:

$$MEE = \frac{MAP \cdot SV \cdot HR \cdot 1.33 \cdot 10^{-4}}{MVO_2 \cdot LVM \cdot 20}(\%)$$

where MAP is mean arterial pressure (mmHg), SV is PET-derived stroke volume (mL), HR is heart rate (min^{-1}), MVO_2 is myocardial oxygen consumption (mL $O_2 \cdot g^{-1}$) derived from k_2,[25] and LVM is left ventricular mass (g). The conversion factors to joules are as previously described.[17,21] MEE has demonstrated higher reproducibility than WMI[26] and accounts for potential changes in LVM, therefore chosen as a secondary endpoint because the technique was developed and validated after study protocol preparation.[21,26]

Hand grip strength, body composition and quality of life

Muscle strength was assessed using a hand dynamometer (Jamar Hand Hydraulic Dynamometer 5030J1, Patterson Medical, Bolingbrook, IL, USA) as the average of three repeated measurements on each hand. Body composition was evaluated using bioelectrical impedance analysis (Tanita BC418MA, Tokyo, Japan) at an exact time of the day. We used the Minnesota Living with Heart Failure Questionnaire for quality-of-life evaluation.

Determination of metformin concentrations in plasma and DNA genotyping

Metformin concentration was quantitated in plasma samples collected at follow-up, 4 h post-intake. The analysis was performed by use of liquid chromatography and tandem mass spectrometry according to a validated method previously published.[27] Genotyping was performed as previously published[28] (online supplementary *Methods S1*).

Sample size and statistics

The sample size calculation was based on the primary endpoint, i.e. between-group change from baseline in WMI. Assuming a standard deviation of 0.55 $mL \cdot mmHg \cdot m^{-2} \cdot 10^6$ derived from previous repeatability data from our group,[26] a total of 36 patients were required to detect a relative WMI difference of 0.6 $mL \cdot mmHg \cdot m^{-2} \cdot 10^6$ between the two treatment groups (a 2-sided α of 0.05 at 80% power) while allowing for 17% dropout. Data were analysed according to the intention-to-treat principle.

Data are presented as mean ± standard deviation or median (interquartile range) as appropriate. Baseline comparison was done using unpaired Student's *t*-test, χ^2 test, or Fisher's exact test. Within-group comparisons of change from baseline were done using paired *t*-test or Wilcoxon signed-rank test. Between-group comparisons of change from baseline were done using unpaired *t*-test or Mann–Whitney test. Linear regression models were used to analyse relationships between treatment and outcome, adjusted for baseline values. Post-hoc analysis of plasma metformin concentration data was performed by two-way repeated measures analysis of variance with group (below-median vs. above-median) and visit and the interaction between them as factors. A two-tailed *P*-value < 0.05 was considered statistically significant. We used a standard statistical software package (STATA/IC 14.1, StataCorp. LP, College Station, TX, USA).

Results

Study population

Of the 54 screened subjects, 36 subjects were randomly assigned to metformin or placebo (*Figure 1*). The unequal treatment assignment (19 vs. 17 patients) was due to a pre-established computer-generated sequence equally balanced at 40 patients to account for dropouts. In each study arm, one patient discontinued treatment due to non-treatment-related adverse events, but all patients completed follow-up examinations, and no drop-in use of metformin occurred. Patients were treated for 93 ± 13 days without group differences in treatment duration ($P = 0.52$). Compliance rates, defined as the proportion of tablets ingested, based on pill counts, relative to the intended number, were 102 ± 6% and 96 ± 10% in the metformin and placebo group, respectively. The stable treatment dose for the metformin group was 1447 ± 550 mg; in the placebo group it was 1765 ± 562 mg ($P = 0.10$).

The clinical characteristics of the patients at baseline are presented in *Table 1*. Baseline medication remained unaltered in all patients throughout the study period. Baseline characteristics did not differ significantly between groups, apart from higher age in the metformin group. Patients with coronary artery disease (CAD) had lower global and anterior wall myocardial blood flow at baseline than non-CAD patients (online supplementary *Table S1*).

