



# Empagliflozin Treatment Is Associated With Improvements in Cardiac Energetics and Function and Reductions in Myocardial Cellular Volume in Patients With Type 2 Diabetes

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**Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of major adverse cardiovascular (CV) events and hospitalization for heart failure (HF) in patients with type 2 diabetes (T2D). Using CV MRI (CMR) and <sup>31</sup>P-MRS in a longitudinal cohort study, we aimed to investigate the effects of the selective SGLT2 inhibitor empagliflozin on myocardial energetics and cellular volume, function, and perfusion. Eighteen patients with T2D underwent CMR and <sup>31</sup>P-MRS scans before and after 12 weeks' empagliflozin treatment. Plasma N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP) levels were measured. Ten volunteers with normal glycemic control underwent an identical scan protocol at a single visit. Empagliflozin treatment was associated with significant improvements in phosphocreatine-to-ATP ratio (1.52 to 1.76,  $P = 0.009$ ). This was accompanied by a 7% absolute increase in the mean left ventricular ejection fraction ( $P = 0.001$ ), 3% absolute increase in the mean global longitudinal strain ( $P = 0.01$ ), 8 mL/m<sup>2</sup> absolute reduction in the mean myocardial cell volume ( $P = 0.04$ ), and 61% relative reduction in the mean NT-proBNP ( $P = 0.05$ ) from baseline measurements. No significant change in myocardial blood flow or diastolic strain was detected. Empagliflozin thus ameliorates the “cardiac energy-deficient” state, regresses adverse myocardial cellular remodeling, and improves cardiac function,**

**offering therapeutic opportunities to prevent or modulate HF in T2D.**

Cardiovascular (CV) disease is the leading cause of morbidity and mortality in patients with type 2 diabetes (T2D) (1). Heart failure (HF) is the most common initial presentation of CV disease in T2D (2). Sodium–glucose cotransporter 2 (SGLT2) inhibitors are associated with a lower risk of HF hospitalization in T2D patients with or at high risk of CV disease (3). In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, selective SGLT2 inhibitor empagliflozin reduced CV mortality and hospitalization for HF by 38% and 35%, respectively (3). Unique for an oral glucose-lowering therapy, SGLT2 inhibitors are therefore licensed for risk reduction of CV disease and mortality, in patients with T2D and established CV disease, in addition to the improvement of glycemic control (4). The reductions in CV death were not accounted for by reductions in atherothrombotic outcomes, as the rates of myocardial infarction (MI) and stroke remained unchanged with therapy. The proposed theory that HF is the outcome most sensitive to SGLT2 inhibition was then also confirmed in the canagliflozin and dapagliflozin trials (5,6).

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Abnormal cardiac energy metabolism plays an important role in the development of cardiac dysfunction in T2D (7). The heart has a high energy demand but minimal energy-storing capacity. Efficient matching of energy supply to demand is therefore essential for maintaining cardiac function. The reasons for the beneficial CV effects of SGLT2 inhibitors are not yet clear; however, restoration of the cellular energy homeostasis has been suggested as a potential mechanism (8). Cardiac  $^{31}\text{P}$ -MRS allows for the measuring of the relative concentration of phosphocreatine (PCr) to ATP in the heart, which is a marker of the myocardium's ability to convert substrate into ATP for active processes and a sensitive index of the energetic state of the myocardium (9). With use of  $^{31}\text{P}$ -MRS, significant reductions in myocardial PCr-to-ATP ratio were shown in patients with T2D previously (10).

In addition to  $^{31}\text{P}$ -MRS, CV MRI (CMR) is the only imaging modality that can noninvasively assess cardiac function, strain, ischemia, perfusion, fibrosis, and scar. With use of CMR, previous studies have identified predictors of adverse CV events in T2D patients including distinct ventricular morphology (11), impaired strain (11,12), and reduced myocardial perfusion (10). CMR is also established as a tool for quantification of diffuse fibrosis with quantification of the extracellular volume fraction (ECV) by T1 mapping (13). This technique can differentiate between cellular (myocytes, fibroblasts, and endothelial and red blood cells) and extracellular (extracellular matrix, blood plasma) compartments (13). Thus, the technique can inform on microscopic changes such as increased myocardial cell volume and extracellular matrix expansion (13). A previous study has shown increased myocardial cell volume without extracellular matrix expansion in T2D patients (14).

Consequently, in a prospective cohort study, using cardiac  $^{31}\text{P}$ -MRS and CMR, we aimed to explore the impact of empagliflozin over a 12-week treatment period on myocardial energetic status, function, strain, and perfusion and track dynamic changes in the cell and matrix compartments in T2D patients. We tested the hypotheses that the treatment with empagliflozin is associated with improvements in cardiac energetics and function, and regression of the adverse myocardial cellular remodeling, offering therapeutic opportunities to prevent or modulate HF in T2D.

## RESEARCH DESIGN AND METHODS

### Participants

This single-center, prospective, longitudinal, observational cohort study complied with the Declaration of Helsinki. It was approved by the national research ethics committee (REC reference no. 18/YH/0168), and informed written consent was obtained from each participant. Twenty-four participants with T2D were prospectively recruited from the Leeds Teaching Hospitals NHS Trust cardiometabolic optimization clinics. Ten participants without diabetes and of similar age, sex, BMI, and comorbidities of

hypertension and ischemic heart disease distribution formed a control group.

### Inclusion and Exclusion Criteria

All subjects had to have the ability to provide informed written consent. T2D was diagnosed according to the World Health Organization criteria (15). Exclusion criteria were previous antero-septal MI, cardiac surgery, angina, moderate or worse valvular heart disease, atrial fibrillation, contraindications to CMR, renal impairment (estimated glomerular filtration rate [eGFR]  $<60$  mL/min/1.73 m<sup>2</sup>), current treatment with insulin, or commencement on any new medication for diabetes control or for CV risk factor modification in the preceding 12 weeks prior to recruitment to the study. The volunteers had normal glycemic control, with glycated hemoglobin (HbA<sub>1c</sub>) values  $\leq 40$  mmol/mol.

### Study Protocol

Study assessments were carried out over two visits 12 weeks apart before and during empagliflozin treatment for T2D patients and on a single visit for the control subjects. Controls did not receive empagliflozin.

