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Acute changes in plasma glucose increases left ventricular systolic function in insulin-treated patients with type 2 diabetes and controls

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Abstract

Aims: We aimed to evaluate the effect of acute hyperglycaemia and hypoglycaemia on cardiac function in patients with type 2 diabetes (T2D) and a control group.

Materials and methods: In a nonrandomized interventional study, insulin-treated patients with T2D (N = 21, mean ± SD age 62.8 ± 6.5 years, body mass index [BMI] 29.0 ± 4.2 kg/m^2, glycated haemoglobin [HbA1c] 51.0 ± 5.4 mmol/mol [6.8 ± 0.5%]) and matched controls (N = 21, mean ± SD age 62.2 ± 8.3 years, BMI 29.2 ± 3.5 kg/m^2, HbA1c 34.3 ± 3.3 mmol/L [5.3 ± 0.3%]) underwent one experimental day with plasma glucose (PG) clamped at three different 30-minute steady-state levels: (1) fasting plasma glucose (FPG); (2) hyperglycaemia (FPG + 10 mmol/L); and (3) hyperinsulinaemic hypoglycaemia (PG <3.0 mmol/L). Cardiac function was evaluated during each steady state by echocardiography.

Results: Acute hyperglycaemia increased left ventricular (LV) ejection fraction from baseline in patients with T2D (mean [95% confidence interval] 4.5 percentage points [1.1; 7.9]) but not in controls (2.0 percentage points [−1.4; 5.4]). Mitral annular peak systolic velocity (s′) increased during hyperglycaemia in both patients and controls (0.4 m/s [0.2;0.6] and 0.6 m/s [0.4; 0.8], respectively), whereas global longitudinal strain rate only increased in the controls (−0.05 s^{-1} [−0.12; 0.02] and −0.11 s^{-1} [−0.18; −0.03], respectively). All measures of LV systolic function increased markedly during hypoglycaemia (*P* <0.01 for all). No interaction between group and PG level on cardiac function was observed.

Conclusions: Acute hyperglycaemia and hypoglycaemia increase LV systolic function, with no difference between patients with T2D and controls. Standardization of PG may improve reproducibility when evaluating LV systolic function in patients with T2D.

1 | INTRODUCTION

Patients with type 2 diabetes (T2D) have more than twice the risk of developing heart failure compared with individuals without the disease, and the prevalence of T2D in patients with heart failure is more than 20%.[1] Although heart failure and T2D often coexist, the effect of acute glycaemic changes on cardiac function as evaluated by echocardiography remains unelucidated.

In T2D, myocardial function may be affected by the metabolic state of hyperglycaemia. Patients with T2D have a substantially altered cardiac metabolism with a shift towards free fatty acid (FFA) utilization.[1] Since FFA oxidation requires more oxygen per carbon unit than glucose oxidation and induces expression of mitochondrial uncoupling protein, the diabetic myocardium is metabolically inefficient.[1] Pharmacological modulation of myocardial substrate metabolism with an increase in glucose utilization and a decrease in FFA utilization for treatment of heart failure have demonstrated promising results.[2] Hence, hyperglycaemia with abundant glucose availability and enhanced endogenous insulin production may promote glucose utilization, potentially enhancing cardiac function. An improved systolic function during hyperglycaemia in patients with T2D has been indicated in previous studies, although no effect on left ventricular ejection fraction (LVEF) was observed, and consequently the practical implications are uncertain.[3,4]

Acute hypoglycaemia has previously been demonstrated to markedly increase LVEF as measured by radionuclide ventriculography in healthy young males due to a substantial sympathoadrenal response.[5] A detailed description of changes in cardiac function during hypoglycaemia in an insulin-treated T2D population with high risk of hypoglycaemia has not previously been performed. As hypoglycaemia has consistently been linked to poor cardiovascular outcome in patients with T2D,[6] the effect of acute hypoglycaemia on cardiac function in a high-risk, T2D population is of interest.

In the present study we delineated the role of acute changes in plasma glucose (PG) on cardiac function in insulin-treated T2D by performing echocardiography during acute hyperglycaemia and hypoglycaemia, respectively, compared with measurements during fasting plasma glucose (FPG) in patients with insulin-treated T2D and matched controls without diabetes.