Myocardial energetics

Baseline WMI was similar between groups. Metformin treatment significantly increased WMI (change from baseline, metformin: 0.6 ± 1.4 $mmHg \cdot mL \cdot m^{-2} \cdot 10^6$ vs. placebo: −0.4 ± 1.1 $mmHg \cdot mL \cdot m^{-2} \cdot 10^6$) with an absolute mean difference of 1.0 (95% confidence interval 0.1, 1.8; $P = 0.028$), equivalent to a 20% relative efficiency increase (*Table 2*; *Figure 2*). MEE also increased significantly with metformin (metformin: 1.5 ± 2.8% vs. placebo: −1.5 ± 5.6%; $P = 0.037$). Metformin significantly reduced MVO_2 (metformin: −0.76 ± 1.2 mL $O_2 \cdot 100\,g^{-1} \cdot min^{-1}$ vs. placebo: 0.84 ± 2.2 mL $O_2 \cdot 100\,g^{-1} \cdot min^{-1}$; $P = 0.014$), corresponding to a 17% relative decrease with metformin. Stroke work remained unaltered (metformin: 0.6 ± 14 J vs. placebo: 2.3 ± 13 J; $P = 0.69$) (online supplementary *Figure S1*). Between-group differences in WMI and MVO_2 change from baseline remained significant after baseline value adjustment. In addition, between-group changes in WMI and MVO_2 remained significant after individual adjustment for CAD status, baseline myocardial blood flow, baseline LVEF, or baseline end-diastolic volume index.

Haemodynamic and echocardiographic parameters

Within- and between-group changes in echocardiographic findings at rest and during exercise are presented in *Table 2*. Blood pressure

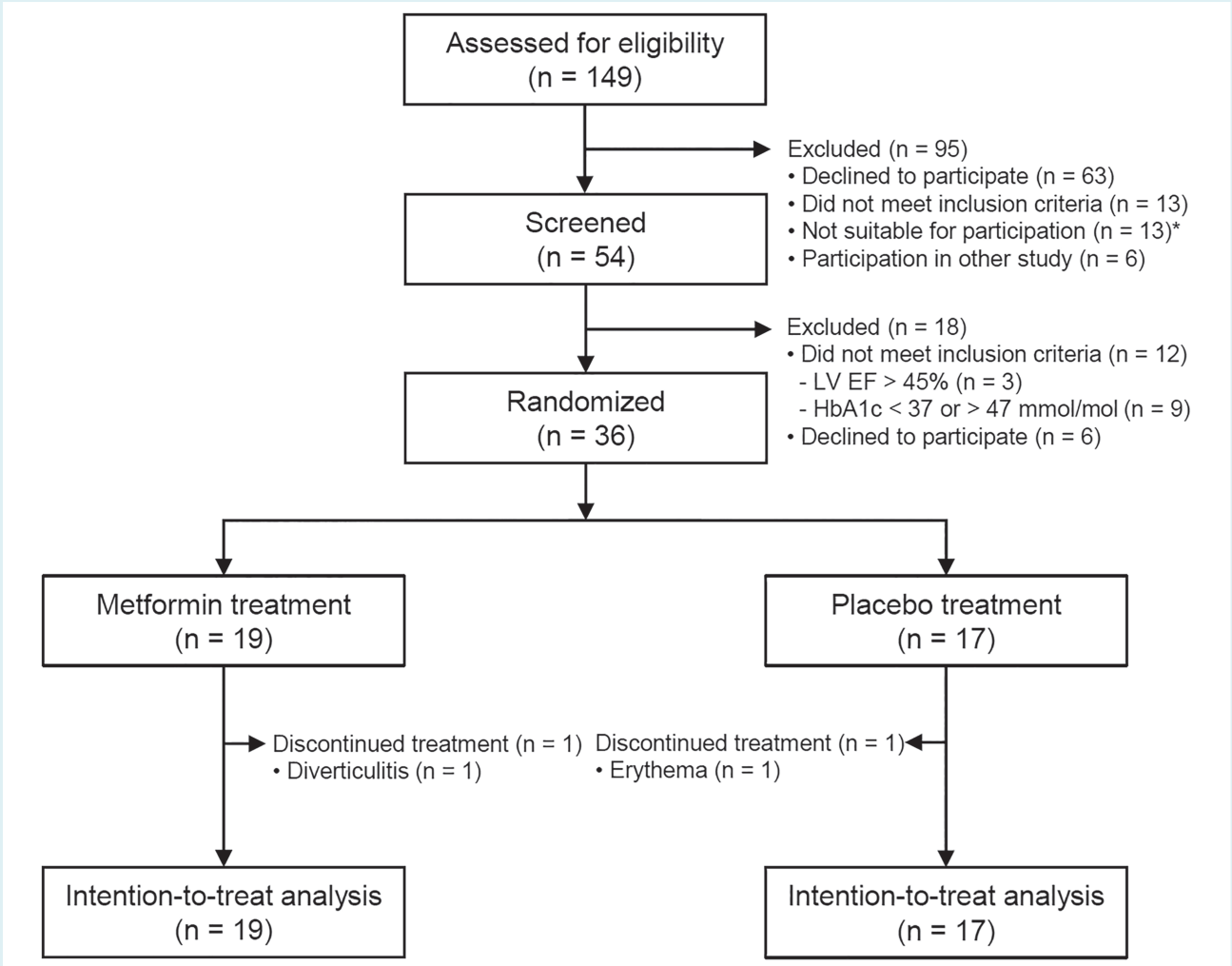

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. HbA1c, glycated haemoglobin; LV EF, left ventricular ejection fraction. *Not able to perform cardiopulmonary exercise testing due to musculoskeletal-related causes ($n = 7$) or co-morbid malignancy ($n = 6$).