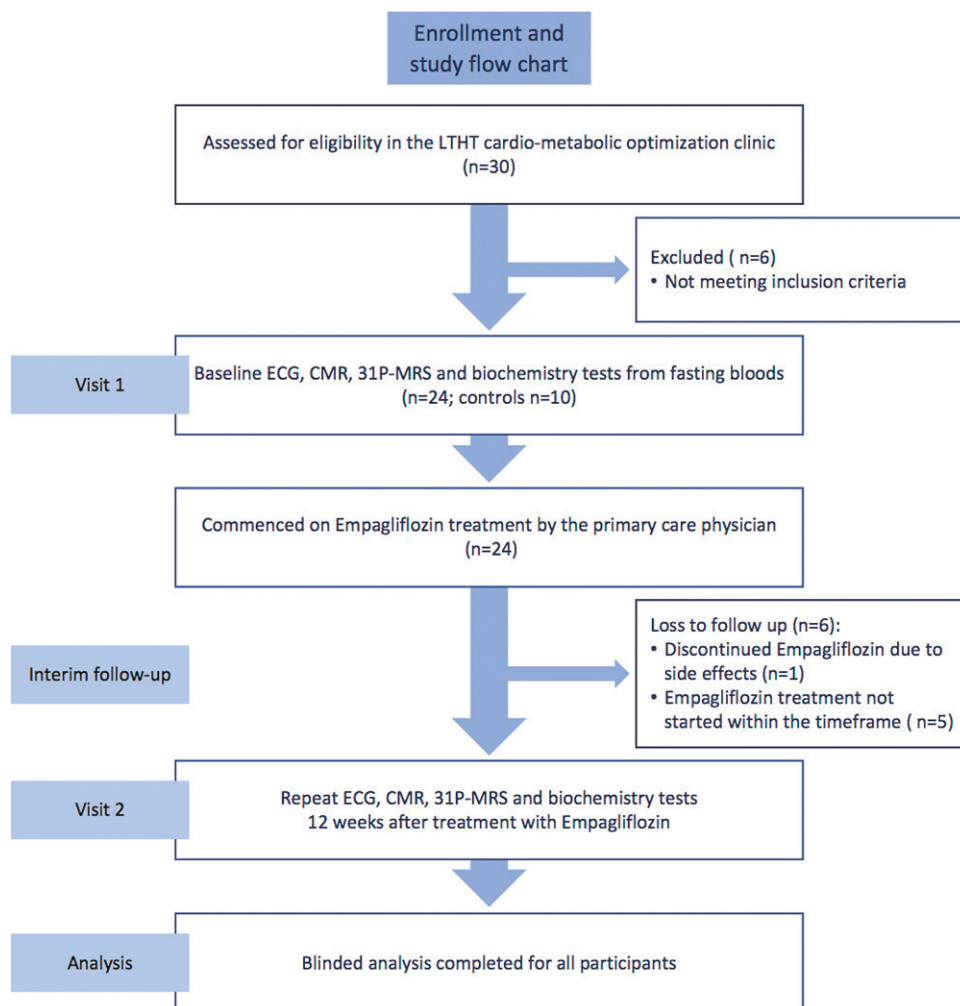
This study was conducted during the pandemic, and there was some variation among primary care physicians in how quickly they were able to respond to the recommendations of the cardiometabolic optimization clinic in commencing patients on empagliflozin with prescriptions. A strict protocol was followed for the time interval between the first scan (within 1 week of the clinic review) and the commencement of the treatment (within 2 weeks from the scan). Participants for whom the time interval between the scan and the empagliflozin treatment initiation exceeded 3 weeks were not invited for the final scan for standardization of the period between the first and the second scan. This led to exclusion of 6 participants from the initial 24 patients invited for the first scan. Study flowchart and details of all study visits with assigned investigations are provided in Fig. 1.

### Anthropometric Measurements

Height and weight were recorded, BMI was calculated, blood pressure (BP) was recorded as an average of three supine measures taken over 10 min (DINAMAP-1846-SX; Critikon Corp.), a resting electrocardiogram (ECG) was recorded on both visits prior to  $^{31}\text{P}$ -MRS and CMR scans, and resting heart rate was recorded from the ECG recordings. A fasting blood sample was taken from each participant for assessments of full blood count, eGFR, insulin, triglyceride, liver function, HbA<sub>1c</sub>, and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels on both visits.

### $^{31}\text{P}$ -MRS

All scans were performed on a 3.0 Tesla MR system (Prisma; Siemens Healthineers, Erlangen, Germany). All participants were scanned at approximately the same time of the day between their first and second scans.  $^{31}\text{P}$ -MRS was performed to obtain the rest PCr-to-ATP ratio from a



**Figure 1**—Study flowchart. Thirty prospective T2D patients who were considered for empagliflozin treatment at the cardiometabolic optimization clinic of the Leeds Teaching Hospitals NHS Trust (LTHT) were screened for the study. Twenty-four prospective patients were recruited between February 2020 and September 2020, and the final patient visit occurred in January 2021. Eighteen patients then successfully completed 12 weeks of empagliflozin treatment within the time frame and underwent a second  $^{31}\text{P}$ -MRS and CMR scan. There were no changes to any of the patients' preexisting medications throughout the study.

voxel placed in the midventricular septum, with the subjects lying supine with the  $^{31}\text{P}$  transmitter/receiver cardiac coil (RAPID Biomedical, Rimpar, Germany) placed over their heart, in the isocenter of the magnet. Coil position was standardized to be placed above the midventricular septum.  $^{31}\text{P}$ -MRS data were acquired with a nongated three-dimensional acquisition-weighted chemical shift imaging sequence (16). The acquisition matrix was  $16 \times 8 \times 8$  for the protocol. Field of view was  $240 \times 240 \times 200$  mm. The acquisition was run with a fixed repetition time of 720 ms.

