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Direct Effects of Glucagon-Like Peptide-1 Receptor Ligands on Myocardial Function in Isolated Hearts from Streptozotocin-Induced Diabetic Rats

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Title

Direct Effects of Glucagon-Like Peptide-1 Receptor Ligands on Myocardial Function in Isolated Hearts from Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Purpose: Glucagon-like peptide-1 (GLP-1) receptor ligands are widely used for the treatment of type 2 diabetes mellitus and obesity and have demonstrated cardioprotective effects beyond glycemic control. This study investigated the direct effects of GLP-1 receptor ligands and the dipeptidyl peptidase-4 inhibitor sitagliptin on myocardial function in isolated hearts from streptozotocin-induced diabetic rats.

Methods: Diabetes was induced in male Wistar rats by a single intraperitoneal injection of streptozotocin (50 mg/kg). Hearts from control and diabetic rats were retrogradely perfused for 30 min using a Langendorff system with GLP-1 (7-36), GLP-1 (9-36), exendin-4 (1-39), sitagliptin, glimepiride, pioglitazone, or metformin. Cardiac functional parameters, plasma total and active GLP-1 concentrations and serum total antioxidant status (TAS), total oxidant status (TOS), total sulfhydryl groups (TSG), advanced oxidation protein products (AOPP), and ischemia-modified albumin (IMA) were assessed.

Results: Diabetic hearts exhibited significantly lower heart rates and impaired left ventricular contractility and relaxation, indicated by reduced left ventricular $+dP/dt_{max}$ and $-dP/dt_{min}$ values, compared with controls. GLP-1 (7-36), GLP-1 (9-36), and exendin-4 (1-39) partially improved contractility and relaxation. Compared with controls, diabetic rats exhibited significantly higher plasma total and active GLP-1 concentrations, increased serum TOS and AOPP levels, and reduced TSG levels, whereas serum TAS and IMA levels remained unchanged.

Conclusion: These findings suggest that GLP-1 receptor ligands partially improve myocardial contractility and relaxation in isolated hearts from streptozotocin-induced diabetic rats, although the mechanisms underlying these effects remain to be elucidated.

Keywords: GLP-1 receptor agonists; diabetes mellitus; myocardial function; oxidative stress; Langendorff perfusion

List of Abbreviations

AOPP: Advanced oxidation protein products, **DM:** Diabetes Mellitus, **DPP-4:** Dipeptidyl peptidase-4, **GIP:** Glucose-dependent insulinotropic polypeptide, **GLP-1:** Glucagon-like peptide-1, **GLP-1 RAs:** Glucagon-like peptide-1 receptor agonists, **IMA:** Ischemia-modified albumin, **KH:** Krebs-Henseleit, **LV:** Left ventricle, **LVDP:** Left ventricular development pressure, **LVEDP:** Left ventricular end-diastolic pressure, **LV+dP/dt$_{max}$:** The maximum rates of left ventricular pressure, **LV-dP/dt$_{min}$:** The minimum rates of left ventricular pressure, **MI:** Myocardial infarction, **RPP:** Rate-pressure product, **STZ:** Streptozotocin, **T2DM:** Type 2 diabetes mellitus, **TAS:** Total antioxidant status, **TOS:** Total oxidant status, **TSG:** Total sulfhydryl groups

1. Introduction

Diabetes mellitus (DM) is a major cardiometabolic disorder affecting approximately 589 million adults worldwide, and its global prevalence is projected to reach nearly 853 million by 2050 (Genitsaridi et al. 2026). Diabetes is associated with reduced quality of life, high morbidity and mortality, and substantial healthcare costs (Preda et al. 2024) . Patients with diabetes have a 2- to 3-fold higher risk of all-cause cardiovascular death and develop cardiovascular disease 10–15 years earlier than those without diabetes (Raghavan et al. 2019; Vetrone et al. 2019; Andreeva-Gateva et al. 2020). Individuals affected by diabetes without myocardial infarction (MI) have the same risk for coronary arterial disease as patients with MI (Bulugahapitiya et al. 2009). The risk for heart failure is increased in patients with diabetes, regardless of the presence of coronary disease and hypertension (Stratton et al. 2000). Thus, one of the major therapeutic goals of diabetes treatment must be cardiovascular risk reduction while improving glycemic control (Preda et al. 2024).

During the selection of the right drug for treating patients with type 2 diabetes mellitus (T2DM), several factors (cardiovascular disease risk, hypoglycemia, weight loss, and side effects) must be assessed, in addition to achieving glycemic regulation (Del Olmo-Garcia and Merino-Torres 2018). According to current evidence, current treatment strategies prioritize cardiovascular risk reduction in addition to glycemic control (Joshi et al. 2024). Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are glucose-lowering agents widely used for the treatment of T2DM in recent decades. Beyond glycemic control, GLP-1RAs reduce all-cause mortality and major adverse cardiovascular events in patients with T2DM (Bethel et al. 2018). Currently the American Diabetes Association (ADA) guidelines recommended GLP-1RAs for patients with T2DM and established cardiovascular disease because of their demonstrated cardiovascular benefit (Bajaj et al. 2026). However, other guidelines suggest conflicting recommendations for using the benefit-to-harm ratio of GLP-1RAs in these patients (Natale et al. 2025).

The incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are peptide hormones released from specialized entero-endocrine cells in the gut after nutrient intake (Gaggini et al. 2025). The incretin effect, impaired in patients with T2DM, is a phenomenon whereby oral glucose leads to a greater stimulation of insulin secretion than an intravenous glucose infusion, even when the same plasma glucose concentration profiles are performed (Nauck and Meier 2016). While awareness of the incretin effect for the maintenance of glucose homeostasis has increased the use of incretin-based therapies in T2DM, it is a fact that they do not actually restore the impaired incretin effect in patients with T2DM (Nauck and Meier 2016). GIP is cleaved from a precursor pro-peptide (pro-GIP) by post-translational processing in K cells located in the mucosa of the duodenum and upper jejunum (Drucker 2006), whereas GLP-1 is a post-translational cleavage product of the preproglucagon from enteroendocrine cells in the intestinal epithelium, in particular from L cells of the distal ileum and colon (Del Olmo-Garcia and Merino-Torres 2018). Both GIP and GLP-1 are physiologically degraded and inactivated by dipeptidyl peptidase-4 (DPP-4) and have a short biological lifetime. While GIP and GLP-1 have structurally similar G protein-coupled receptors, they could also exhibit their biological actions through other receptors (Joshi et al. 2024). GLP-1 (7-36 amide) is generated through the cleavage of pre-proglucagon, and the ubiquitously expressed enzyme DPP-4 generates the metabolite GLP-1 (9-36 amide), which cannot activate GLP-1R but may still exhibit other GLP-1R–independent effects in the cardiovascular system, including endothelial cells, vascular smooth muscle cells, atrial and ventricular cardiomyocytes (Marx et al. 2022).

Cardiovascular disease remains the leading cause of death in diabetes, with several mechanisms involved (Drucker 2026). While diabetes alone is considered a cardiovascular risk equivalent, clarifying the role of antidiabetics in cardiovascular pathophysiology is essential (Bertoluci and Rocha 2017). Among available medication groups, GLP-1RAs are recognized as a cornerstone in treating T2DM patients with cardiovascular disease (Sposito et al. 2018). Beyond diabetic heart failure, there are clinical studies in the literature supporting the use of GLP-1RAs also in other subtypes of heart failure due to their potential direct cardioprotective and vascular effects (Abdelhamid et al. 2025). On the other hand, mechanisms exploring the actions of the GLP-1 and/or GIP on the cardiovascular system are not entirely understood. Observations from clinical studies have shown that GLP-1RAs could reduce cardiovascular morbidity in T2DM, but in patients with severe heart failure, increasing heart rate with GLP-1RAs might not be beneficial. DPP-4 activity was associated with the risk of major adverse cardiovascular events in patients with T2DM presenting with ST-segment elevation myocardial infarction (STEMI) (Gaggini et al. 2025). But it is known that both GLP-1 and GIP raise heart rate (Nauck et al. 2021). Reliable studies on the safety and efficacy of GLP-1RAs in patients with heart failure are lacking (Marx et al. 2022).