2 | MATERIALS AND METHODS

2.1 | Approvals and registrations

The present study contains echocardiographic data from a study evaluating the effect of acute glycaemic fluctuations on risk of cardiac arrhythmias in patients with T2D.[7] Haemodynamic evaluation by echocardiography was a defined secondary endpoint, which was planned to be published separately. The study was carried out at the Steno Diabetes Centre, Copenhagen and the Centre for Clinical Metabolic Research, Gentofte Hospital, Hellerup, Denmark from May 2017 to July 2019. Written informed consent was obtained from all participants prior to inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Ethical Committee of the Capital Region of Denmark (ID No. H-16046212) and the Danish Data Protection Agency (ID No. HGH-2017-030). The study was registered at ClinicalTrials.gov (NCT03150030).

2.2 | Patients and methods

The study included 21 patients with insulin-treated T2D, glycated haemoglobin (HbA1c) ≤58 mmol/mol (7.5%) and at least one microvascular complication. Furthermore, a control group of 21 individuals without diabetes or any first-degree relatives with diabetes and matched for age, sex and body mass index (BMI) was included. Exclusion criteria were prior cardiac arrhythmia, implantable cardioverter defibrillator or pacemaker, severe heart failure (LVEF <25%), structural heart disease, and thyroid dysfunction except for well-treated myxoedema and anaemia. The study consisted of one three-step, experimental clamp procedure with three consecutive phases of 30-minute steady-state PG: (1) a FPG phase; (2) a hyperglycaemic phase (FPG + 10 mmol/L); and (3) a hyperinsulinaemic hypoglycaemic phase (PG <3.0 mmol/L). Hyperglycaemia was obtained by an individualized 20% (W/V) glucose infusion. Hypoglycaemia was obtained by an individualized bolus of human insulin (Actrapid®, Novo Nordisk, Bagsværd, Denmark; 9.1 international units [IU] and 2.5 IU times body surface area [BSA; m^2] estimated by the Mosteller formula in patients with T2D and controls, respectively) and a continuous intravenous infusion (20 IU/h and 5 IU/h times BSA, respectively). PG levels were measured bedside every fifth minute and blood samples for subsequent analyses were drawn every tenth minute.

2.3 | Blood samples and analyses

Details on sampling and handling of blood samples for analysis of counterregulatory hormones are described elsewhere.[7] For measurement of FFA, whole blood was drawn into tubes containing serum clot activator and kept for at least 20 minutes at room temperature and stored at −80°C before being analysed using an enzymatic colorimetric method (Cobas 8000; Roche Diagnostics, Basel, CH). For measurement of C-peptide, blood was drawn into a lithium-heparin tube, placed on ice until centrifugation and stored at −20°C before being analysed using a sandwich electrochemiluminescence immunoassay (Atellica IM Analyzer; Siemens Healthineers, Erlangen, DE). All samples were centrifuged at 4°C and approximately 2900 g for 15 minutes and stored until batch analyses could be performed.

2.4 | Echocardiography

At each phase, an echocardiography was performed by the first author (A.A.) after 10 minutes of steady-state PG. Echocardiography was performed on a Vivid E9 system (GE Vingmed Ultrasound, Horten, Norway) and digitally stored. Three consecutive heart cycles were recorded for each view and analysis was performed blinded to ID, group and phase with GE EchoPac software version 201 after completion of the final experimental day. Chamber quantification was performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[8] Left ventricular (LV) mass was calculated with the formula: LV mass (g) $= 0.8 \times [1.04 \times \{(\text{LV internal diameter} + \text{posterior wall thickness} + \text{septal wall thickness})^3 - \text{LV internal diameter}^3\}] + 0.6$ and indexed according to BSA. LVEF was estimated using the Simpson's biplane method. Global longitudinal strain was measured by two-dimensional speckle tracking as mean peak systolic strain from the 18 LV segments in apical views and was only calculated if at least 12 segments could be analysed. Longitudinal mitral annular peak systolic velocity (s′) and longitudinal mitral annular peak early diastolic velocity (e′) were measured with tissue Doppler and calculated as average peak velocity, with the sample volume placed adjacent to the mitral leaflets in apical four-chamber view, two-chamber view and apical long-axis view. Mitral inflow velocities (peak early [MVE] and peak atrial [MVA]) were recorded from the apical four-chamber view using pulsed-wave Doppler with the sample volume placed at the tips of mitral leaflets. Tricuspid annular plane systolic excursion (TAPSE) was measured applying M-mode, with the sample volume placed at the basal segment of the right ventricular free wall in apical four-chamber view. Heart rate was determined from the heart rate registered at apical four-chamber images.