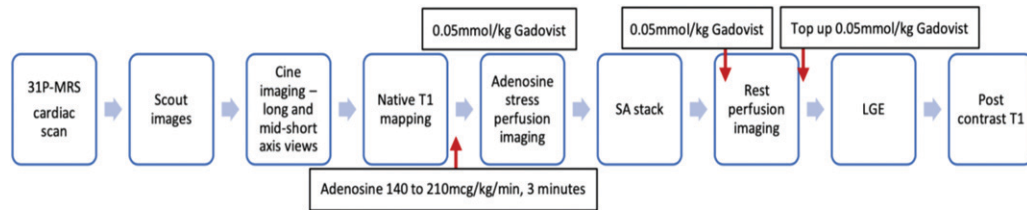
#### CMR

$^{31}\text{P}$ -MRS study was followed by CMR on the same study visit, with use of the same scanner after a coil change. Participants were advised to avoid caffeine for 24 hours before the study. Following the  $^{31}\text{P}$ -MRS, the CMR

protocol (Fig. 2) consisted of cine imaging with a steady-state free precession (SSFP) sequence, native and postcontrast T1 mapping, stress and rest perfusion, and late gadolinium enhancement (LGE).

Native T1 maps were acquired in three short-axis slices using a breath-held modified look-locker inversion recovery (MOLLI) acquisition (ECG triggered, native 5s(3s)3s scheme; postcontrast 4s(1s)3s(1s)2s scheme; single shot, parallel imaging factor 2; prepulse delay 350 ms; trigger delay set for end diastole; flip angle 20 degrees; matrix  $400 \times 400$ ; slice thickness 8 mm). Postcontrast T1 mapping acquisition was performed 15 min after last contrast injection.

Perfusion imaging used free-breathing, motion-corrected (MOCO) automated in-line perfusion mapping (17). For stress perfusion imaging, adenosine was infused at a rate of  $140 \mu\text{g}/\text{kg}/\text{min}$  and increased up to a maximum of  $210 \mu\text{g}/\text{kg}/\text{min}$  according to hemodynamic and symptomatic



**Figure 2**—Multiparametric scan protocol. Multiparametric MRI included cardiac  $^{31}\text{P}$ -MRS (20 min). This was followed by CMR, which included cine imaging to assess LV volumes, mass and ejection fraction, and strain parameters; native precontrast and postcontrast T1 mapping for measuring myocardial cellular volume and ECV; adenosine stress perfusion imaging for assessment of myocardial rest and stress blood flow and myocardial perfusion reserve; LGE imaging for assessment of myocardial scarring and infarction. Control subjects underwent identical MRI protocols at a single visit. The same scan protocol was repeated for patients with T2D after 12 weeks of empagliflozin treatment with an identical second scan protocol.

response (a significant hemodynamic response to adenosine stress was defined as  $>10$  bpm increase in heart rate or BP drop  $<10$  mmHg and more than one adenosine-related symptom, e.g., chest tightness, breathlessness) (18). A minimum 10-min interval was kept between perfusion acquisitions to ensure equilibration of gadolinium kinetics and resolution of all hemodynamic effects of adenosine. For perfusion imaging, an intravenous bolus of 0.05 mmol/kg gadobutrol (Gadovist, Leverkusen, Germany) was administered at 5 mL/s followed by a 20-mL saline flush with an automated injection pump (MEDRAD MRXperion Injection System; Bayer). Perfusion mapping was performed and implemented on the scanner with the Gadgetron streaming software image reconstruction framework as previously described (17).

LGE imaging was performed with a phase-sensitive inversion recovery sequence in matching left ventricular (LV) short-axis planes and long-axis planes  $>8$  min after contrast administration to exclude the presence of previous MI or regional fibrosis (19).

### Quantitative Analysis

All  $^{31}\text{P}$ -MRS postprocessing analysis was performed offline with blinding to all participant details including the visit number by S.T. and N.J. (both with 2 years of CMR experience) after completion of the study, and E.L. reviewed all  $^{31}\text{P}$ -MRS results. The anonymization codes were only unlocked once all data analysis was completed.  $^{31}\text{P}$ -MRS data were analyzed with software within MATLAB, version R2012a (MathWorks, Natick, MA) as previously described (20).

CMR image analysis was performed by S.T., and all scan contours were subsequently reviewed by E.L. ( $>8$  years of CMR experience; level 3 accreditation), using cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada), who was also blinded to participant details and visit number. Images for biventricular volumes and function were analyzed as previously described (21). The left atrium (LA) volume and ejection fraction were calculated with the biplane area-length method in the horizontal and vertical long axes as previously described (22). Strain

measurements were performed with cvi42 Tissue Tracking from balanced SSFP from the short-axis images and the horizontal long-axis and vertical long-axis views. The peak circumferential systolic strain and peak early longitudinal and circumferential diastolic strain rates and global longitudinal strain (GLS) were measured (11).

Myocardial perfusion image reconstruction and processing were implemented with use of the Gadgetron software framework as previously described (17). Rest/stress myocardial blood flow (MBF) was measured for each of the 16 segments with use of the American Heart Association classification. Segments with late gadolinium hyperenhancement were excluded from analysis. MBF values for all remaining segments were averaged to provide a global value. T1 maps and ECV were analyzed with cvi42 software (Circle Cardiovascular Imaging) from a region of interest in the midwall of the septum from a noninfarcted segment using the native precontrast and native postcontrast T1 times of myocardium, blood pool, and hematocrit as previously described (23).

Myocardial cell volume was calculated from T1 maps as previously described with the following calculation:  $\text{LVM}/1.05 \times [1 - \text{ECV}]$  (19).

### Statistical Analysis

Statistical analysis was performed with SPSS (IBM SPSS Statistics, version 26.0). Categorical data were compared with Pearson  $\chi^2$  test. Continuous variables are presented as mean  $\pm$  SD and were checked for normality with the Shapiro-Wilk tests. Comparisons of all  $^{31}\text{P}$ -MRS, CMR, and biochemistry data between pre- and post-empagliflozin treatment were performed with two-tailed paired  $t$  test or Mann-Whitney  $U$  test as appropriate.  $P \leq 0.05$  was considered statistically significant.

A priori sample size calculations were performed before the study to detect a biologically significant 10% relative increase of the primary efficacy end point myocardial PCr-to-ATP (in T2D: mean  $\pm$  SD  $1.74 \pm 0.24$ ) (10), with 90% power at  $\alpha = 0.05$ . A total of 18 T2D patients were needed.