Preclinical and clinical studies show that naturally secreted GLP-1 and GIP directly modulate cardiovascular functions via their multifaceted actions (Avogaro and Fadini 2025). In addition to their glucose-lowering effects, it was demonstrated that they have antioxidant effects in both *in vitro* and *in vivo* experimental models (Alharby et al. 2019). Several studies have demonstrated the beneficial effects of incretins on cardiovascular functions by suppressing oxidative stress (Li et al. 2017). Increased oxidative stress can lead to the development of diabetes and diabetic complications due to damage to DNA, RNA, proteins, and lipids (Oh and Jun 2017). Therefore, managing oxidative stress with GLP-1 and GIP agonisms may be a promising therapeutic strategy for improving cardiovascular functions in T2DM (Luna-Marco et al. 2024). Both GIPRs and GLP-1Rs are present in the four cardiac chambers (Müller et al. 2025; Llongueras-Espí et al. 2025). In addition, the GLP-1R is also present on the sinoatrial node (Zheng et al. 2024). Thus, studies are needed to explore the effects and underlying mechanisms of GLP-1 and GIP on the cardiovascular system in patients with heart failure (HF). Therefore, the present study investigated the direct effects of GLP-1RAs and DPP-4 inhibitor sitagliptin on myocardial function in isolated spontaneously beating hearts from streptozotocin-induced diabetic and control rats. Furthermore, we evaluated circulating GLP-1 concentrations and systemic oxidant/antioxidant status to explore their associations with cardiac function.

2. Materials and Methods

2.1. Animals

All experimental procedures were approved by the Institutional Animal Care and Use Committee of Akdeniz University Faculty of Medicine (Approval No. 2013.08.64). All animal experiments were conducted in accordance with the ARRIVE 2.0 guidelines and *Guide for the Care and Use of Laboratory Animals* (Percie du Sert et al. 2020). Adult male Wistar rats (250–300 g; 10-12 weeks of age; Akdeniz University Animal Research Center, Antalya, Turkey) were housed in stainless steel cages (4 per cage) in an air-conditioned room (22 ± 2℃; 12-h light/12-h dark cycle) and had free access to standard chow and tap water. To induce DM, rats were administered a single intraperitoneal injection of freshly prepared streptozotocin (STZ) solution (50 mg/kg) after overnight fasting. Then, they received 2% sucrose in their drinking water and standard chow (ad libitum) for the

first 48 hours after treatment to reduce the severity of the initial hypoglycemic phase following the STZ injection. After 72 hours and one week, blood glucose concentrations were measured from tail vein blood obtained using a sterile needle with test strips (Glucostix, Bayer Diagnostics) and a glucometer (Glucometer GX, Bayer Diagnostics). Weight-matched control rats were injected with STZ-vehicle (0.1 M citrate buffer). Systolic blood pressure and heart rate were measured using the Harvard Rat Tail Blood Pressure Monitor and the Harvard Universal Oscillograph at baseline, week 6, and week 12. Three consecutive measurements were obtained over a 30-min period, and their mean values were used for analysis.

2.2. Functional studies on ex vivo isolated heart preparations

Twelve weeks after STZ injection, following body weight and blood glucose measurements, rats were euthanized by cervical decapitation, and the hearts were rapidly excised and immersed in ice-cold heparinized Krebs-Henseleit (KH) buffer containing (in mM): NaCl 119, KCl 5.4, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25, EDTA 0.25, and glucose 5.0. Hearts were cannulated via the ascending aorta for retrograde perfusion at 37℃ under constant pressure (70 mmHg) using KH buffer. A left atrial incision was made to expose the mitral annulus. A distilled water-filled latex balloon was connected via polyethylene tubing to a pressure transducer (Model LS0702; MAY Systems, Turkey), which was connected to a data acquisition system (Model MP35; BIOPAC Systems Inc., Goleta, CA, USA). The balloon was then inserted into the left ventricle (LV) through the mitral valve. The initial balloon volume was set to generate a left ventricular end-diastolic pressure (LVEDP) of approximately 5 mmHg. Hearts were allowed to stabilize for 15-20 minutes before baseline recordings were obtained. Heart rate (HR) left ventricular development pressure (LVDP), LVEDP, LV $+dP/dt_{max}$, LV $-dP/dt_{min}$, and rate-pressure product (RPP) were continuously recorded. LVDP was calculated as the difference between peak systolic pressure and LVEDP. RPP was calculated as the product of LVDP and HR.

2.3. Biochemical Analyses

Blood samples were collected from the rats immediately after euthanasia into EDTA-coated tubes containing protease, esterase, and DPP-4 inhibitors, as well as into gel-barrier biochemistry tubes. Samples were centrifuged within 30 minutes of collection, and the separated plasma and serum were stored at -80 °C until biochemical analyses were performed. Total GLP-1 and active GLP-1 levels were measured using commercially available rat-specific ELISA kits (Millipore, Burlington, MA, USA) (Catalog No: EZGLP1T-36K for total GLP-1 and Catalog No: EGLP-35K for active GLP-1). Total antioxidant status (TAS) was determined using a novel automated measurement method, developed by Erel in 2004 (Erel 2004). Total oxidant status (TOS) assay was performed according to the principle that oxidants present in the sample oxidize the ferrous ion–o-dianisidine complex to ferric ion (Erel 2005). Total sulfhydryl groups (TSG) were measured spectrophotometrically using Ellman reagent (5,5'-dithiobis-2-nitrobenzoic acid) (Koster et al. 1986). Ischemia-modified albumin (IMA) measurement was performed by using the method described by Bar-Or et al. (Bar-Or et al. 2000). Advanced oxidation protein products (AOPP) level was used as a measure of oxidative stress since in vivo plasma levels of AOPP closely correlate with levels of dityrosine, a hallmark of oxidized proteins, and with pentosidine, a marker of protein glycation closely related to oxidative stress (Witko-Sarsat et al. 1996).

2.4. Drugs

STZ and glimepiride were purchased from Cayman Chemical (Ann Arbor, MI, USA). GLP-1 (7-36), GLP-1 (9-36), and exendin-4 (1-39) were obtained from Tocris. Exendin (9-39) and sitagliptin were obtained from Abcam (Cambridge, MA, USA) and AdooQ BioScience (Irvine, CA, USA), respectively. Pioglitazone and metformin were purchased from TCI Chemicals (Tokyo, Japan). The chemicals required for the KH solution were obtained from Merck (Darmstadt, Germany). GLP-1 (7-36), GLP-1 (9-36), exendin-4 (1-39), exendin (9-39), and sitagliptin were freshly prepared in distilled water. STZ was dissolved in 0.1 M citrate buffer.

2.5. Statistical Analysis

Data are presented as means ± SEM. Body weight, food intake, blood pressure, heart rate, and blood glucose were analyzed using two-way ANOVA followed by post-hoc Student's Newman-Keuls tests. Group comparisons were performed using the unpaired Student's t-test. Pearson correlation analysis was conducted to explore the correlation between the GLP-1 levels, heart rate, and systemic oxidant/antioxidant status parameters in experimental groups. A significance level of $P < 0.05$ was considered statistically significant.

3. Results

Significant interactions were detected between STZ treatment and time for body weight, food intake, and blood glucose levels (Table 1). There were significant effects of STZ treatment on body weight, food intake, and blood glucose levels but not on blood pressure between control and STZ-treated animals ($P < 0.0001$; $P < 0.0001$; $P < 0.0001$; NS, respectively) (Table 1). Body weight did not change significantly over time ($P = 0.4752$), but food intake and blood glucose levels showed a significant difference in time between controls and STZ-treated animals ($P < 0.0001$; $P < 0.0001$, respectively) (Table 1). Blood pressure and heart rate did not vary with time and/or between STZ-treated and control rats (Table 1).

Table 1. General characteristics for STZ-induced diabetic rats and age-matched controls.