2.5 | Statistical analysis and calculations

Statistical analyses were performed with SAS studio version 3.71 (SAS Institute Inc.). Data that followed an approximate normal distribution were presented as mean ± SD when describing baseline characteristics or the clamp procedure and mean (95% confidence interval) when describing endpoints. To evaluate changes in C-peptide, FFA and cardiac function within each group and phase-group interaction, a general linear mixed model with phase as a repeated factor, ID as random factor and an unrestricted covariance structure was applied. Adjustment for multiple testing was performed with false discovery rate, and *P* values <0.05 were taken to indicate statistical significance.

3 | RESULTS

3.1 | Participants

Detailed data on baseline characteristics were previously published elsewhere[7] and are therefore included in Table S1. Both the groups consisted of 24% women, and age and BMI were similar

TABLE 1 Left ventricular structure as measured by echocardiography

	T2D (N = 21)	Controls (N = 21)	*P*
LV mass index, g/m^2	103 (26)	114 (42)	0.317
LV end diastolic diameter, cm	4.48 (0.41)	4.44 (0.59)	0.779
Interventricular septum thickness, cm	1.25 (0.17)	1.35 (0.27)	0.150
Left ventricular posterior wall thickness, cm	1.12 (0.16)	1.14 (0.20)	0.647

Note: Data are presented as mean (SD).
Abbreviations: LV, left ventricular; T2D, type 2 diabetes.

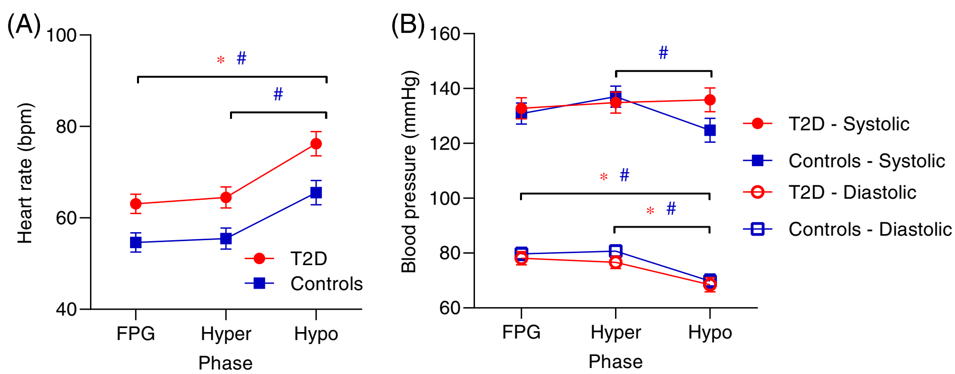

FIGURE 1 Heart rate and blood pressure. A, Heart rate and B, blood pressure during each phase of the experimental day in patients with type 2 diabetes (N = 21) and controls (N = 21; mean ± SE). A general linear mixed model with phase as a repeated factor, ID as random factor and an unrestricted covariance structure was applied. *P <0.05 in the type 2 diabetes group, #p <0.05 in the controls. Abbreviations: FPG, fasting plasma glucose; hyper, hyperglycaemia; hypo, hypoglycaemia; T2D, type 2 diabetes

TABLE 2 Left and right ventricular systolic function during acute changes in plasma glucose