A second a priori sample size calculation was performed to detect a 10% difference in the PCr-to-ATP ratio in T2D compared with control subjects with no diabetes. Our pilot PCr-to-ATP ratio data (mean  $\pm$  SD for T2D  $1.74 \pm 0.24$  and control  $2.12 \pm 0.26$ , with 80% power at  $\alpha = 0.05$ ) suggested that eight control subjects would be needed to detect an 18% relative difference in the PCr-to-ATP ratio (10).

### Data and Resource Availability

The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request. In accord with the authors' data management plan incorporating University of Leeds (UoL) guidance on data deposition and sharing, compliant with the Data Protection Act 2018, the authors are happy to provide the study data upon request. The quantitative data generated from clinical measurements underpin this research publication and will be made available to the scientific community, commerce, government, and education, together with details of the software required to view data sets or replicate statistical analyses. Transfer of data will be agreed in advance and take place in an anonymized and secure, approved formatting following UoL policy. The publication will be open-access. UoL data protection and sharing policies are available from [https://www.leeds.ac.uk/secretariat/data\\_protection.html](https://www.leeds.ac.uk/secretariat/data_protection.html) and <https://library.leeds.ac.uk/research-data-policies>.

## RESULTS

### Participant Characteristics

Demographics and clinical and biochemical data are shown in Table 1. Of the 24 consecutive T2D patients recruited at baseline, 18 (13 male, mean  $\pm$  SD age  $67 \pm 11$  years, BMI  $29 \pm 4$  kg/m<sup>2</sup>, diabetes duration  $11 \pm 8$  years, HbA<sub>1c</sub>  $60 \pm 13$  mmol/mol [ $7.6 \pm 1.2\%$ ]) completed 12 weeks' treatment of empagliflozin (Fig. 1) as well as baseline and follow-up imaging. All 10 control subjects (8 male, age  $67 \pm 9$  years, BMI  $28 \pm 2$  kg/m<sup>2</sup>) completed the imaging studies. Control subjects matched the study group for age, sex/gender, and BMI and for comorbidities of hypertension and previous history of ischemic heart disease. There were no significant differences in systolic or diastolic BP or resting heart rates between the groups at baseline. Triglyceride levels and fasting glucose levels were also higher in the T2D patients. All the T2D patients were on statin therapy, while only 40% of the control subjects were receiving statins; therefore, T2D patients had lower total cholesterol and LDL levels. The HDL levels were higher in the control group. Eight patients had a prior diagnosis of coronary artery disease (CAD) in the right coronary artery (RCA) territory (44%).

### Completeness of Follow-up and Adherence

Of the 24 participants recruited at baseline, 6 T2D patients received baseline assessments but did not complete the

study. One participant stopped empagliflozin treatment early due to experiencing frequent urinary infections, and in the case of five patients to whom a recommendation was made to commence empagliflozin treatment this was not started within 3 months of the baseline scan. These 6 patients had clinical characteristics and CMR findings similar to those of the 18 patients completing the study (these details are provided in a separate table with the supplementary material). Among the 18 patients enrolled who completed the study, adherence and side effects were assessed by telephone interview. None of the 18 patients completing the 12-week treatment experienced any side effects. There were no changes to any of the patients' preexisting medications throughout the study.

### Baseline Differences in Myocardial Energetics and CMR Parameters

Cardiac <sup>31</sup>P-MRS and CMR results for T2D patients and control subjects are summarized in Table 2. Biventricular volumes, LV mass, and the maximum left atrial volumes are indexed by body surface area. The mean  $\pm$  SD PCr-to-ATP ratio was 26% lower in T2D patients compared with control subjects at baseline ( $1.52 \pm 0.4$  vs.  $2.1 \pm 0.5$ , respectively;  $P = 0.002$ ).

Baseline LV mass and myocardial cell volumes were numerically higher in T2D patients compared with control subjects; however, these differences were not statistically significant (Table 2). LV ejection fraction (LVEF) was significantly decreased in patients with diabetes (mean  $\pm$  SD for T2D  $52 \pm 13\%$  vs. control  $63 \pm 4\%$ ,  $P = 0.01$ ). Eight (44%) T2D patients had LVEF  $>55\%$ , six (33%) between 45% and 55%, one (6%) between 35% and 45%, and three (17%)  $<35\%$  at baseline (two patients without prior CAD and one with a previous RCA territory MI). All control subjects had LVEF  $>55\%$ , and four control subjects had previous RCA territory MI. GLS ( $P = 0.002$ ), peak circumferential systolic strain, and circumferential diastolic strain ( $P = 0.01$  and  $P = 0.02$ , respectively) rates were all significantly impaired in patients with diabetes at baseline.

Mean stress MBF in the T2D group was 20% lower than in control subjects ( $P = 0.04$ ), while rest MBF values were comparable. The reductions in global stress MBF in the T2D patients with prior diagnosis of CAD were 15% lower than in control subjects, while this was 25% in T2D patients without prior CAD.

### Changes in Clinical Findings and Cardiac Biomarkers With Empagliflozin Treatment

Changes in clinical and biochemical data with empagliflozin treatment are shown in Table 3. Empagliflozin treatment was associated with significant improvements in systolic (mean  $\pm$  SD  $134 \pm 13$  to  $120 \pm 13$  mmHg,  $P = 0.001$ ) and diastolic ( $79 \pm 7$  to  $74 \pm 6$  mmHg,  $P = 0.01$ ) BP and in resting heart rate ( $66 \pm 10$  to  $60 \pm 10$  bpm,  $P = 0.02$ ). While all patients experienced weight loss, with an average reduction of 2.2 kg over 12 weeks, the numeric changes in weight and in BMI did not reach