Parameter	Groups	n		Weeks						
			Baseline	2nd	4th	6th	8th	10th	12th	*One way ANOVA*
Body weight, (g)	Control		238.3 ± 5.2	240.2 ± 5.9	245.3 ± 6.5	250.2 ± 6.0	258.1 ± 5.2	264.3 ± 5.1^{+}	270.3 ± 8.1^{++}	p=0.0005***
	Diabetic		236.8 ± 5.3	228.3 ± 7.2	216.6 ± 5.2	209.4 ± 6.3^{+}	200.0±5.2^{+++}	188.3±6.2^{+++}	182.2±5.7^{+++}	p< 0.0001***
	Two way ANOVA		Time: F=0,9256, p = 0,4752 Treatment: F=181,2, p < 0,0001*** Interaction (Time X Treatment): F=14,14, p < 0,0001***							
Food intake, (g/day)	Control		92.4 ± 5.8	99.5 ± 5.2	102.6 ± 6.2	104.2 ± 5.1	110.9 ± 5.3	115.3 ± 4.3^{++}	118.5 ± 3.6^{+++}	p< 0.0001***
	Diabetic		89.2 ± 18.2	109.5 ± 18.2	131.4 ± 8.2	142.6 ± 10.3^{++}	163.3±9.6^{+++}	166.4±9.9^{+++}	168.4±11.3^{+++}	p< 0.0001***
	Two way ANOVA			Time: F=8.359, p < 0,0001*** Treatment: F=39.42, p < 0,0001*** Interaction (Time X Treatment): F=2.549, p = 0.0183*						

Blood pressure, mm Hg	Control		108.2 ± 11.2	-	-	106.8 ± 10.2	-	-	102.2 ± 9.9	p=0.9154
	Diabetic		106.5 ± 11.2	-	-	103.5 ± 10.2	-	-	108.5 ± 12.2	p=0.9516
	Two way ANOVA			Time: F=0.02520, NS Treatment: F=0.001997, NS Interaction (Time X Treatment): F=0.1102, NS						
Heart rate, beats/min	Control		322.4 ± 6.3	-	-	326.6 ± 8.1	-	-	330.7 ± 10.3	p=0.7847
	Diabetic		328.9 ± 8.1	-	-	332.2 ± 9.9	-	-	324.3 ± 12.3	p=0.8594
	Two way ANOVA		Time: F=0.08082, NS Treatment: F=0.06294, NS Interaction (Time X Treatment): F=0.2972, NS							
Blood glucose, mg/dL			Baseline	72nd hour	7th day				12th week	
	Control		120.4 ± 5.1	121.9 ± 4.5	122.4 ± 5.3	-	-	-	123.5 ± 5.3	p=0.9795
	Diabetic		117.5±5.2	384.3±14.7^{+++}	402.9±16.2^{+++}	-	-	-	430.5±16.6^{+++}	p< 0.0001***
	Two way ANOVA			Time: F=99,11, p < 0,0001*** Treatment: F=827,0, p < 0,0001*** Interaction (Time X Treatment): F=96,01, p < 0,0001***						

The data were represented as mean ± S.E.M. * P < 0.05, ** P < 0.01, *** P < 0.001. $^{+}$ P < 0.05, $^{++}$ P < 0.01, $^{+++}$ P < 0.001, compared to baseline.

3.1. Effects of GLP-1 analogs, sitagliptin, and other antidiabetic agents on cardiac function parameters

Isolated heart preparations from diabetic rats exhibited significantly lower HR than those from control rats (Figs. 1-7). Perfusion of isolated heart preparations from diabetic or control rats with GLP-1 (7-36) (10^{-7} M), GLP-1 (9-36) (10^{-7} M), exendin-4 (1-39) (10^{-7} M), sitagliptin (10^{-7} M), glimepiride (10^{-5} M), pioglitazone (10^{-5} M) or metformin (10^{-3} M) for 30 min did not cause significant alterations in HR, LVDP and LVEDP (Figs. 1-7).

LV $+dP/dt_{max}$ and LV $-dP/dt_{min}$ values were lower in isolated diabetic hearts compared with control hearts (Figs. 1-7). Furthermore, GLP-1 (7-36) (10^{-7} M), GLP-1 (9-36) (10^{-7} M), or exendin-4 (1-39) (10^{-7} M) treatments resulted in significantly increased $+dP/dt_{max}$ and $-dP/dt_{min}$ values as compared with basal levels of the diabetic hearts (Figs. 1-3). There were no significant differences in $+dP/dt_{max}$ and $-dP/dt_{min}$ values with a 30-minute perfusion of sitagliptin (10^{-7} M), glimepiride (10^{-5} M), pioglitazone (10^{-5} M), and metformin (10^{-3} M) in diabetic hearts (Figs. 4-7). RPP values were lower in all diabetic hearts compared to control hearts for GLP-1 (7-36), sitagliptin, glimepiride, pioglitazone, and metformin experiments (Figs. 1, 4-7) whereas these decreases did not reach statistical significance in the GLP-1 (9-36) and exendin-4 (1-39) experiments (Figs. 2 and 3). Furthermore, RPP did not change significantly during the 30-minute perfusion period of any treatment tested (Figs. 1-7).

3.2. Correlation analysis of plasma GLP-1 levels, heart rate, and systemic oxidant/antioxidant status

Compared to control rats, diabetic rats displayed significantly higher levels of total plasma GLP-1, active plasma GLP-1, serum TOS and serum AOPP, and lower TSG levels, whereas serum TAS and IMA levels remained unchanged (Table 2). In addition, the correlation analysis results demonstrated a positive correlation between the serum AOPP and total GLP-1 levels in the control rats and a negative correlation between the total GLP-1 levels and the serum levels of TAS in diabetic rats (Table 3). Heart rate did correlated significantly with any systemic oxidant/antioxidant status parameters in either the control or diabetic group (Table 4).

Table 2. Plasma GLP-1 levels and serum oxidant/antioxidant status parameters in control and diabetic rats.

		Total GLP-1 (pM)	Active GLP-1 (pM)	TAS (μmol/l)	TOS (nmol/l)	TSG (μmol/l)	AOPP (μmol/l)	IMA (U/l)
Control	n=104	211.5 ± 107.1	29.4 ± 20.2	1799 ± 0.4	3853 ± 1.2	522.8 ± 93.7	26.14 ± 11.9	143.1 ± 30.3
Diabetic	n=85	392.1 ± 243.8	57.9 ± 58.1	1678 ± 0.5	4374 ± 1.7	411.1 ± 106.2	39.92 ± 20.1	147.3 ± 29.5
p values		p<0.0001	p<0.0001	p>0.05	p<0.05	p<0.0001	p<0.0001	p>0.05

TAS, total antioxidant status; **TOS,** total oxidant status; **TSG,** total sulfhydryl groups; **AOPP,** advanced oxidation protein products; **IMA,** ischemia-modified albumin. Data are presented as mean ± SD. P values indicate comparisons between control and diabetic groups.

Table 3. Correlation of GLP-1 levels with systemic oxidant/antioxidant status parameters of isolated whole heart preparations in control and diabetic rats.

	Control		Diabetic	
	Total GLP-1	Active GLP-1	Total GLP-1	Active GLP-1
	211.5±107	29.4±20	392.1±244[&]	57.9±58[&]
	Correlation coefficient (r)		Correlation coefficient (r)	
	0.04	0.13	-0.04	-0.18
TAS	-0.03	0.22	-0.22 *	-0.07
TOS	0.02	0.11	0.18	0.09
TSG	-0.02	-0.04	0.16	0.05
IMA	-0.04	-0.03	0.16	-0.05
AOPP	0.41 ***	0.15	0.20	0.14

TAS: total antioxidant status, **TOS:** total oxidant statues, **TSG:** total sulfhydryl groups, **IMA:** ischemia modified albumin, **AOPP:** Advanced oxidation protein products, **&**: P<0.0001 vs. control group, * P<0.05, *** P<0.0001.

Table 4. Correlations between heart rate and systemic oxidant/antioxidant status parameters in isolated whole heart preparations from control and diabetic rats.

	Control	Diabetic
	Heart rate (beat.min)	Heart rate (beat.min)
	207.4 ± 3.0 (n=72)	157.7 ± 2.9 (n=72)
	Correlation coefficient (r)	Correlation coefficient (r)
TAS	0.22	0.09
TOS	- 0.15	- 0.05
TSG	- 0.04	- 0.09
IMA	- 0.22	0.05
AOPP	- 0.01	0.04

TAS, total antioxidant status; **TOS,** total oxidant status; **TSG,** total sulfhydryl groups; **IMA,** ischemia-modified albumin; **AOPP,** advanced oxidation protein products.

4. Discussion

To our knowledge, this study provides novel evidence that GLP-1 receptor ligands exert direct myocardial effects in isolated hearts from STZ-induced diabetic rats and explores whether these effects are associated with systemic oxidant/antioxidant status. In this study, diabetes induction with STZ did not cause significant changes in the mean blood pressure or heart rate of rats over a 12-week period. Similarly, it was reported that the blood pressure and heart rate of diabetic rats did not show a statistically significant difference from those of control rats in measurements made in the 2–3 month period after diabetes induction with 65 mg/kg STZ (Homma et al. 1993). On the other hand, also in line with earlier studies, Langendorff-perfused whole heart preparations from diabetic rats were found to have significantly lower basal heart rates compared to controls (Li et al. 1989; Borges et al. 2006; Malone et al. 2007).