and HR measured during PET and echocardiographic assessments were similar. The changes from baseline in resting systolic and diastolic blood pressure, HR, and cardiac index did not differ between treatment groups (*Table 3*). Equally, changes from baseline in LVEF and left ventricular global longitudinal strain (GLS) did not differ significantly between metformin and placebo treatment, either during rest or exercise (online supplementary *Figure S2*). No differences in LVM and diastolic indices containing measures of left ventricular end-diastolic filling pressure, i.e. E/e' and left atrial volume, were observed between treatment groups.

Metabolic effects

Metformin lowered HbA1c (metformin: $-0.1 \pm 0.2\%$ vs. placebo: $0.1 \pm 0.2\%$; $P = 0.02$) (online supplementary *Figure S2*). The reduction in HbA1c levels and baseline HbA1c levels did not correlate with changes in MVO_2 and WMI. Metformin treatment had no impact on the HOMA-IR index ($P = 0.24$), fasting glucose ($P = 0.48$), or insulin levels ($P = 0.19$). We observed a significant weight reduction with metformin treatment (metformin: -1.9 ± 2.0 kg vs. placebo: 0.3 ± 2.1 kg; $P = 0.003$), with an equal reduction in fat mass and fat-free mass (*Table 3*). No correlation between weight reduction and changes in WMI or MVO_2 was observed in the metformin group. We observed a trend towards decreased whole-body basal metabolic rate with metformin treatment ($P = 0.06$). Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were unchanged with metformin treatment.

Venous blood metabolites and N-terminal prohormone of brain natriuretic peptide

We observed no difference in changes in circulating levels of lactate, free fatty acids, 3-hydroxybutyrate, and N-terminal prohormone

Table 1 Baseline clinical characteristics by treatment group

	Metformin ($n = 19$)	Placebo ($n = 17$)
General		
Female sex	2 (11)	5 (29)
Age (years)	68 [62–73]	61 [54–66]
BMI (kg/m^2)	28.8 ± 4.6	28.1 ± 6.7
NYHA functional class		
II	16 (84)	13 (76)
III	3 (16)	4 (24)
LVEF (%)	36 ± 9	39 ± 6
SBP (mmHg)	121 ± 15	114 ± 15
DBP (mmHg)	73 ± 10	73 ± 10
HR (bpm)	66 ± 11	64 ± 9
NT-proBNP (mmol·L^{-1})	353 [222–896]	364 [94–744]
HbA1c (%)	5.8 ± 0.3	5.6 ± 0.2
Clinical history		
CAD	12 (63)	8 (47)
CRT	8 (42)	6 (35)
Medication		
ACEI or ARB[a]	18 (95)	17 (100)
Beta-blocker	19 (100)	16 (94)
MRA	14 (74)	11 (65)
Diuretic	11 (58)	7 (41)

Data are presented as *n* (%), or mean ± standard deviation, or median [interquartile range].
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]None of the patients was eligible for neprilysin inhibitors at inclusion.

of brain natriuretic peptide between groups, and circulating catecholamine levels were unaltered (*Table 3*).

Plasma metformin levels

In the metformin-treated patients, median plasma metformin concentration at follow-up was 1268 ng·mL^{-1} (interquartile range 803–2002 ng·mL^{-1}). WMI at follow-up correlated with plasma metformin levels ($r = 0.59$; $P = 0.01$), which remained significant after weight loss adjustment. We observed a greater efficiency increase in patients with above-median plasma metformin concentrations (above-median: 1.3 ± 1.4 mmHg·mL·m^{-2}·10^6 vs. below-median: -0.2 ± 0.9 mmHg·mL·m^{-2}·10^6; interaction: $P = 0.02$, group: $P = 0.02$, time: $P = 0.06$), corresponding to a 25% vs. −4% relative change in WMI (*Figure 3*). No correlation between plasma metformin levels and weight loss, HbA1c decrease, change in insulin, glucose, free fatty acids levels, or HOMA-IR index was detected.

All investigated single nucleotide polymorphisms were in Hardy–Weinberg equilibrium. The genotype distribution is presented in online supplementary *Table S2*. When categorised as diplotypes (none, one, or two variant alleles), a trend towards reduced MEE response with increased number of *MATE1* variants was found ($P = 0.06$), whereas no impact of *OCT1*, *OCT2*, or *MATE2-K* variant diplotypes was detected (online supplementary *Figure S3*).

Functional parameters

We observed no significant between-group changes from baseline in 6-min walking distance, quality of life, hand grip strength, peak systolic blood pressure, peak HR, exercise capacity expressed as metabolic equivalent of task, respiratory exchange rate, or peak exercise oxygen uptake.