**Table 1—Baseline clinical characteristics of the study cohort**

Variable	Control subjects (n = 10)	T2D patients (n = 18)	P
Age, years	67 ± 9	67 ± 11	1
BMI, kg/m <sup>2</sup>	28 ± 2	29 ± 4	0.9
Male	8 (80)	13 (72)	0.5
Diabetes duration, years	—	11 ± 8	—
Smoking	2 (20)	8 (45)	0.2
Heart rate, bpm	62 ± 9	66 ± 10	0.3
Systolic BP, mmHg	139 ± 16	134 ± 13	0.8
Diastolic BP, mmHg	77 ± 7	79 ± 7	0.5
Hemoglobin, g/L	145 ± 11	140 ± 17	0.41
Hematocrit, L/L	0.45 ± 0.03	0.43 ± 0.05	0.26
Total cholesterol, mmol/L	5.3 ± 1.6	4.4 ± 1.2	0.1
HDL, mmol/L	1.7 ± 0.45	1.36 ± 0.37	0.03
LDL, mmol/L	3.01 ± 1.29	2.31 ± 1.13	0.1
TG, mmol/L	1.33 ± 0.65	2.46 ± 1.63	0.05
Creatinine, μmol/L	71 ± 9.6	77 ± 22	0.4
eGFR, mL/min/1.73 m <sup>2</sup>	83 ± 9	71 ± 37	0.3
HbA <sub>1c</sub> , mmol/mol; %	38 ± 2; 6 ± 0.2	60 ± 13; 7.6 ± 1.2	0.0001
Insulin, pmol/L	35 ± 29	139 ± 126	0.02
NT-proBNP, ng/L	135 (35–156)	199 (40–1,289)	0.3
CV disease history			
CAD	4 (40)	8 (44)	0.8
Prior MI	4 (40)	8 (44)	0.8
PCI	4 (40)	5 (28)	0.5
CABG	0 (0)	0 (0)	1
Hypertension	6 (60)	15 (83)	0.2
Stroke	0 (0)	1 (6)	0.4
Medications			
Metformin	0 (0)	15 (83)	
Sulfonylurea	0 (0)	2 (11)	
Gliptin	0 (0)	1 (6)	
Thiazolidinediones	0 (0)	0 (0)	
GLP-1RA	0 (0)	0 (0)	
Aspirin	6 (60)	13 (72)	
Statins	7 (70)	18 (100)	
ACEI	6 (60)	12 (66)	
ARB	0 (0)	6 (33)	

Data are means ± SD or median (IQR) for continuous variables and n (%) for categorical variables. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; GLP-1RA, glucagon-like peptide 1 receptor agonists; PCI, percutaneous coronary intervention; TG, triglyceride.

statistical significance. Plasma NT-proBNP levels decreased by 61% after treatment (median 199 ng/L [interquartile range (IQR) 40–1,289] vs. 118 ng/L [IQR 58–409],  $P = 0.05$ ).

#### Changes in Myocardial Energetics and CMR Parameters With Empagliflozin Treatment

Changes in <sup>31</sup>P-MRS and CMR findings with empagliflozin treatment are summarized in Table 4. Treatment with empagliflozin was associated with significant improvements in myocardial energetics (PCr-to-ATP ratio 1.52 to 1.76,  $P = 0.009$ ) (Fig. 3) in all except 1 of the 18 patients

independent of baseline LVEF and irrespective of the presence of CAD. There were also significant improvements in LVEF (mean ± SD 52 ± 13% vs. 59 ± 15%,  $P = 0.001$ ) (Fig. 4).

Treatment with empagliflozin was also associated with significant reductions in LV end diastolic volumes (LVEDV) (mean ± SD 164 ± 50 to 149 ± 38 mL,  $P = 0.02$ ) and LV end systolic volumes (LVESV) (83 ± 45 to 65 ± 39 mL,  $P = 0.001$ ) as well as LVEDV indexed to body surface area (86 ± 27 to 79 ± 21 mL/m<sup>2</sup>,  $P = 0.02$ ) and LVESV indexed to body surface area (44 ± 25 to 35 ± 21 mL/m<sup>2</sup>,  $P = 0.001$ ). The numeric reductions associated with

**Table 2—Baseline comparison of CMR findings**

Variable	Control subjects (n = 10)	T2D patients (n = 18)	P
LVEDV (mL)	149 ± 41	163 ± 50	0.5
LVEDV index (mL/m <sup>2</sup> )	80 ± 17	86 ± 27	0.5
LVESV (mL)	54 ± 16	83 ± 45	0.06
LVESV index (mL/m <sup>2</sup> )	29 ± 7	44 ± 25	0.07
LV stroke volume (mL)	95 ± 27	81 ± 20	0.13
LVEF (%)	63 ± 4	52 ± 13	0.01
LV mass (g)	100 ± 29	119 ± 33	0.1
LV mass index (g/m <sup>2</sup> )	53 ± 12	61 ± 15	0.2
LV mass-to-LVEDV ratio (g/mL)	0.64 ± 0.09	0.76 ± 0.27	0.2
RV end diastolic volume (mL)	156 ± 43	151 ± 34	0.7
RV end diastolic volume index (mL/m <sup>2</sup> )	84 ± 18	79 ± 19	0.5
RV end systolic volume (mL)	65 ± 20	71 ± 25	0.5
RV end systolic volume index (mL/m <sup>2</sup> )	35 ± 9	38 ± 15	0.57
RV stroke volume (mL)	92 ± 26	78 ± 17	0.09
RV ejection fraction (%)	59 ± 5	53 ± 9	0.06
Peak circumferential strain (%)	−21 ± 2	−17 ± 4	0.01
GLS (%)	−14 ± 3	−10 ± 3	0.002
Peak diastolic circumferential strain rate (1/s)	1.1 ± 0.2	1.0 ± 0.2	0.2
Peak diastolic longitudinal strain rate (1/s)	0.8 ± 0.2	0.7 ± 0.2	0.2
LA maximum volume index (mL/m <sup>2</sup> )	35 ± 15	30 ± 16	0.8
LA ejection fraction (%)	58 ± 11	48 ± 13	0.05
Native T1 (ms)	1,241 ± 83	1,285 ± 104	0.2
Extracellular volume (%)	25 ± 3	25 ± 3	1
Cell volume (mL/m <sup>2</sup> )	75 ± 22	91 ± 30	0.15
MBF, rest (mL/g/min)	0.6 ± 0.1	0.6 ± 0.3	1
MBF, stress (mL/g/min)	2.0 ± 0.5	1.6 ± 0.5	0.05
MPRI	3.3 ± 0.9	2.9 ± 1.5	0.4

Data are means ± SD. MPRI, myocardial perfusion index; RV, right ventricular.

empagliflozin treatment in LV mass (119 ± 33 to 109 ± 29 g,  $P = 0.06$ ) and LV mass indexed to the body surface area (61 ± 15 to 56 ± 12 g/m<sup>2</sup>,  $P = 0.07$ ) did not reach statistical significance.