Regarding GLP-1, most previous studies have been conducted *in vivo* in intact animals. *In vivo*, GLP-1 has been reported to increase heart rate in rodents (Barragán et al. 1999; Yamamoto et al. 2002; Sheikh 2013). Consistently, functional GLP-1 receptor knockout mice (GLP-1R-/-) were found to have a lower resting heart rate compared to wild-types (Gros et al. 2003). However, there is limited evidence in the literature that GLP-1 and its analogs directly affect heart rate in isolated cardiac tissue; studies have generally focused on ischemia-perfusion models and on myocardial function and recovery. In an earlier ex-vivo study, it has been reported that 30 min

perfusion with KH solution containing 500 pmol/l GLP-1 did not produce a significant effect on the isolated rat heart rate under both normal and low-flow ischemic conditions (Zhao et al. 2006). Similarly, the application of 0.3 nM GLP-1 analogue lixisenatide for 2 hours did not cause a significant change in heart rate in the rat myocardial ischemia-reperfusion model (Wohlfart et al. 2013). Furthermore, infusion of isolated perfused rat heart with 20 µmol/l DPP-4 inhibitor valine pyrrolidine and GLP-1 (10^{-11}–10^{-8} mol/litter) for 30-minute did not cause a significant change in heart rate (Huisamen et al. 2008). Our data are also in agreement with other ex-vivo studies, which demonstrated that perfusion of isolated whole heart preparations obtained from control rats with GLP-1 analogs GLP-1 (7-36) (10^{-7} M), GLP-1 (9-36) (10^{-7} M), exendin-4 (1-39) (10^{-7} M) or the DPP-4 inhibitor sitagliptin (10^{-7} M) for 30 minutes did not cause a significant change in heart rate. GLP-1 (7-36) (10^{-7} M), GLP-1 (9-36) (10^{-7} M), exendin-4 (1-39) (10^{-7} M), and the DPP-4 inhibitor sitagliptin (10^{-7} M) did not produce a statistically significant change in heart rate in isolated whole heart preparations from diabetic and control rats. In contrast, Axelsen et al. demonstrated that the addition of the GLP-1 agonist ZP131 to the perfusion buffer at concentrations of 10, 50 and 100 nM did not produce a significant change in heart rate in isolated perfused heart preparations obtained from control rats, but a significant increase in heart rate compared to baseline values was observed in insulin-resistant rats only with ZP131 at a concentration of 100 nM (Axelsen et al. 2012). This discrepancy may be due to differences in experimental diabetic models and/or GLP-1 analogs used in these studies. Further experimental studies are needed to confirm and to explain these diverse results from experimental diabetic rat whole heart specimens.

Studies performed on isolated papillary muscle and perfused whole heart preparations have shown that diabetic cardiomyopathy is associated with impaired systolic performance and left ventricular relaxation (Litwin et al. 1990). In this study, measurements performed on isolated whole heart preparations obtained from control and diabetic animals showed that 12 weeks of diabetes resulted in impaired cardiac contractility (left ventricular $+dP/dt_{max}$) and relaxation (left ventricular $-dP/dt_{min}$); however, no significant difference was observed between isolated whole hearts from diabetic and control rats in terms of LVDP and LVEDP values (Fig 1-7). In line with our study results, it has been reported that peak systolic pressure in isolated whole heart preparations of diabetic rats is not different from control hearts, but maximal and minimal dP/dt are significantly lower in diabetic hearts compared to control hearts (Okayama et al. 1994; De Angelis et al. 2000). In the present study, we have also demonstrated that perfusion of isolated whole heart preparations with GLP-1 (7-36) (10^{-7} M), GLP-1 (9-36) (10^{-7} M) and exendin-4 (1-39) (10^{-7} M) for 30 minutes resulted in statistically significant increases in left ventricular maximal and minimal dP/dt values in diabetic isolated whole heart preparations (Figures 1-3). The increases observed in minimal dP/dt with GLP-1 (7-36) and GLP-1 (9-36) reached the values observed in the control hearts (Figures 1 and 2). A similar increase was not observed in isolated whole heart preparations obtained from control and diabetic group rats perfused with sitagliptin (10^{-7} M), glimepiride (10^{-5} M), pioglitazone (10^{-5} M), or metformin (10^{-3} M) (Figures 4-7).

The significant differences between the RPP values in the isolated whole heart preparations of DM and control rats were found to be mainly due to the significant differences in heart rate between the control and diabetes rats, since no significant differences were observed in LVDP values between the two groups in our study (Figures 1-7). Similarly, we found no significant changes in RPP by GLP-1 analogs between the control and diabetic hearts. However, GLP-1 has been reported to reduce myocardial contractility in isolated rat ventricular myocytes (Vila Petroff et al. 2001) and isolated rat whole heart preparations (Zhao et al. 2006). On the other hand, in a regional

ischemia model in rats, GLP-1 infusion caused neither significant alterations in ventricular function (Bose et al. 2005) nor led to improvement (Zhao et al. 2006). In a different species, dogs, GLP-1 infusion has been reported to cause improvement in left ventricular systolic function in dilated cardiomyopathy, but a similar effect was not observed in normal dogs (Nikolaidis et al. 2004). The results of studies on the myocardial function parameters of GLP-1 may vary depending on the pathological model and animal species. Although the mechanism behind the observed positive effect of GLP-1 analogs on cardiac contractility and relaxation in diabetic animals has not been elucidated, it could be explained by an increase in myocardial cAMP (Green et al. 2008) and nitric oxide (Zhao et al. 2006) that GLP-1 analogs may induce via GLP-1 receptors, which may contribute in the observed effects.

A meta-analysis of clinical studies on the cardiovascular effects of antidiabetic drugs reported that different GLP-1 agonists may have varying degrees of effect on heart rate, that the heart rate-increasing effects of these agents may vary depending on the patients' basal heart rates, and that the highest increases were observed in patient subgroups with the lowest basal values (Robinson et al. 2013). Consistently, our previous study in isolated atrial preparations showed that different GLP-1 analogs caused varying degrees of increase in heart rate; conversely, the maximal effects of GLP-1 (7-36), GLP-1 (9-36), and exendin-4 (1-39) on heart rate were found to be quite similar in the diabetic rats with lower basal heart rates and the control rats. It has been suggested that some of the variability observed in the effects of GLP-1 analogs on heart rate in clinical studies may be attributable to concomitant antidiabetic treatments (Robinson et al. 2013). Metformin, commonly used to treat diabetes, has been reported to affect cardiac function in insulin-resistant rats (Apaijai et al. 2012). Therefore, in the present study we also investigated the effects of antidiabetic agents such as metformin, pioglitazone, and glimepiride on isolated whole heart preparations from diabetic and control rats. Metformin and pioglitazone did not alter heart rate, consistent with our results in isolated diabetic rat atrium preparations. However, sitagliptin and glimepiride increased heart rate in isolated diabetic rat atrium preparations, while they did not have a significant effect on heart rate in isolated whole heart preparations from both control and diabetic animals. Results from current clinical and experimental studies suggest that reflex mechanisms may also play a role in the effects of both GLP-1 analogs and other antidiabetic drugs on heart rate, and that these effects need to be clarified through further studies.

GLP-1 signaling is glucose-dependent. The organism minimizes the risk of hypoglycemia by reducing insulin secretion during the transition from a hyperglycemic to an euglycemic state using the GLP-1 pathway. Hyperglycemia increases reactive oxygen species in ex vivo hypothalamic sections, and antioxidants reverse this effect (Cani et al. 2007). In the present study, oxidative stress parameters TOS and AOPP were significantly higher in diabetic compared to control animals, indicating increased oxidative stress in diabetic rats. The significant decrease in TSG levels and the lack of a significant difference in TAS levels between the groups supported the view that the 12-week diabetes period causes a certain degree of decrease in antioxidant capacity secondary to increased oxidative stress, although this was not reflected in the total antioxidant capacity of rats. Three months of diabetes has also been reported to cause similar changes in oxidant status in rat hearts (Wohaieb and Godin 1987). Taken together, the current findings suggested that the direct myocardial effects of GLP-1 receptor ligands and sitagliptin on heart rate in isolated whole heart preparations did not have a specific relationship with serum total GLP-1, active GLP-1, and systemic oxidant/antioxidant status parameters. However, significant relationships observed between the GLP-1 analogs and the parameters examined under specific conditions require further investigation in further studies.