Safety

In the metformin group, two serious cardiac events were observed; one patient with an implantable cardioverter-defibrillator experienced a 30 min episode of ventricular tachycardia, and one patient had an episode of orthostatic hypotension. In the placebo group, one patient developed asymptomatic atrial flutter. There were 12 episodes of gastrointestinal side effects in the metformin group and nine in the placebo group, thus no un-blinding side effects. In both groups, these episodes typically occurred during study drug initiation or up-titration, but ceased after few days or after dose reduction.

Discussion

The present study investigated the effects of 3 months of metformin vs. placebo therapy on myocardial efficiency and MVO_2 in symptomatic HF patients with reduced LVEF and without T2DM. The main findings of the present randomised, double-blind study are: (i) addition of metformin to optimal medical HF treatment improved myocardial efficiency; (ii) metformin treatment reduced MVO_2 while preserving stroke work; (iii) metformin lowered HbA1c levels and induced a significant weight reduction; and (iv) patients with above-median plasma metformin levels displayed greater WMI increase.

Metformin effects on myocardial oxygen consumption and myocardial efficiency

Heart failure metabolism is characterised by mitochondrial dysfunction[2] and reduced ability of the myocardium to convert metabolic energy into mechanical work, i.e. reduced myocardial efficiency.[17] Accordingly, our study population displayed reduced myocardial efficiency at baseline, which is consistent with previous findings in HF patients.[29] MVO_2 was also comparable with previously published levels.[30]

We demonstrated a significant energy-sparing effect of metformin that reduced MVO_2 by 17% and induced a 20% relative increase in myocardial efficiency as compared with placebo treatment. This effect was achieved in addition to beta-blocker therapy, which has been shown to increase efficiency by 39% and reduce

Table 2 Cardiac energetics and echocardiographic data by treatment group

	Metformin (n = 19)		Placebo (n = 17)			
	Baseline	Follow-up	Baseline	Follow-up	Treatment effect	P-value
Echocardiography						
Rest						
LVEF (%)	36 ± 9	37 ± 10	39 ± 6	38 ± 11	1.0 (−4.3, 6.3)	0.72
LV GLS (%)	11.7 ± 3.6	12.1 ± 3.6	12.5 ± 3.3	12.1 ± 4.1	0.5 (−1.0, 1.9)	0.50
EDVi (mL·m^{-2})	81 [72–98]	75 [64–103]	83 [70–93]	74 [67–96]	0.2(−10.8,11.1)	0.98
E/e′	12 [11–14]	11 [9–14]	11 [9–14]	11 [9–15]	1 (−2, 5)	0.51
LVOT-CI (L·min^{-1}·m^{-2})	2.3 ± 0.6	2.4 ± 0.6	2.2 ± 0.7	2.3 ± 0.5	0.1 (−0.2, 0.3)	0.60
Stress						
LVEF max (%)	39 ± 11	39 ± 11	41 ± 11	41 ± 11	0.1 (−5.0, 5.2)	0.97
LV GLS max (%)	12.9 ± 4.4	13.0 ± 4.2	13.5 ± 4.8	13.8 ± 5.2	−0.1 (−1.6, 1.4)	0.88
LVOT-CI max (L·min^{-1}·m^{-2})	4.7 ± 1.3	4.7 ± 1.3	4.6 ± 1.4	5.2 ± 1.4	−0.6 (−1.3, 0.1)	0.09
^{11}C-acetate PET						
WMI (mL·mmHg·m^{-2}·10^{6})	4.8 ± 1.3	5.4 ± 1.8	4.9 ± 1.5	4.5 ± 1.2	1.0 (0.1, 1.8)	0.028*
MEE (%)	16.9 ± 5.4	18.4 ± 4.6**	21.5 ± 7.7	20.0 ± 7.4	3.0 (0.0, 5.9)	0.037*
k mono (min^{-1}·10^{-2})	5.7 [4.9–6.4]	5.4 [4.5–5.9]	5.3 [4.6–5.8]	5.9 [5.4–6.2]	−1.1 (−2.1, −0.2)	0.016*
MVO_2 (mL O_2·100g^{-1}·min^{-1})	8.1 [7.4–10.3]	7.5 [6.9–9.4]**	7.6 [6.6–9.9]	8.5 [7.9–10.0]	−1.6 (−2.8, −0.4)	0.014*
Stroke work (J)	58 ± 17	58 ± 17	60 ± 22	62 ± 19	−2 (−11, 7)	0.69
MBF (mL·min^{-1}·g^{-1})	0.6 [0.5–0.7]	0.5 [0.5–0.7]	0.5 [0.5–0.6]	0.5 [0.4–0.6]	0.0 (−0.4, 0.1)	0.51
LV mass index (g·m^{-2})	98 ± 25	97 ± 22	92 ± 25	94 ± 29	−4 (−10, 2)	0.24
CI (L·min^{-1}·m^{-2})	2.4 ± 0.6	2.5 ± 0.5	2.5 ± 0.5	2.4 ± 0.4	0.1 (−0.2, 0.4)	0.45