While GLS also improved (mean ± SD −10.2 ± 2.0% to −13.1 ± 4.1%,  $P = 0.01$ ), no significant changes were detected in diastolic strain rates or in LA function. There was a significant reduction in myocardial cell volume (92 ± 30 to 84 ± 27 mL/m<sup>2</sup>,  $P = 0.04$ ).

There were no significant changes in MBF or myocardial perfusion reserve after empagliflozin treatment.

## DISCUSSION

Although SGLT2 inhibitors are unique as glucose-lowering agents in their ability to reduce CV events, including preventing or delaying the onset of HF (3), the mechanisms behind these effects have remained incompletely understood. This study has shown for the first time that

empagliflozin treatment improves the cardiac energy homeostasis and reduces myocardial cellular volume in T2D patients. These changes were accompanied by improvements in LVEF, GLS, and BP control, and reductions in NT-proBNP levels, after 12 weeks of treatment. These favorable effects were observed despite no other changes to medications.

Our data also confirm the previous finding that empagliflozin does not improve myocardial blood flow or perfusion reserve in diabetes, while it improves BP control and reduces resting heart rates (24). The changes in HbA<sub>1c</sub>, lipid profile, and renal function tests were in line with previous reports of large clinical trials of SGLT2 inhibitors (3).

### Cardiac Energy Starvation in Diabetes

Diabetes is a disorder of metabolic dysregulation. It is well established that cardiac energy levels are reduced in T2D patients and even simple exercise activity exacerbates

**Table 3—Changes in clinical parameters after empagliflozin treatment**

Variable	Baseline (n = 18)	Follow-up (n = 18)	P
BMI, kg/m <sup>2</sup>	29 ± 4	27 ± 4	0.09
Heart rate, bpm	66 ± 10	60 ± 9	0.02
Systolic BP, mmHg	134 ± 13	120 ± 13	0.001
Diastolic BP, mmHg	79 ± 7	74 ± 6	0.01
Hemoglobin, g/L	140 ± 17	142 ± 19	0.17
Hematocrit, L/L	0.43 ± 0.05	0.44 ± 0.05	0.03
Total cholesterol, mmol/L	4.4 ± 1.2	4.5 ± 1.5	0.6
HDL, mmol/L	1.36 ± 0.37	1.28 ± 0.35	0.06
LDL, mmol/L	2.31 ± 1.13	2.11 ± 1.23	0.3
TG, mmol/L	2.46 ± 1.63	2.32 ± 1.26	0.7
Creatinine, μmol/L	77 ± 22	81 ± 19	0.4
eGFR, mL/min/1.73 m <sup>2</sup>	71 ± 37	70 ± 36	0.5
HbA <sub>1c</sub> , mmol/mol; %	60 ± 13; 7.6 ± 1.2	56 ± 9; 7.2 ± 0.8	0.3
Insulin, pmol/L	139 ± 126	175 ± 143	0.4
NT-proBNP, ng/L	199 (40–1,289)	118 (58–409)	0.05
<b>Medications</b>			
Metformin	15 (83)	15 (83)	1
Sulfonylurea	2 (11)	2 (11)	1
Gliptin	1 (6)	1 (6)	1
Thiazolidinediones	0 (0)	0 (0)	1
Glucagon-like peptide 1 receptor agonists	0 (0)	0 (0)	1
Aspirin	13 (72)	13 (72)	1
Statin	18 (100)	18 (100)	1
ACEI	12 (66)	12 (66)	1
ARB	6 (33)	6 (33)	1

Data are means ± SD or median (IQR) for continuous variables and n (%) for categorical variables. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; TG, triglyceride.

the preexisting energy-starved state further (10). Energy starvation is detectable even in asymptomatic T2D patients, preceding other abnormalities such as reductions in LVEF or increase in LV mass (10). This suggests that myocardial energy metabolism offers both early diagnostic and therapeutic opportunities to prevent or modulate diabetic HF.

In the aerobic setting, >90% of the ATP produced by the heart is derived from mitochondrial oxidative phosphorylation. Mitochondrial creatine kinase catalyzes the transfer of the high-energy phosphate bond in ATP to creatine to form PCr (9). PCr is the primary energy reserve compound in the heart. This molecule is smaller and less polar than ATP and therefore able to diffuse out of the mitochondria to the myofibrils. Impaired ATP transfer and use may limit contractile function by means of a decrease in the average ATP concentration or an increase in the concentration of free ADP (9). Myocardial ATP levels are protected by PCr until the advanced stages of HF (9). A decreased PCr-to-ATP ratio is a predictor of mortality (25), linked to contractile dysfunction (25,26), and is a well-established complication of diabetes (10).

### Potential Mechanisms for the Modulation of Myocardial Energy Metabolism With Empagliflozin

There are multiple components of cardiac energy metabolism that are potentially involved in establishing a myocardial energy-starved state and impaired contractility in T2D patients (7). These include reduced myocardial blood supply (10), loss of myocardial metabolic flexibility in fuel selection (27), and dysfunction of the mitochondria (28). While the reasons for empagliflozin's beneficial effects on myocardial energetics are not yet clear, as each of these components of metabolism are amenable to pharmacological intervention, their modulation could potentially contribute to the observed beneficial effects of empagliflozin on myocardial energetics.