GLP-1RAs have been repositioned from diabetes and obesity drugs to multifaceted cardiometabolic treatments with increasing evidence on HF. Clinical trials now provide the comprehensive evidence to date supporting the use of GLP-1RAs in HF patients with or without T2DM. To our knowledge, this study is the first to investigate the direct myocardial effects of GLP-1 receptor ligands and the DPP-4 inhibitor sitagliptin in isolated hearts from STZ-induced diabetic rats while also examining their relationship with circulating GLP-1 concentrations and systemic oxidant/antioxidant status. Our findings demonstrate that GLP-1 receptor ligands partially restored impaired myocardial contractility and relaxation in diabetic hearts, whereas sitagliptin and the other antidiabetic agents tested did not produce comparable direct myocardial effects. These beneficial effects were not associated with circulating GLP-1 concentrations or systemic oxidant/antioxidant status, suggesting that local cardiac mechanisms may contribute to the cardioprotective actions of GLP-1 receptor ligands. Further studies are warranted to elucidate the intracellular pathways underlying these direct myocardial effects.

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Statements and Declarations

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Conflicts of Interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

CRediT authorship contribution statement

Esra Akcabag: Investigation, Formal analysis, Writing – original draft. **Zinnet Sevval Aksoyalp and Feride Oner:** Investigation, Formal analysis. **Zeliha Bayram:** Formal analysis. **Gul Ozbey:** Formal analysis, Writing – review and editing. **Cahit Nacitarhan:** Software. **Sebahat Ozdem:** Methodology. **Arda Tasatargil:** Supervision. **Sadi S. Ozdem:** Conceptualization, Methodology, Validation, Supervision, Formal analysis, Software, Writing – review and editing. All authors read and approved the final manuscript.

Ethics approval

All applicable international, national, and institutional guidelines for the care and use of animals were followed. The experimental protocol was approved by the **Akdeniz University Local Animal Ethics Committee** (Protocol no. 2013.08.64).

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Figure Captions

Fig. 1. Effects of GLP-1 (7–36) on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). GLP-1, glucagon-like peptide-1. *P < 0.05 vs. control; #P < 0.05 vs. DM baseline.

Fig. 2. Effects of GLP-1 (9–36) on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). GLP-1, glucagon-like peptide-1. *P < 0.05 vs. control; #P < 0.05 vs. DM baseline.

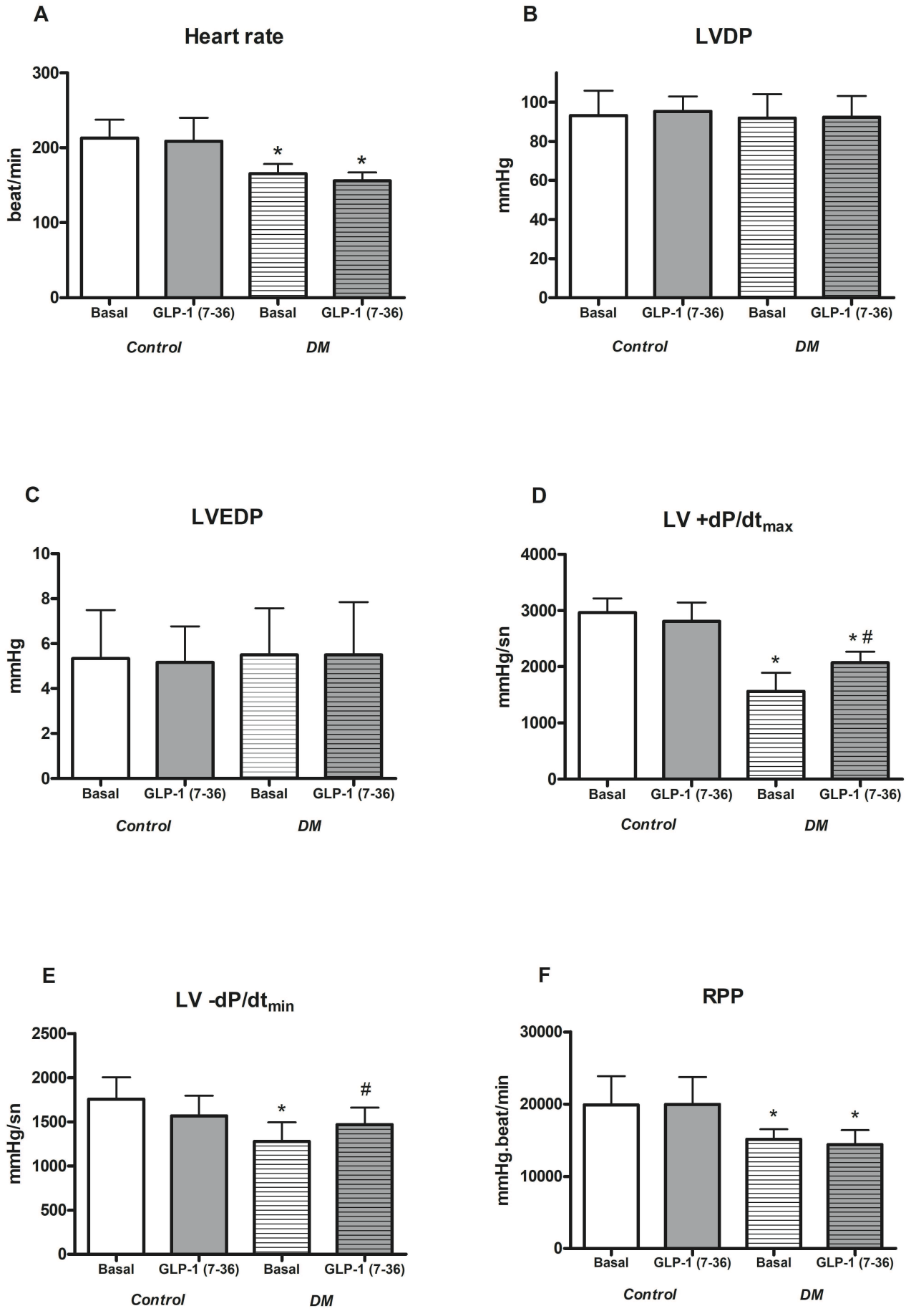
Fig. 3. Effects of exendin-4 (1–39) on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). EXE-4 (1–39), exendin-4 (1–39). *P < 0.05 vs. control; #P < 0.05 vs. DM baseline.