FPG			Hyperglycaemia				Hypoglycaemia					
Group	Mean	95% CI	ΔMean	Δ95% CI	*P* (ref. FPG)	Adj. *P*	ΔMean	Δ95% CI	*P* (ref. FPG)	Adj. *P* (ref. FPG)	*P* (ref. hyper)	Adj. *P* (ref. hyper)
LV ejection fraction, %[a]												
T2D	55.9	53.7; 58.0	4.5	1.1; 7.9	0.011	0.037	8.0	4.0; 12.0	<0.001	0.002	0.071	0.179
Controls	58.1	56.0; 60.2	2.0	−1.4; 5.4	0.253	0.438	8.4	4.4; 12.3	<0.001	<0.001	0.002	0.008
ΔGroup			2.5	−2.3; 7.4	0.291	0.471	−0.4	−6.0; 5.3	0.879	0.954		
Global longitudinal strain, %												
T2D	−18.2	−19.6; −16.8	−1.0	−2.5; 0.5	0.189	0.351	−4.4	−6.4; −2.5	<0.0001	<0.001	<0.001	0.003
Controls	−20.0	−21.4; −18.7	−1.5	−3.0; 0.0	0.054	0.153	−2.8	−4.8; −0.9	0.006	0.024	0.135	0.285
ΔGroup			0.5	−1.6; 2.6	0.649	0.789	−1.6	−4.4; 1.2	0.254	0.436		
Global longitudinal strain rate, s^{-1}												
T2D	−0.91	−0.99; −0.84	−0.05	−0.12; 0.02	0.180	0.346	−0.53	−0.67; −0.40	<0.0001	<0.001	<0.0001	<0.001
Controls	−0.94	−1.02; −0.87	−0.11	−0.18; −0.03	0.005	0.023	−0.47	−0.60; −0.33	<0.0001	<0.001	<0.0001	<0.001
ΔGroup			0.06	−0.05; 0.16	0.270	0.454	−0.07	−0.25; 0.12	0.492	0.704		
s′ (TDI), cm/s												
T2D	5.2	4.7; 5.7	0.4	0.2; 0.6	<0.001	0.005	2.5	1.9; 3.1	<0.0001	<0.001	<0.0001	<0.001
Controls	5.3	4.9;5.8	0.6	0.4; 0.8	<0.0001	<0.001	2.5	1.9; 3.0	<0.0001	<0.001	<0.0001	<0.001
ΔGroup			−0.2	−0.5; 0.1	0.214	0.380	0.0	−0.8; 0.8	0.961	0.969		
TAPSE, cm												
T2D	2.6	2.4;2.8	0.1	−0.1; 0.3	0.190	0.351	0.2	−0.1; 0.5	0.131	0.285	0.557	0.739
Controls	2.8	2.6;3.0	0.2	0.0; 0.4	0.067	0.174	0.2	−0.1; 0.5	0.167	0.327	0.919	0.964
ΔGroup			−0.1	−0.3; 0.2	0.700	0.817	0.0	−0.4; 0.4	0.924	0.964		

Note: Changes in left and right ventricular systolic function during acute hyperglycaemia and acute hypoglycaemia compared to fasting plasma glucose.

Abbreviations: adj., Adjusted; FPG, fasting plasma glucose; hyper, hyperglycaemia; LV, left ventricular; s′, longitudinal mitral annular peak systolic velocity; ref, reference; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; T2D, type 2 diabetes.

[a]Changes in left ventricular ejection fraction are presented as percentage points.