### Modulation of Myocardial Perfusion With Empagliflozin

Reduced myocardial perfusion in T2D patients has been demonstrated in previous studies (10,29), and among several mechanisms, abnormalities in coronary microcirculation have been proposed as a cause of diabetic HF (29). This study showed significant improvements in myocardial function and PCr-to-ATP ratio without improvements in myocardial rest or stress blood flow or myocardial



**Table 4—Changes in CMR findings with empagliflozin treatment**

Variable	Baseline (n = 18)	Follow-up (n = 18)	P
LVEDV (mL)	164 ± 50	149 ± 38	0.02
LVEDV index (mL/m <sup>2</sup> )	86 ± 27	79 ± 21	0.02
LVESV (mL)	83 ± 45	65 ± 39	0.001
LVESV index (mL/m <sup>2</sup> )	44 ± 25	35 ± 21	0.001
LV stroke volume (mL)	81 ± 20	84 ± 16	0.39
LVEF (%)	52 ± 13	59 ± 15	0.001
LV mass (g)	119 ± 33	109 ± 29	0.06
LV mass index (g/m <sup>2</sup> )	61 ± 15	56 ± 12	0.07
LV mass-to-LVEDV ratio (g/mL)	0.76 ± 0.27	0.75 ± 0.18	0.6
RV end diastolic volume (mL)	151 ± 34	155 ± 32	0.5
RV end diastolic volume index (mL/m <sup>2</sup> )	79 ± 19	83 ± 24	0.3
RV end systolic volume (mL)	71 ± 25	76 ± 27	0.4
RV end systolic volume index (mL/m <sup>2</sup> )	38 ± 15	41 ± 22	0.4
RV stroke volume (mL)	78 ± 11	80 ± 12	0.7
RV ejection fraction (%)	53 ± 9	53 ± 11	0.9
Peak circumferential strain (%)	−17.4 ± 4.1	−18.8 ± 4.9	0.3
GLS (%)	−10.2 ± 2.9	−13.1 ± 4.1	0.01
Peak diastolic circumferential strain rate (1/s)	1 ± 0.2	1.1 ± 0.3	0.4
Peak diastolic longitudinal strain rate (1/s)	0.7 ± 0.2	0.7 ± 0.2	0.9
LA maximum volume indexed (mL/m <sup>2</sup> )	30 ± 16	28 ± 11	0.9
LA ejection fraction (%)	48 ± 13	48 ± 15	0.2
Native T1 (ms)	1,285 ± 104	1,310 ± 42	0.6
Extracellular volume (%)	24 ± 3	25 ± 3	0.1
Cell volume (mL/m <sup>2</sup> )	92 ± 30	84 ± 27	0.04
MBF, rest (mL/g/min)	0.62 ± 0.3	0.66 ± 0.3	0.4
MBF, stress (mL/g/min)	1.6 ± 0.5	1.4 ± 0.3	0.08
MPR	2.9 ± 1.5	2.3 ± 0.8	0.06

Data are means ± SD. MPR, myocardial perfusion reserve; RV, right ventricular.

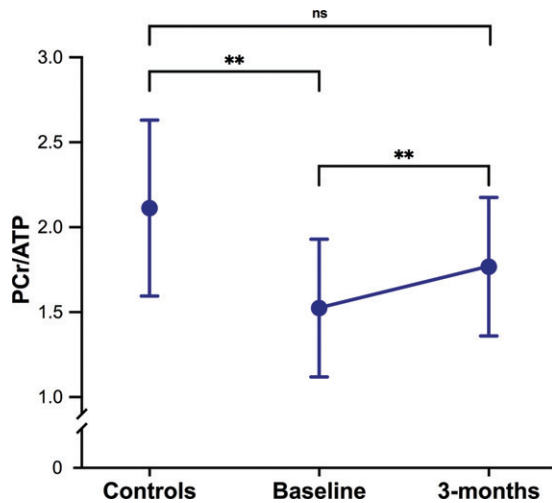
perfusion reserve, ruling out modulation of myocardial perfusion as a key mechanism responsible for the beneficial CV effects of empagliflozin.

#### **Improvements in BP Control and Body Weight Reductions With Empagliflozin**

In this study, the decreases in systolic and diastolic BP were significant and these were accompanied by numeric reductions in LV mass after 12 weeks of empagliflozin treatment. Although the changes in LV mass did not reach statistical significance the trends suggest a sustained reduction in afterload. Reductions in myocardial PCr-to-ATP ratio have previously been documented in patients with hypertension and in obesity (30,31). Consequently, in this study, observed improvements in BP control and reductions in body weight in response to empagliflozin treatment likely contributed to the observed improvements in myocardial PCr-to-ATP ratio. Moreover, reduction in preload through the diuretic

properties of the SGLT2 inhibitors has been proposed among their additional mechanistic benefits (32,33), though we have detected a trend but not a significant reduction in left atrial volumes after 12 weeks of empagliflozin treatment, which would be in support of this.

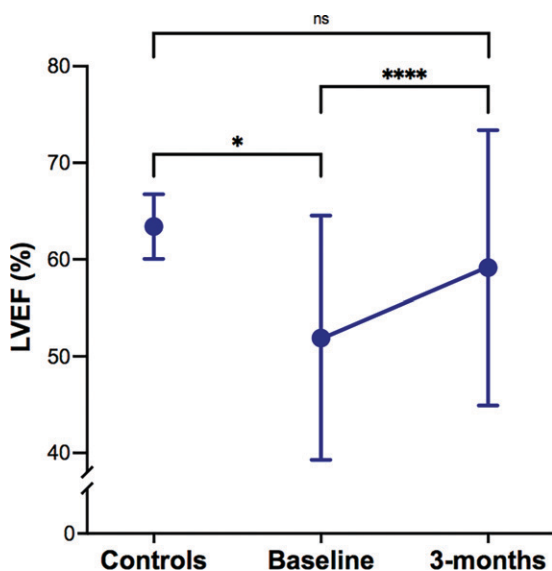
We have also detected a significant reduction in resting heart rate after 12 weeks of empagliflozin treatment, accompanying the improvements in BP and reductions in NT-proBNP levels. The relationship between resting heart rate and body weight is well established, with reduction of body weight resulting in decreased heart rate (34) and the increase of BMI to be an independent predictor of increased annual resting heart rate (35). The changes in resting heart rate might be contributing to the improvements in myocardial energetics. Supporting this, a previous study has shown that reductions in resting heart rates were accompanied by significant improvements in myocardial PCr-to-ATP ratio with 3 months of  $\beta$ -blocker treatment in patients with HF with reduced ejection fraction (HFrEF) (36).



**Figure 3**—Comparisons of myocardial PCr-to-ATP ratio (PCr/ATP) between patients with T2D and control subjects at baseline and the changes in PCr-to-ATP ratio before and after 12 weeks' empagliflozin treatment. ns, non-significant. \*\* $P = 0.002$  between control subjects and baseline;  $P = 0.009$  between baseline and 3-month follow-up.