Data are presented as mean ± standard deviation, or median [interquartile range]. Treatment effect (between-group change from baseline) are presented as mean difference (95% confidence intervals).
CI, cardiac index; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MBF, myocardial blood flow; MEE, myocardial external efficiency; MVO_2, myocardial oxygen consumption; WMI, work metabolic index; PET, positron emission tomography.
*$P < 0.05$, between-group unpaired t-test.
**$P < 0.05$, within-group paired t-test.

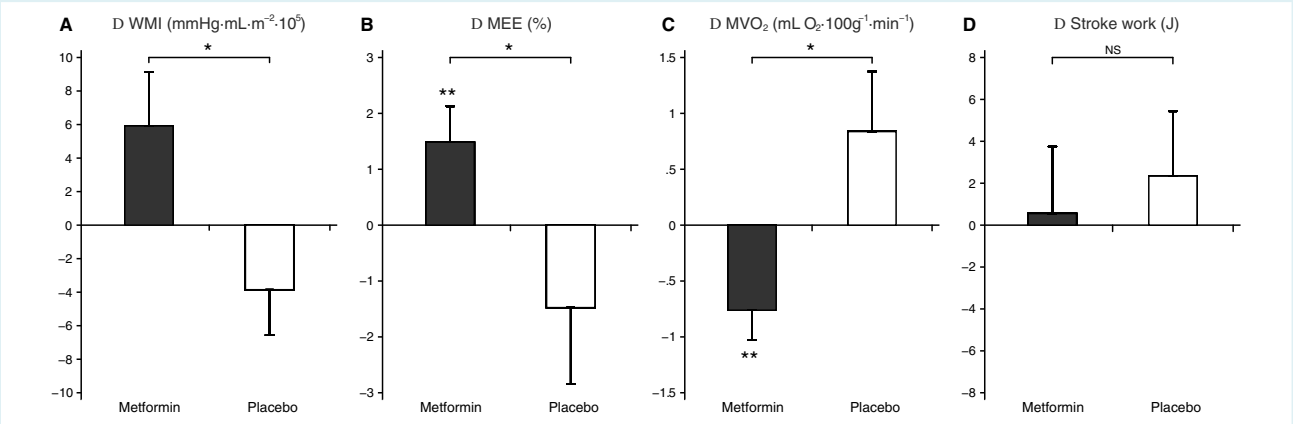

Figure 2 Absolute change from baseline to follow-up with standard error of means in (*A*) work metabolic index (WMI), (*B*) myocardial external efficiency (MEE), (*C*) myocardial oxygen consumption (MVO_2), and (*D*) positron emission tomography-derived stroke work between metformin and placebo treatment. *$P < 0.05$, between-group unpaired t-test; **$P < 0.05$, within-group paired t-test.

MVO_2 by 24%,[29] as well as to cardiac resynchronisation therapy that increased efficiency by 13% with unaltered MVO_2 in a small study.[30] Myocardial efficiency has demonstrated prognostic value as a predictor of mortality in an invasive HF study,[16] likely because it accounts for both myocardial work and its metabolic cost. Equally, energy-sparing treatments for HF, such as beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers have been shown to improve prognosis. Therefore, our findings demonstrate favourable effects of metformin on cardiac energetic endpoints important to prognosis.