TABLE 3 Diastolic function during acute changes in plasma glucose

Group	FPG		Hyperglycaemia				Hypoglycaemia					
	Mean	95% CI	ΔMean	Δ95% CI	*P* (ref. FPG)	Adj. *P*	ΔMean	Δ95% CI	*P* (ref. FPG)	Adj. *P* (ref. FPG)	*P* (ref. hyper)	Adj. *P* (ref. hyper)
MVE velocity, m/s												
T2D	0.78	0.72; 0.85	0.05	0.00; 0.10	0.063	0.170	−0.04	−0.12; 0.04	0.280	0.464	0.022	0.065
Controls	0.75	0.69; 0.85	0.06	0.01; 0.11	0.015	0.047	0.02	−0.06; 0.10	0.681	0.817	0.210	0.380
ΔGroup			−0.02	−0.09; 0.05	0.631	0.776	−0.06	−0.17; 0.05	0.294	0.471		
MVA velocity, m/s												
T2D	0.75	0.68; 0.81	0.04	0.00; 0.08	0.073	0.179	0.03	−0.04; 0.10	0.396	0.593	0.755	0.8623
Controls	0.64	0.57; 0.70	0.06	0.01; 0.10	0.015	0.047	0.11	0.03; 0.18	0.004	0.020	0.146	0.291
ΔGroup			−0.02	−0.08; 0.05	0.592	0.749	−0.08	0.17; 0.02	0.127	0.285		
E/A ratio												
T2D	1.08	0.96; 1.19	0.00	−0.09; 0.09	0.969	0.969	−0.13	−0.23; −0.03	0.014	0.046	0.008	0.030
Controls	1.22	1.10; 1.34	−0.01	−0.10; 0.08	0.827	0.923	−0.17	−0.27; −0.07	0.002	0.011	0.001	0.007
ΔGroup			0.01	−0.12; 0.14	0.854	0.942	0.04	−0.10; 0.19	0.570	0.740		
MV inflow deceleration time, ms												
T2D	238	215; 260	−6	−32; 19	0.601	0.749	42	11; 72	0.008	0.030	<0.001	0.006
Controls	232	208; 255	8	−18; 34	0.546	0.739	44	13; 75	0.006	0.024	0.009	0.032
ΔGroup			−14	−51; 22	0.426	0.629	−3	−46; 40	0.894	0.954		
e′												
T2D	6.1	5.4; 6.7	0.5	0.2; 0.8	0.004	0.020	0.3	−0.3; 0.8	0.308	0.484	0.372	0.567
Controls	6.9	6.3; 7.5	0.5	0.2; 0.9	0.002	0.009	0.4	−0.1; 1.0	0.131	0.285	0.595	0.749
ΔGroup			−0.3	−0.9; 0.3	0.350	0.543	−0.2	−0.10; 0.5	0.562	0.739		
E/e′ (TDI)												
T2D	13.2	11.9; 14.5	−0.2	−1.0; 0.6	0.552	0.739	−1.1	−2.4; 0.2	0.096	0.230	0.141	0.287
Controls	11.4	10.1; 12.8	−0.0	−0.9; 0.8	0.959	0.969	−0.4	−1.7; 0.9	0.556	0.739	0.516	0.729
ΔGroup			−0.2	−1.4; 1.0	0.707	0.817	−0.7	−2.6; 1.2	0.446	0.649		
LAESV index, mL/m^2												
T2D	22.6	18.8; 26.5	0.7	−2.7; 4.0	0.694	0.817	−2.7	−5.9; 0.5	0.100	0.234	0.036	0.105
Controls	28.2	24.3; 32.0	0.5	−2.8; 3.8	0.764	0.862	−2.4	−5.5; 0.8	0.137	0.285	0.064	0.170
ΔGroup			0.2	−4.6; 4.9	0.948	0.969	−0.3	−4.8; 4.2	0.894	0.954		

Note: Changes in diastolic function during acute hyperglycaemia and acute hypoglycaemia compared with fasting plasma glucose.

Abbreviations: e′, longitudinal mitral annular peak early diastolic velocity; E/A ratio, MVE/MVA ratio; E/e′, MVE/e′ ratio; FPG, fasting plasma glucose; hyper, hyperglycaemia; LAESV, left atrium end systolic volume; MV, mitral valve; MVA, peak atrial mitral inflow velocity; MVE, peak early mitral inflow velocity; ref, reference; TDI, tissue Doppler imaging; T2D, type 2 diabetes.

in the T2D group (62.8 ± 6.5 years, BMI 29.0 ± 4.2 kg/m^2, HbA1c 51.0 ± 5.4 mmol/mol [6.8 ± 0.5%]) and the control group (age 62.2 ± 8.3 years, BMI 29.2 ± 3.5 kg/m^2, HbA1c 34.3 ± 3.3 mmol/mol [5.3 ± 0.3%]). The mean diabetes duration was 15.3 ± 6.6 years. A total of 16 patients (76%) received oral glucose-lowering treatment, including sodium-glucose cotransporter-2 inhibitors (seven patients [33%]). Treatment for hypertension including beta-blockers was more frequent in the patients with T2D (86% vs. 19%). Blood pressure was similar in the two groups, whereas resting heart rate was higher in the patients with T2D (67 ± 11 beats/min vs. 60 ± 10 beats/min). Treatment with statins was more frequent in patients with T2D (16 [76%] vs. 1 [5%]) and LDL cholesterol was lower in patients with T2D (1.9 ± 0.6 vs. 3.2 ± 1.1). There was no difference in LV structure between the two groups (Table 1) and none of the participants had any previous cardiovascular disease. LVEF was ≥50% in all participants except one in the control group (LVEF 47%).

3.2 | Glycaemia and counterregulatory hormones

During the FPG phase, mean PG was 6.9 ± 1.5 mmol/L and 5.4 ± 0.5 mmol/L in patients with T2D and controls, respectively. During the hyperglycaemic phase, mean PG increased to 16.4 ± 1.8 mmol/L and 15.6 ± 1.3 mmol/L, respectively, whereas mean PG was 2.5 ± 0.4 mmol/L in both groups during the hypoglycaemic phase. Both groups had similar increases in glucagon, somatotropin and noradrenalin during hypoglycaemia, whereas a greater increase in cortisol was observed in the patients with T2D.