#### Modulation of Metabolic Flexibility With Empagliflozin

It is generally accepted that metabolic flexibility is impaired in T2D with reduced use of carbohydrates and oxidative preference for fatty acids (FA) (27). The free energy yielded by ATP hydrolysis is affected by the substrate oxidized, and this is lower when FA are used compared with glucose (37). Therefore, at any given level of cardiac work, an increased dependence on FA relative to carbohydrates decreases cardiac efficiency (38). Exploring the impact of empagliflozin



**Figure 4**—Comparisons of LVEF between patients with T2D and control subjects at baseline and the changes in LVEF before and after 12 weeks' empagliflozin treatment. ns, non-significant. \* $P = 0.01$ ; \*\*\*\* $P = 0.001$ .

on metabolic flexibility, a recent study showed no significant change in myocardial FA or glucose uptake in 13 T2D patients on [ $^{11}\text{C}$ ]palmitate and [ $^{18}\text{F}$ ]fluorodeoxyglucose positron emission tomography (24).

#### Enhanced Ketone Metabolism With Empagliflozin

As a class effect, SGLT2 inhibitors increase blood  $\beta$ -hydroxybutyrate levels, therefore inducing mild ketosis. We have not measured plasma ketone levels in this study, but this effect is well established (39). It is widely speculated that mild ketosis may potentially contribute to the cellular energy-restoring effects of empagliflozin (40,41). Because the energetic properties of ketones are more favorable than FA (42), increased myocardial ketone oxidation could potentially mitigate myocardial energy starvation in diabetes and compensate for defects in mitochondrial energy generation (37). As myocardial ketone consumption is in direct proportionality to the circulating ketone levels (42), ketosis associated with administration of SGLT2 inhibitors might lead to a shift toward oxidation of ketone bodies. However, this remains speculation, as SGLT2 inhibition-associated changes in myocardial ketone use remain to be shown in T2D patients.

#### Changes in Myocardial Remodeling With Empagliflozin

In this study, we could monitor dynamic changes in myocardial tissue characteristics before and after empagliflozin treatment. CMR-derived ECV reflects the presence and extent of myocardial fibrosis and correlates well with histological findings (43). The ECV measured by T1 mapping divides the myocardium into cell and matrix compartments and allows calculation of cell and matrix volumes (13). While several alterations in LV geometry have previously been demonstrated in diabetes, in our study the only structural abnormality detected was a significant increase in cell volume in T2D patients, while there were no differences in LV mass or LV volumes between the patients and the control subjects.

The cellular components of the myocardium include cardiomyocytes, fibroblasts, endothelial cells, and red blood cells. Hypertrophy of the cellular components of the myocardium has been demonstrated on histopathology from myocardial biopsy samples obtained from T2D patients even in early stages of the disease (44). The mechanism promoting cellular hypertrophy in the diabetic heart include hyperglycemia, insulin resistance, and oxidative stress-induced enhanced expression of several cardiomyocyte hypertrophic genes, such as  $\beta$ -myosin heavy chain, insulin-like growth factor 1 receptor, and BNP (45). Suggesting reversal of this cellular remodeling process in diabetes, we have observed significant reductions in cell volume with empagliflozin treatment. Reductions in BP and body weight with empagliflozin treatment likely contributed to this finding.

Contrary to the cellular components, there were no differences in CMR-derived extracellular matrix volume (extracellular matrix and capillaries), which reflects the presence and extent of myocardial fibrosis at baseline between T2D patients and control subjects. Moreover, no significant change was detected in the ECV with empagliflozin treatment.

Our study was not powered to show changes in LV mass. The changes in LV mass with empagliflozin treatment have been inconsistent in the literature. While a larger clinical study showed significant reductions in LV mass indexed to the body surface area, but not in LV mass in patients with T2D and CAD after empagliflozin treatment (46), this finding was not replicated in another study with similar cohort size (47), which demonstrated significant reductions in both LV mass and LV mass indexed to the body surface area with empagliflozin in HFrEF patients without diabetes. Moreover, in another study of HFrEF patients with T2D/prediabetes, no significant reductions were detected either in LV mass or in LV mass indexed to the body surface area with empagliflozin treatment (48). These discrepancies in clinical outcomes in response to empagliflozin treatment highlight the importance of careful consideration of the differences in study cohorts in interpretation of clinical outcomes looking at varying populations.

### Limitations

While our study shows significant improvements in myocardial PCr-to-ATP ratio and function, we have not performed invasive studies to assess the impact of treatment on mitochondrial oxidative capacity in myocardial samples or on metabolic flexibility by measuring transmyocardial extraction of energy fuels with coronary sinus sampling studies (49). Consequently, we cannot speculate on the impact of empagliflozin on myocardial metabolic flexibility or mitochondrial oxidative capacity as the causes of the observed beneficial outcomes on myocardial energetics. Future studies using invasive techniques will be required to investigate these. While in line with the study objectives, our sample size was powered to detect changes in the primary end point but not powered for correlation analyses.

Moreover, while dobutamine stress  $^{31}\text{P}$ -MRS is frequently used in research studies and adds valuable information on the response of the cardiac energetics to increased workloads, this protocol requires a long duration of dobutamine infusion. Subjecting T2D patients with existing CV comorbidities such as prior MI (40% of the study participants) to long periods of dobutamine infusion was deemed an excessive risk and burden on study subjects and could also have led to higher dropout rates. Consequently, dobutamine stress spectroscopy studies were not performed.

While our study was not designed to investigate the effects of empagliflozin in subpopulations of patients with preserved and reduced ejection fraction, this important question is currently being investigated in another study (50).

### Conclusion

This is the first study to show that treatment with empagliflozin ameliorates the “cardiac energy-deficient state” and is associated with reductions in myocardial cellular volume in T2D patients. These changes were accompanied by improved cardiac function, reduced NT-proBNP levels, and improvement in BP control. This study, through use of the myocardial PCr-to-ATP ratio to monitor the early energetic response of the heart to treatment, and CMR to monitor structural and functional changes, provides significant mechanistic insights into the mechanisms of action that give empagliflozin its beneficial CV effects.

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