Table 3 Physical capacity, body composition and blood samples by treatment group

	Metformin (n = 19)		Placebo (n = 17)			
	Baseline	Follow-up	Baseline	Follow-up	Treatment effect	P-value
CPX						
SBP (mmHg)	121 ± 15	118 ± 19	114 ± 15	114 ± 15	−3 (−11, 4)	0.37
DBP (mmHg)	73 ± 10	71 ± 10	73 ± 10	73 ± 13	−3 (−9, 3)	0.33
HR (bpm)	66 ± 11	65 ± 9	64 ± 9	65 ± 8	−3 (−8,2)	0.24
RER	1.04 ± 0.02	1.06 ± 0.02	1.04 ± 0.02	1.04 ± 0.02	0.01 (−0.02, 0.05)	0.42
VO_2 max (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)	17.0 ± 3.9	17.3 ± 4.0	19.0 ± 5.7	18.9 ± 5.4	0.3 (−1.1, 1.6)	0.69
Resting VO_2 (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)	5.4 ± 1.5	4.8 ± 1.0	5.1 ± 1.4	5.5 ± 1.5	−0.8 (−1.8, 0.1)	0.09
VAT (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$)	14.7 ± 2.9	14.9 ± 3.0	15.3 ± 4.4	15.8 ± 4.3	−0.2 (−1.4, 0.9)	0.68
METs (mL·$kg^{-1} \cdot min^{-1}$)	4.9 ± 1.1	4.9 ± 1.1	5.4 ± 1.6	5.4 ± 1.6	0.1 (−0.3, 0.5)	0.69
6MWT						
Distance (m)	517 ± 93	522 ± 90	532 ± 95	546 ± 83	−9 (−33, 16)	0.48
Borg scale	14 ± 3	14 ± 2	14 ± 2	14 ± 2	−1 (−2, 1)	0.45
Quality of life	18 [8–26]	18 [10–28]	21 [10–24]	17 [10–31]	0 (−7, 8)	0.93
Hand grip strength (kg)	42 ± 8	42 ± 9	40 ± 10	40 ± 10	0.1 (−1.3, 1.6)	0.85
Bioimpedance						
Weight (kg)	90.1 ± 13.9	88.2 ± 13.6**	87.2 ± 21.1	87.5 ± 21.2	−2.2 (−3.6, −0.8)	0.003*
Waist/hip ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.0 (−0.1, 0.1)	0.56
BMR (kJ)	7.8 ± 1.2	7.7 ± 1.2	7.4 ± 1.6	7.4 ± 1.6	−0.1 (−0.3, 0.1)	0.06
Fat% (%)	29.0 ± 6.6	28.6 ± 6.2	30.4 ± 10.5	30.6 ± 10.4	−0.6 (−1.8, 0.7)	0.35
Fat mass (kg)	26.5 ± 8.0	25.5 ± 7.6	27.5 ± 13.2	27.9 ± 13.2	−1.4 (−2.8, 0.0)	0.053
FFM (kg)	64 ± 9	63 ± 9	60 ± 13	60 ± 13	−1 (−2, 0)	0.07
TBW (kg)	47 ± 7	46 ± 7	44 ± 9	44 ± 10	−1 (−2, 0)	0.08
Biochemistry						
HbA1c (%)	5.8 ± 0.3	5.7 ± 0.3	5.6 ± 0.2	5.7 ± 0.2	−0.2 (−0.3, 0.0)	0.02*
eGFR (mL·$min^{-1} \cdot 1.73\ m^{-2}$)	73 ± 23	74 ± 22	85 ± 16	86 ± 16	1 (−6, 7)	0.82
NT-proBNP (ng·L^{-1})	353 [222–896]	442 [194–1190]	364 [94–744]	357 [103–562]	316 (−61, 694)	0.24
Insulin (pmol·L^{-1})	47 [29–114]	49 [27–78]	39 [26–62]	44 [27–71]	−19 (−49, 11)	0.19
HOMA-IR index	2.8 [1.0–4.2]	2.1 [0.9–3.3]	2.1 [1.0–2.5]	2.0 [0.9–2.8]	−0.7 (−2.0, 0.5)	0.24
Glucose (mmol·L^{-1})	5.9 ± 0.7	5.8 ± 0.5	5.8 ± 0.5	5.8 ± 0.5	−0.1 (−0.5, 0.3)	0.48
FFA (mmol·L^{-1})	0.5 ± 0.2	0.5 ± 0.2	0.8 ± 0.4	0.6 ± 0.3	0.2 (0.0, 0.5)	0.11
Lactate (mmol·L^{-1})	1.3 ± 0.4	1.6 ± 0.8	1.2 ± 0.5	1.2 ± 0.3	0.3 (−0.1, 0.7)	0.12
Metanephrine (pmol·L^{-1})	33 [27–43]	33 [32–43]	25 [16–49]	37 [23–50]	−3 (−14, 9)	0.62
Normetanephrine (pmol·L^{-1})	80 [60–101]	77 [52–107]	73 [49–81]	69 [64–89]	−4 (−28, 20)	0.72

Data are presented as mean ± standard deviation, or median [interquartile range]. Treatment effect (between-group change from baseline) are presented as mean difference (95% confidence intervals).

6MWT, 6-min walk test; BMR, basal metabolic rate; CPX, cardiopulmonary exercise testing; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FFA, free fatty acids; FFM, free fat mass; HbA1c, glycated haemoglobin; HR, heart rate; HOMA-IR, homeostatic model assessment of insulin resistance; METs, metabolic equivalent; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RER, respiratory exchange rate; SBP, systolic blood pressure; TBW, total body water; VAT, ventilatory anaerobic threshold; VO_2, oxygen consumption.

*$P < 0.05$, between-group unpaired t-test.