3.3 | Heart rate and blood pressure

Heart rate was higher in the patients with T2D compared to controls during the FPG phase ($P = 0.008$) and remained unchanged during the hyperglycaemic phase in both groups (Figure 1). During hypoglycaemia, the heart rate increased, with no difference between the groups. Diastolic blood pressure decreased during hypoglycaemia in both groups, whereas systolic blood pressure only decreased in controls when compared to the hyperglycaemic phase but not the FPG phase (Figure 1).

3.4 | Left ventricular systolic function

In the patients with T2D, LVEF increased during hyperglycaemia compared with the FPG phase, whereas a nonsignificant increase was observed in controls (Table 2). Global longitudinal strain increased in both groups during hyperglycaemia, however, the changes were nonsignificant. An increase in LV contractile velocity as measured by s' was highly significant in both groups during hyperglycaemia, whereas the global longitudinal strain rate only increased significantly in controls. During hypoglycaemia, a marked increase in all measures of LV systolic function was observed (Table 2). No interaction between group and phase on LV systolic function was found.

3.5 | Left ventricular diastolic function

An increase in MVE and MVA was observed in both the patients with T2D and controls during hyperglycaemia, however, the increase was only significant in controls (Table 3). Accordingly, mitral inflow velocity E/A ratio remained stable during hyperglycaemia. During hypoglycaemia, mitral inflow velocity E/A ratio decreased in both groups compared to both the FPG phase and the hyperglycaemic phase. MVE deceleration time remained unchanged during the hyperglycaemic phase compared to the FPG phase in both groups, whereas it increased in both the patients with T2D and controls during hypoglycaemia. During the hyperglycaemic phase, e′ increased in both groups, whereas no difference in e′ was observed during the hypoglycaemic phase. No change in E/e′ was observed during the clamp procedure and there was no interaction between group and phase on LV diastolic function (Table 3).

3.6 | Right ventricular systolic function

When compared with the FPG phase, no significant change in right ventricular function as measured by TAPSE was found in the patients with T2D and controls during either hyperglycaemia or hypoglycaemia (Table 2).

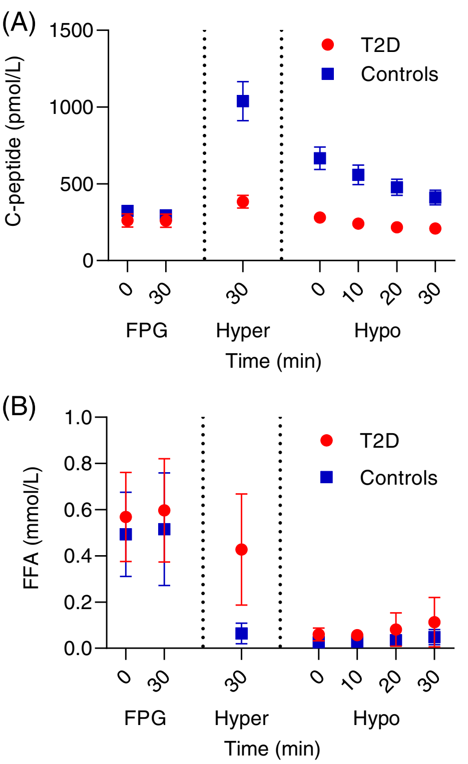

FIGURE 2 C-peptide and free fatty acids. Levels of A, C-peptide and B, free fatty acids during each phase of the experimental day in patients with type 2 diabetes (N = 21) and controls (N = 21) (mean ± SE). A general linear mixed model with phase as a repeated factor, ID as random factor and an unrestricted covariance structure was applied. Abbreviations: FPG, fasting plasma glucose; hyper, hyperglycaemia; hypo, hypoglycaemia; T2D, type 2 diabetes

3.7 | C-peptide and FFA levels

Plasma levels of C-peptide were similar at baseline ($P = 0.30$) and increased in both groups during hyperglycaemia, although the increase was only significant in the control group ($P = 0.12$ and $P < 0.0001$; Figure 2A). Plasma levels of C-peptide were higher in controls at the end of the hyperglycaemic and hypoglycaemic phase ($P < 0.0001$ and $P < 0.001$, respectively). Serum levels of FFA were similar in the two groups at baseline ($P = 0.20$) and were suppressed during hyperglycaemia in both patients with T2D and controls ($P = 0.002$ and $P < 0.0001$, respectively), although to lower levels in controls ($P < 0.0001$; Figure 2B). During hypoglycaemia, FFA levels were markedly suppressed in both groups, but were higher in the group of patients with T2D at the end of the hypoglycaemia period ($P < 0.0001$).