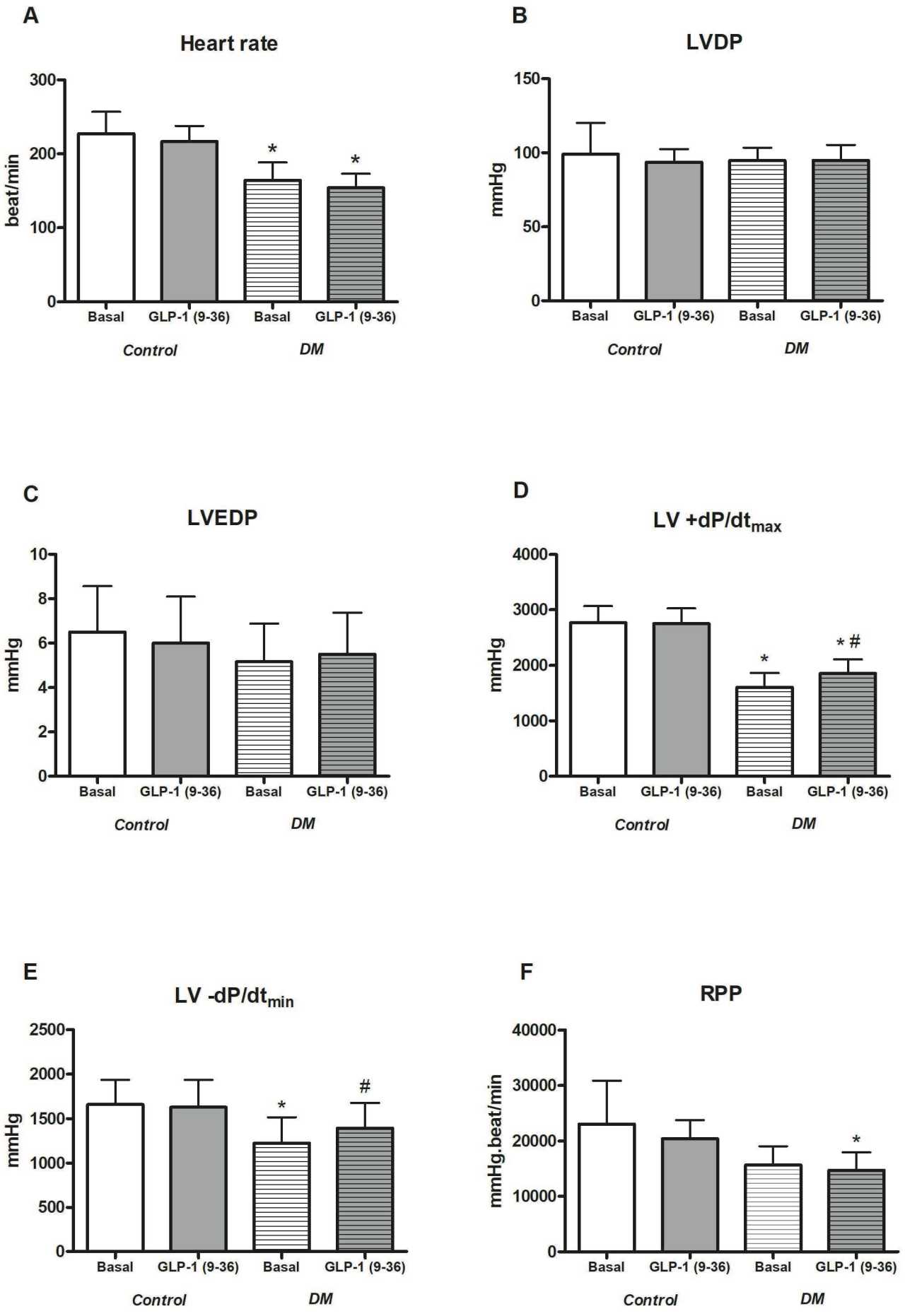
Fig. 4. Effects of sitagliptin on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). *P < 0.05 vs. control.

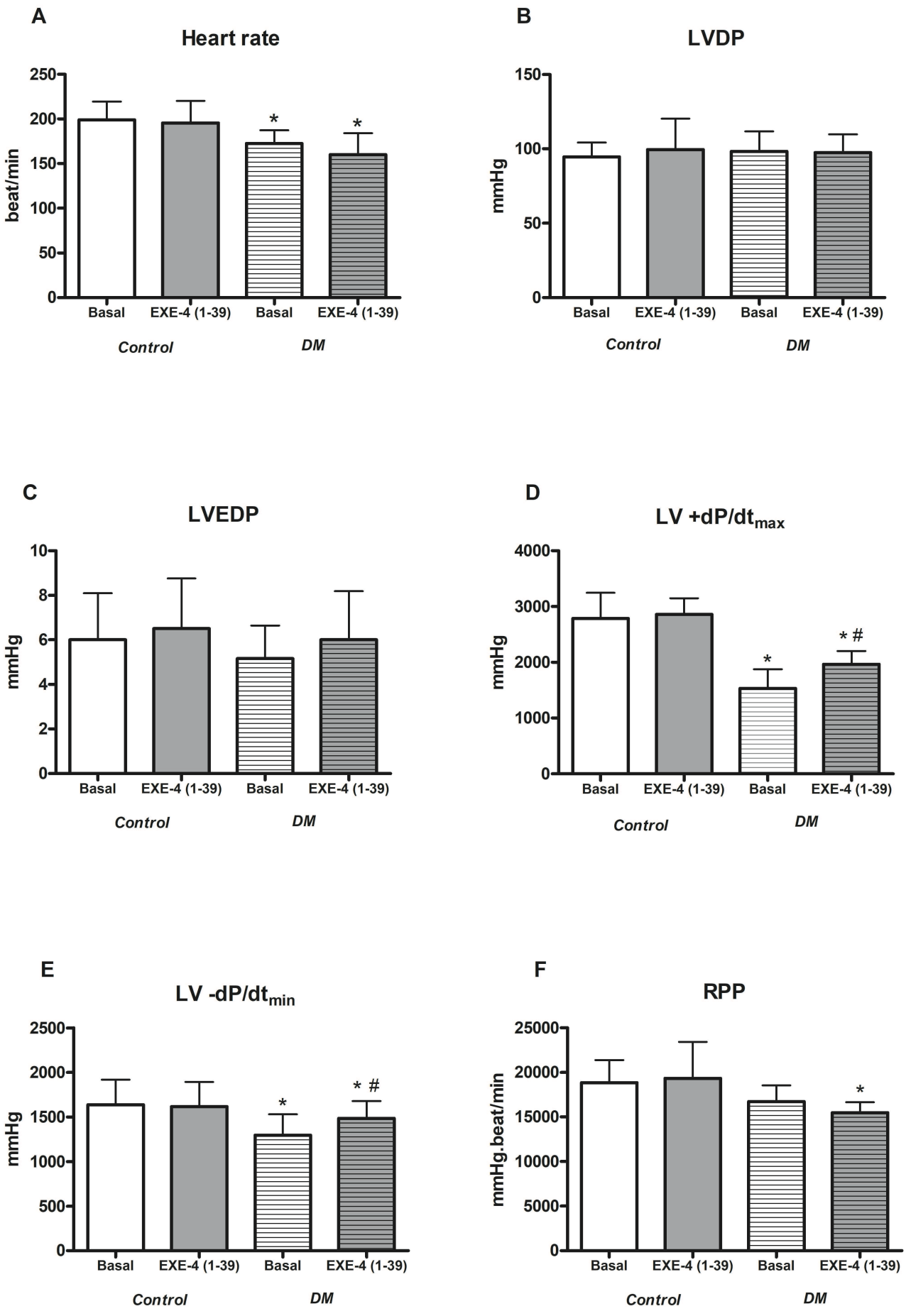
Fig. 5. Effects of glimepiride on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). *P < 0.05 vs. control.

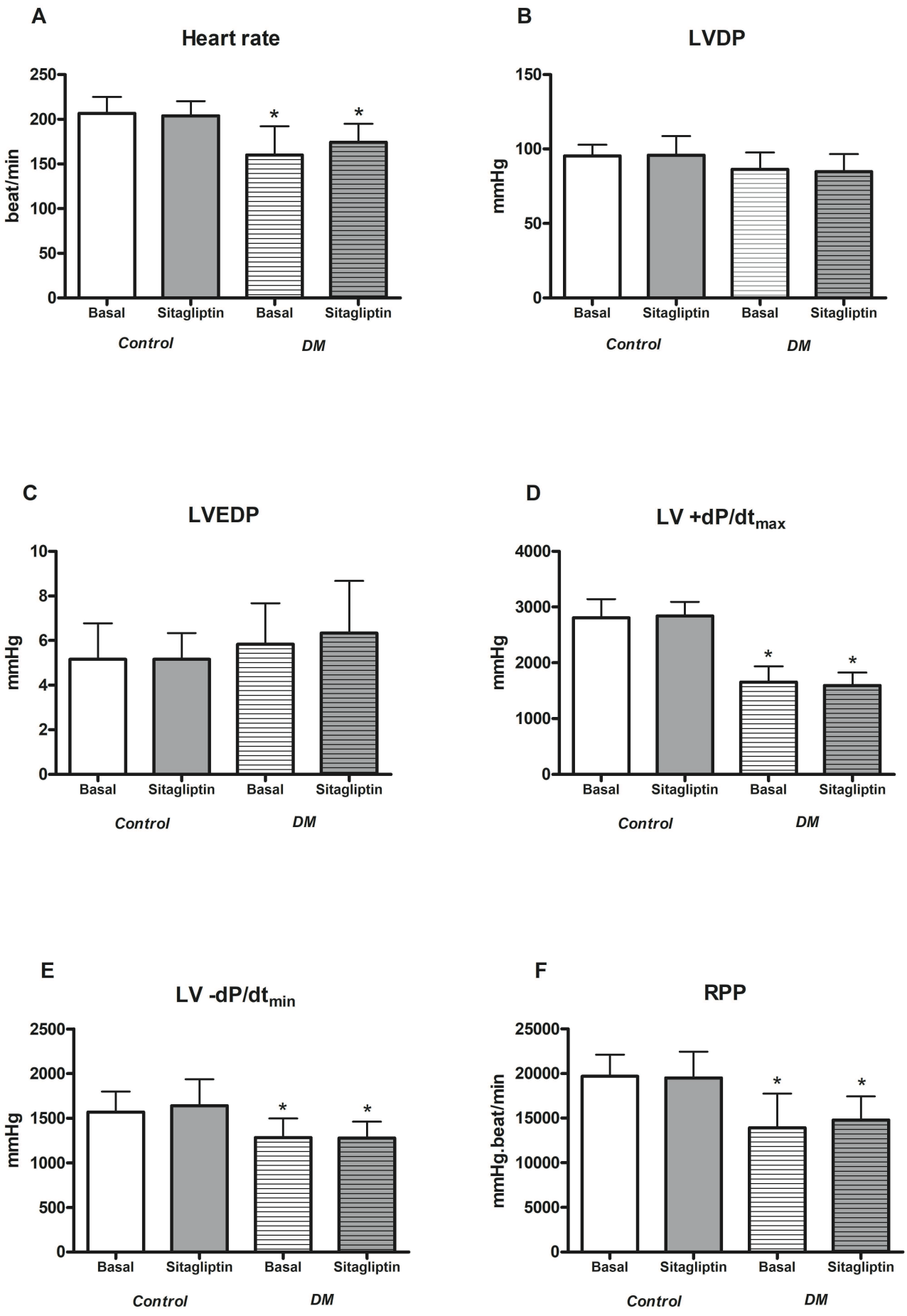
Fig. 6. Effects of pioglitazone on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). *P < 0.05 vs. control.