**$P < 0.05$, within-group paired t-test.

Experimental HF models report that metformin improves myocardial cell mitochondrial respiration and ATP synthesis.[11,31] Myocardial mitochondrial activity is closely coupled to MVO_2 as 95% of cardiac cellular energy demand is covered by mitochondrial oxidative phosphorylation.[2] We measured MVO_2 using a robust and validated non-invasive technique of ^{11}C-acetate PET,[20,21,26,32] thereby translating the experimental discoveries to humans. The present study thus implies a beneficial effect of metformin on mitochondrial function in the failing heart. Possible mechanisms may comprise improved mitochondrial respiration with AMPK activation,[11] altered myocellular redox state through mitochondrial glycerol-3-phosphate dehydrogenase inhibition,[14,15] or by activation of other AMP-sensitive enzymes, as shown in liver,[33] that ultimately may lead to lessened mitochondrial uncoupling and improved ATP production.[11]

A shift in myocardial metabolic substrate uptake and metabolism could also contribute to the observed improvement in myocardial efficiency with metformin. In theory, a complete shift from pure fatty acid oxidation to pure carbohydrate oxidation results in an approximately 12% increase in ATP per unit of oxygen[17] and a similar efficiency improvement if mechanical work is unchanged. However, PET studies in T2DM patients demonstrated

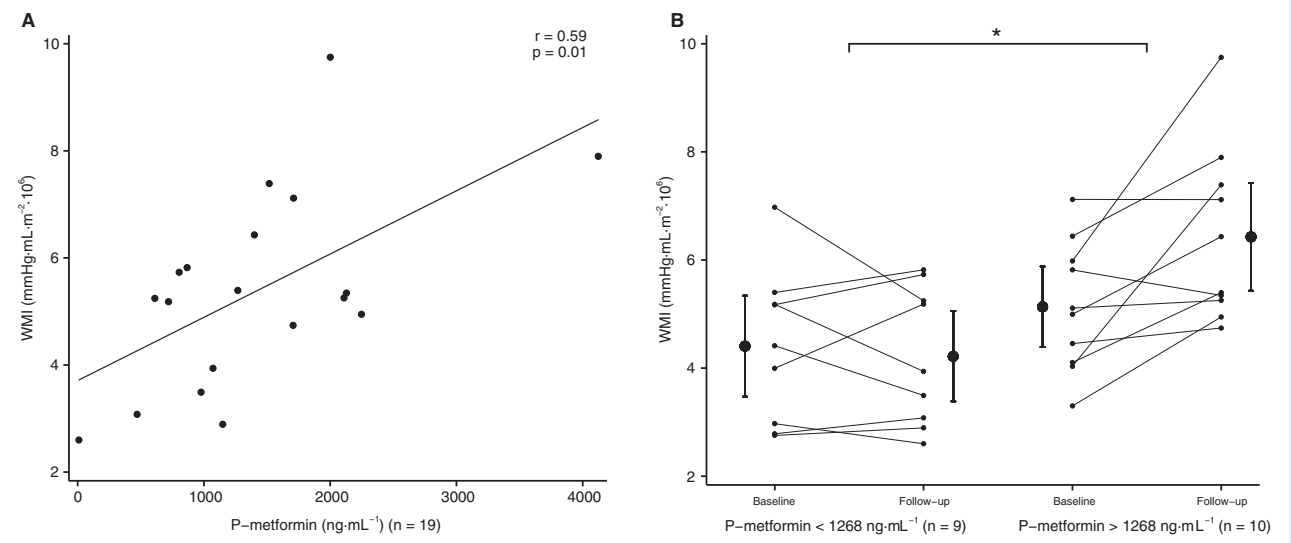

Figure 3 (*A*) Scatter plot with regression line for plasma metformin levels and work metabolic index (WMI) in metformin-treated patients at follow-up. (*B*) Individual and mean absolute WMI change in metformin-treated patients dichotomized by plasma metformin level. *$P < 0.05$, between-group unpaired *t*-test.

unchanged or slightly reduced fatty acid and glucose utilisation with metformin treatment.[34] Furthermore, metformin treatment did not change the circulating levels of myocardial energy substrates or the whole-body respiratory exchange rate. Overall, a metformin-induced shift in substrate oxidation seems unlikely to explain the 20% relative increase in myocardial efficiency.

Left ventricular function and metformin treatment

Several experimental studies have reported beneficial effects of metformin on left ventricular function and cardiac output.[10,11,13] A recent randomised study in non-diabetic non-HF patients reported that metformin induces regression of left ventricular hypertrophy.[5] Yet the present study is only the second clinical randomised trial investigating the effects of metformin on left ventricular function in HF patients. Wong *et al.*[8] found no significant change in LVEF with metformin treatment in 62 non-diabetic HF patients with an average LVEF of 33%. A larger randomised study in 380 non-diabetic acute myocardial infarction patients with a mean LVEF of 54% showed no effect on LVEF of 1 g metformin vs. placebo per day.[35] In the present study, we conducted studies of left ventricular systolic and diastolic function both during rest and exercise stress and observed a 1% non-significant increase in resting LVEF and GLS with metformin treatment, which is consistent with the findings of Wong *et al.*[8] Notably, the power calculation for the present study was not based on changes in LVEF or GLS, and a type II error cannot be excluded. Previous studies indicate a close relationship of efficiency with systolic function as a WMI increase may lead to an LVEF increase.[30] Therefore, our findings advocate that the impact of metformin on left ventricular systolic function be further investigated.