4 | DISCUSSION

We report that acute hyperglycaemia increases LVEF in insulin-treated patients with T2D. A smaller, nonsignificant increase in LVEF was also found in the controls during hyperglycaemia. The remaining measures of LV systolic function including global longitudinal strain, global longitudinal strain rate and s′ all increased during hyperglycaemia, although the increases were only significant for global longitudinal strain rate (controls) and s′ (both groups). All measures of LV systolic function increased significantly during hypoglycaemia. Interestingly, no interaction between group and PG level on cardiac function was observed, indicating that the effects observed in the present study are independent of diabetes status. Our findings may have important clinical implications. Currently, there are no recommendations on standardization of PG when evaluating cardiac function in patients with T2D.[9] In the present study, acute hyperglycaemia resulted in an almost five percentage points increase in LVEF in patients with T2D, which could potentially influence clinical decision-making, for example, the initiation of pharmacological treatment of heart failure.[9] Likewise, asymptomatic hypoglycaemia during echocardiographic evaluation could result in falsely elevated systolic function and underestimation of diastolic dysfunction, although hypoglycaemic symptoms, adreno-sympathetic response and changes in cardiac function are closely related.[5,10] Hence, hypoglycaemia with a clinically relevant effect on cardiac function may often be symptomatic and noticed by clinicians.

The present study adds knowledge to other studies which have indicated a potential harmful effect of acute glycaemic changes in critically ill and vulnerable patients.[11,12] Studies have indicated that targeting normal glycaemic levels in critically ill patients with diabetes increases mortality, especially in patients with elevated HbA1c levels on admission.[11,12] Although this is partly explained by an increase in hypoglycaemia,[13] a decline in cardiac systolic function due to acute glycaemic normalization—as indicated by the present study and a previous study by Goldweit et al[14]—cannot be excluded.

In a previous study in patients with T2D and healthy controls, 50 g dextrose intravenous infusion increasing PG to 27 mmol/L in the patients with T2D did not have a significant effect on LVEF.[4] However, the statistical method applied (comparing absolute means instead of change from baseline) may have masked an effect, and mean LVEF did rise from 63% to 66%, whereas it was unchanged in controls, in whom PG remained <10 mmol/L. In patients with type 1 diabetes (T1D), acute normalization of PG leads to a decline in LVEF, whereas normalization of long-term glycaemic control as evaluated by HbA1c had no effect on LVEF.[14] Together with the findings from the present study, this may indicate an impact of acute glycaemic fluctuations on LV systolic function. In a study by Nielsen et al, 9 to 12 hours of hyperglycaemia obtained by reduction of insulin dose and discontinuation of oral antidiabetics increased measures of LV systolic velocity in patients with T2D both with and without heart failure, whereas LVEF did not change.[3] Importantly, insulin levels declined during hyperglycaemia compared to the normoglycaemic day.[3] In the present study, only a small, nonsignificant increase in endogenous insulin secretion was observed during hyperglycaemia in patients with T2D, whereas it increased markedly in controls. Hence, it is unlikely that the increase in LV systolic function during hyperglycaemia found in the present study could be explained by an inotropic effect of increased endogenous insulin production. Nevertheless, LVEF as measured by radionuclide ventriculography increases at rest in patients with T2D during a hyperinsulinaemic-euglycaemic clamp and in healthy individuals following administration of intravenous insulin before reaching hypoglycaemia, and an independent effect of increased endogenous insulin secretion cannot be excluded.[15,16] However, the enhanced systolic function during hyperglycaemia is more likely to be explained by a combination of metabolic and physiological variables. Simultaneous hyperglycaemia and increased endogenous insulin secretion increases myocardial glucose extraction and myocardial glucose utilization in healthy individuals.[17] Although endogenous insulin secretion did not increase significantly in patients with T2D, it is likely that myocardial glucose extraction and utilization have increased during hyperglycaemia in the present study through a glucose mass effect.[18] This could potentially enhance LV systolic function by inducing a more energy-efficient state.[1] Importantly, glucose extraction may increase during hyperglycaemia in T2D despite an impaired ability to suppress levels of FFA.[18] Acute hyperglycaemia also increases intracellular calcium in cardiac myocytes due to increased calcium influx, potentially increasing myocardial contractility.[19] Lastly, the osmotic effect of hyperglycaemia may expand plasma volume and thereby increase preload. However, in patients with T1D, the improvement in LV contractility during hyperglycaemia could only partly be explained by plasma volume expansion.[20] Notably, all three proposed mechanisms act independently of diabetes status, which is in accordance with the observation of no interaction between group and phase.