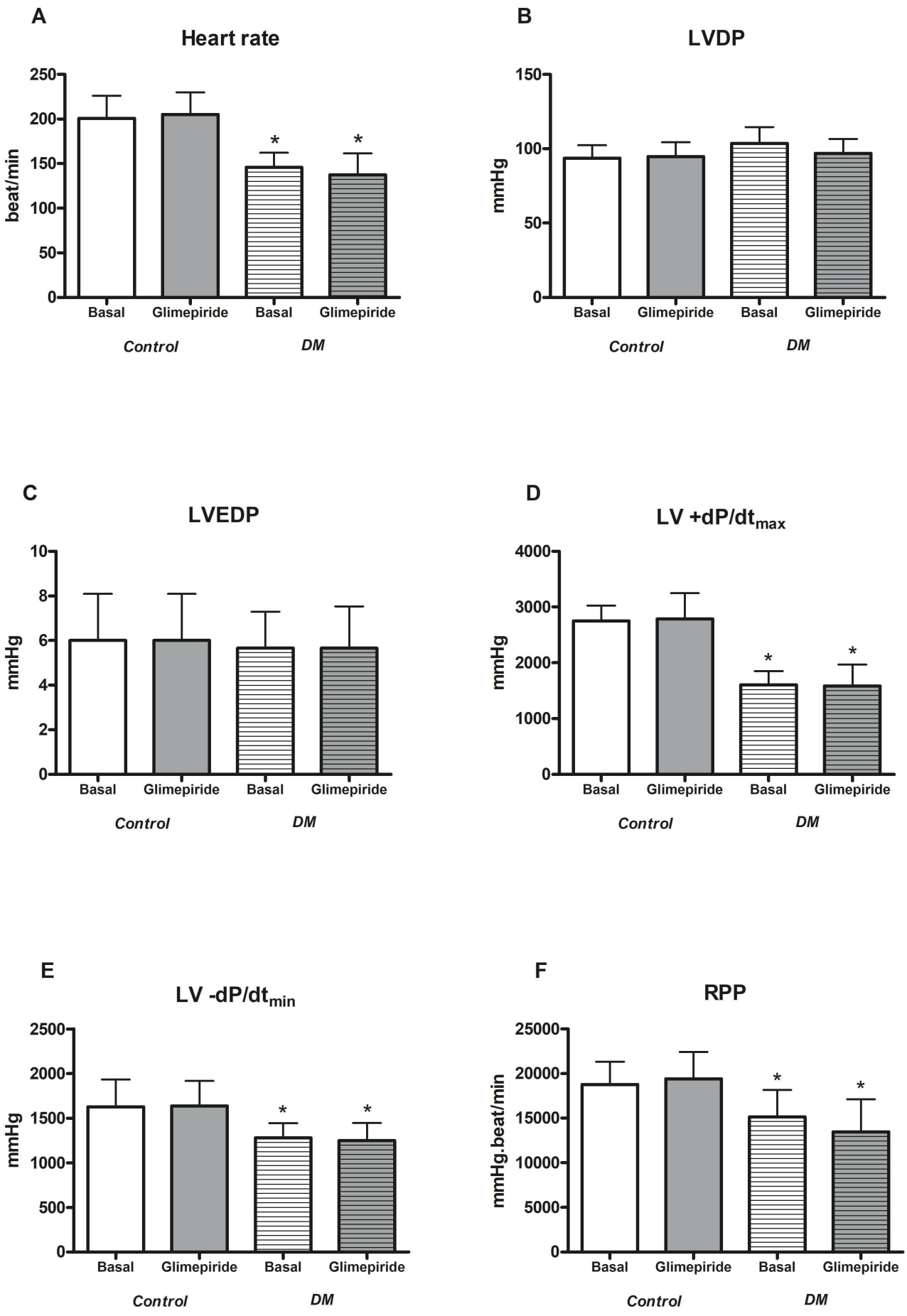
Fig. 7. Effects of metformin on myocardial function in isolated rat hearts. Responses in isolated perfused hearts from control and diabetic (DM) rats: (A) heart rate (HR); (B) left ventricular developed pressure (LVDP); (C) left ventricular end-diastolic pressure (LVEDP); (D) maximum rate of left ventricular pressure change (LV $+dP/dt_{max}$); (E) minimum rate of left ventricular pressure change (LV $-dP/dt_{min}$); and (F) rate-pressure product (RPP = LVDP × HR). *P < 0.05 vs. control.