Whole-body effects of metformin

The prognosis of HF patients worsens when insulin resistance progresses to overt T2DM.[3] Still, it remains unknown whether prophylactic treatment with metformin to counteract this process is beneficial. In the present study, metformin treatment caused a slight reduction in HbA1c levels as compared with placebo as previously found.[8] HbA1c did not correlate with changes in MVO_2 or myocardial efficiency in the present study, and we observed no effect of metformin on fasting glucose, free fatty acid, insulin levels, and insulin resistance index, i.e. HOMA-IR index. Therefore, our findings support that the beneficial effect of metformin on cardiac energetics was independent of glycaemic and metabolic control.

We observed a significant weight loss associated with metformin therapy, which is consistent with previous findings in a comparable HF population.[8] Muscle mass and fat mass were equally reduced conforming to the assumed mechanism of reduced caloric intake.[7] Clinical signs of congestion, such as lower extremity oedema and natriuretic biomarkers, and echocardiographic measures of left ventricular filling pressure were unaltered, which argues against a diuretic effect. Although unintentional weight loss predicts a poor outcome in HF, a diet- and drug-induced weight loss may, in fact, improve functional class in HF.[36]

Metformin may display blood pressure-lowering effects[5] possibly conferred through reduced systemic sympathetic activity, which may affect efficiency. We did not detect an afterload-reducing effect of metformin in our study population that already received comprehensive neurohormonal blockade therapy, and circulating catecholamine levels were unaltered.

Plasma metformin levels and efficiency increase

We measured plasma metformin levels after 3 months of therapy and observed a high inter-individual variability as previously shown.[28] In patients with above-median vs. below-median plasma metformin levels, we found a 25% increase vs. 4% decrease in WMI. Hence, metformin levels differentiated responders from non-responders, and we therefore hypothesise that this reflects a relation between cardiac exposure levels and the magnitude of pharmacodynamic response. Thus, measurements of circulating metformin levels in HF patients is a topic for future research in personalised medicine.

Genetic variation in genes encoding metformin membrane transporter proteins, i.e. *OCT* and *MATE*, may affect metformin pharmacokinetics,[28] and we therefore genotyped the study population. Despite a limited sample size, we observed a trend towards a diminished effect on efficiency with increasing number of variants in *MATE1*. Together, these observations may encourage further exploration of the impact of pharmacogenetics on metformin-induced cardiac effects to separate responders from non-responders.

Limitations

First, our sample size may have limited the ability to detect significant differences in echocardiographic parameters and exercise capacity. In addition, the study duration was limited to 3 months, which is perhaps too short a period to detect improvements in left ventricular function. Even so, the study duration was sufficient to disclose both whole-body and myocardial metabolic effects of metformin. Second, myocardial ^{11}C-acetate turnover only reflects a semiquantitative index of myocardial oxidative metabolism, and the presumed relationship between ^{11}C-clearance rate and MVO_2 is based on studies performed predominantly during normal physiological conditions.[17] We minimised the influence of these inherent limitations with a paired study design and with metabolic standardisation (i.e. fasting state) during PET examinations. Third, despite randomisation, patients in the metformin group were older, which may have affected the findings. Yet, exploratory analyses revealed no correlation between patient ages and the specified endpoints or metabolic parameters. Finally, we observed a concurrent efficiency decrease in the placebo group. However, a recent test–retest study in a comparable HF population has demonstrated similar decreases in WMI and MEE after only 47 days of follow-up.[37] It is therefore conceivable that the observed efficiency decrease is in part attributable to disease progression.

Conclusions

Metformin treatment in HF patients with reduced LVEF improved myocardial efficiency through reduced MVO_2. Metformin plasma levels may differentiate responders from non-responders. These energy-sparing effects of metformin encourage further large-scale investigations in HF patients without diabetes.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Methods S1. Supplementary methods.

Figure S1. Effect of metformin on cardiac energetics.

Figure S2. Effects of metformin on systolic function, physical capacity, and metabolic parameters.

Figure S3. The impact of variant diplotypes in genes encoding metformin transporter proteins on cardiac energetics.

Table S1. Global and regional myocardial perfusion at baseline by CAD status.

Table S2. Genotype distribution of the study population ($n = 36$).

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