An increase in e′ was observed in both groups during hyperglycaemia, whereas the increase in MVE was only significant in controls ($P = 0.06$ vs. $P = 0.02$), indicating improved LV relaxation and compliance.[21] Because early diastolic relaxation of the left ventricle is an active, energy-consuming process, it is likely to be enhanced by improved energy efficiency or an increase in plasma volume in a similar manner to that suggested above. Alternatively, improved systolic contraction may have led to increased restoring forces.[22] MVA also increased in controls ($P = 0.02$), which could be explained by improved atrial contractility in response to improved metabolic efficiency.[21] In patients with T2D, the increase in MVA was nonsignificant ($P = 0.07$). Nevertheless, supported by comparable numeric chances, it seems most likely that a similar effect may exist in patients with T2D.

During hypoglycaemia, all measures of LV systolic function increased markedly. Similar effects have previously been demonstrated in healthy young men, however, this is the first study to demonstrate that these effects persist in patients with T2D.[16] The increase in LV systolic function during hypoglycaemia has been demonstrated to be mediated through stimulation of cardiac beta-adrenergic receptors.[5] Accordingly, we found a marked increase in noradrenaline and heart rate during hypoglycaemia without any group difference and, in line with this, no interaction between group and phase on cardiac function. The observed decline in measures of LV diastolic function during hypoglycaemia may also be explained by a sympathetic response with an increase in heart rate, since E/A ratio is inversely related to heart rate.[23]

The present study has some limitations. Antecedent hypoglycaemia reduces neuroendocrine counterregulatory response including catecholamines, resulting in an attenuated effect on LVEF during hypoglycaemia.[10,24] Two participants experienced episodes of mild (level 1) hypoglycaemia within 48 hours prior to the experiment, potentially attenuating the increase in LV systolic function in the patients with T2D. Furthermore, four patients with T2D and one participant in the control group were unable to complete the experimental day, mainly due to vasovagal symptoms, nausea and vomiting during the decline in PG and were subsequently replaced, which could potentially have biased the data.[7] The reported changes in cardiac function during hypoglycaemia should be seen in the context of rapid glycaemic fluctuations. Nevertheless, rapid and large glycaemic fluctuations are not unusual in patients with insulin-treated T2D.[25] The use of two-dimensional echocardiography for estimation of LVEF is associated with inter- and intraobserver variability as well as temporal variability, which could be improved by a three-dimensional technique.[26] The echocardiographic examinations were all performed by the same physician and were analysed in a blinded fashion after completion of the study, which improves the reliability of the observed changes.

In conclusion, we demonstrate that LV systolic function increases during acute hyperglycaemia and acute hypoglycaemia. Notably, we did not observe any difference between patients with T2D and controls, indicating that the underlying mechanisms are independent of diabetes status. Our findings may have clinical implications because the magnitude of observed changes could affect clinical decision-making in patients with T2D and heart failure. Standardization of PG may improve reproducibility when evaluating LV systolic function in patients with T2D.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Andreas Andersen, Peter G. Jørgensen, Jonatan I. Bagger, Mikkel B. Christensen, Tommi B. Lindhardt, Gunnar Gislason, Filip K. Knop and Tina Vilsbøll designed the study and wrote the protocol. Ulrik Pedersen-Bjergaard contributed with participant recruitment. Andreas Andersen and Maria P. A. Baldassarre conducted the experiments. Andreas Andersen analysed the echocardiographies, performed the statistical analyses and wrote the first draft. All authors critically revised the manuscript and approved the final version. Andreas Andersen and Tina Vilsbøll are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the present study are not publicly available due Danish data protections laws but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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