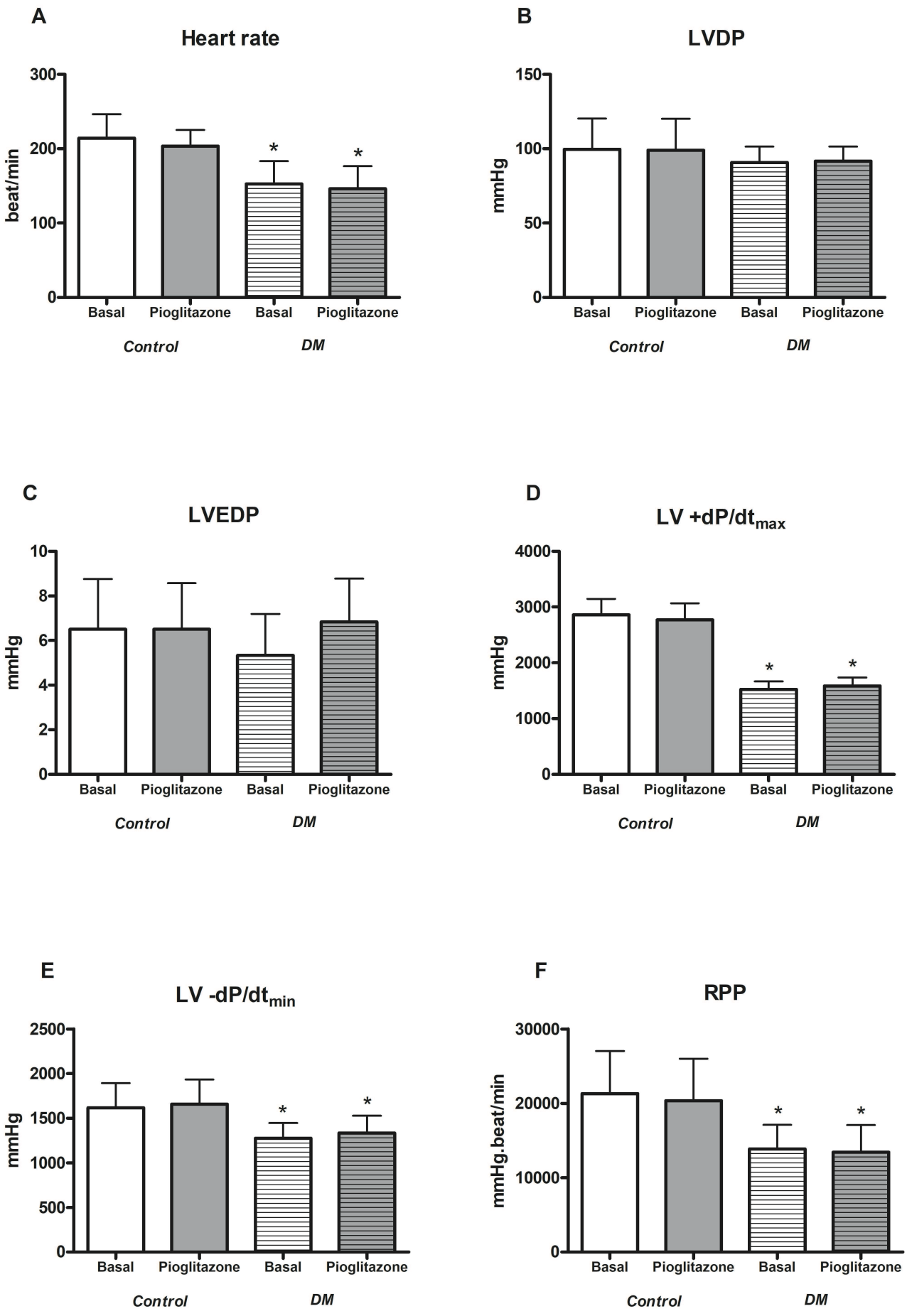

A
Heart rate
beat/min
300
200
100
0
*
*
Basal
GLP-1 (7-36)
Basal
GLP-1 (7-36)
Control
DM
B
LVDP
mmHg
100
80
60
40
20
0
Basal
GLP-1 (7-36)
Basal
GLP-1 (7-36)
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
GLP-1 (7-36)
Basal
GLP-1 (7-36)
Control
DM
D
LV +dP/dtmax
mmHg/sn
4000
3000
2000
1000
0
*
* #
Basal
GLP-1 (7-36)
Basal
GLP-1 (7-36)
Control
DM
E
LV -dP/dtmin
mmHg/sn
2500
2000
1500
1000
500
0
*
#
Basal
GLP-1 (7-36)
Basal
GLP-1 (7-36)
Control
DM
F
RPP
mmHg.beat/min
30000
20000
10000
0
*
*
Basal
GLP-1 (7-36)
Basal
GLP-1 (7-36)
Control
DM

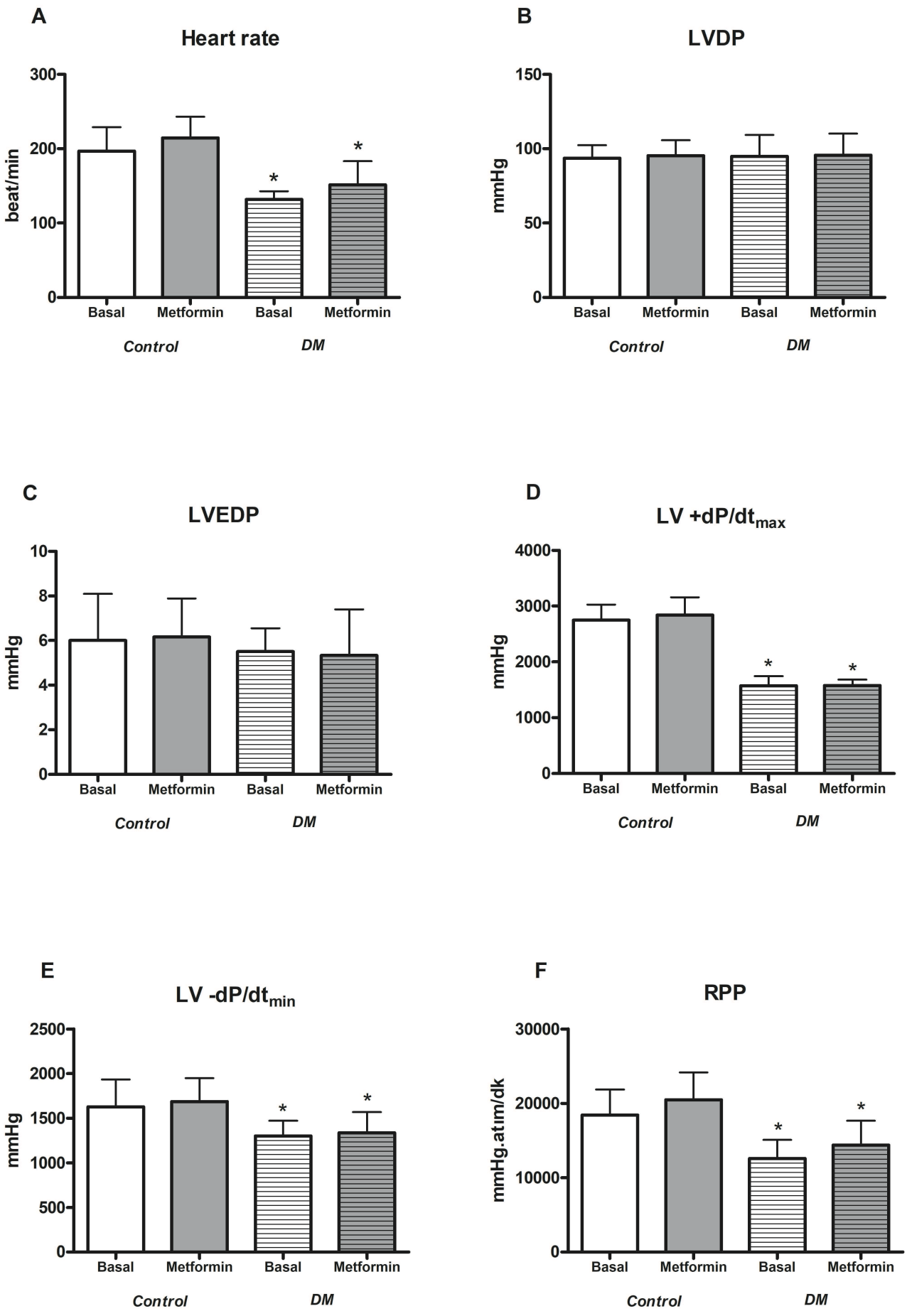

A
Heart rate
beat/min
300
200
100
0
*
*
Basal
GLP-1 (9-36)
Basal
GLP-1 (9-36)
Control
DM
B
LVDP
mmHg
150
100
50
0
Basal
GLP-1 (9-36)
Basal
GLP-1 (9-36)
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
GLP-1 (9-36)
Basal
GLP-1 (9-36)
Control
DM
D
LV +dP/dtmax
mmHg
4000
3000
2000
1000
0
*
*#
Basal
GLP-1 (9-36)
Basal
GLP-1 (9-36)
Control
DM
E
LV -dP/dtmin
mmHg
2500
2000
1500
1000
500
0
*
#
Basal
GLP-1 (9-36)
Basal
GLP-1 (9-36)
Control
DM
F
RPP
mmHg.beat/min
40000
30000
20000
10000
0
*
Basal
GLP-1 (9-36)
Basal
GLP-1 (9-36)
Control
DM


A
Heart rate
beat/min
250
200
150
100
50
0
*
*
Basal
EXE-4 (1-39)
Basal
EXE-4 (1-39)
Control
DM
B
LVDP
mmHg
150
100
50
0
Basal
EXE-4 (1-39)
Basal
EXE-4 (1-39)
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
EXE-4 (1-39)
Basal
EXE-4 (1-39)
Control
DM
D
LV +dP/dtmax
mmHg
4000
3000
2000
1000
0
*
* #
Basal
EXE-4 (1-39)
Basal
EXE-4 (1-39)
Control
DM
E
LV -dP/dtmin
mmHg
2500
2000
1500
1000
500
0
*
* #
Basal
EXE-4 (1-39)
Basal
EXE-4 (1-39)
Control
DM
F
RPP
mmHg.beat/min
25000
20000
15000
10000
5000
0
*
Basal
EXE-4 (1-39)
Basal
EXE-4 (1-39)
Control
DM


A
Heart rate
beat/min
250
200
150
100
50
0
*
*
Basal
Sitagliptin
Basal
Sitagliptin
Control
DM
B
LVDP
mmHg
150
100
50
0
Basal
Sitagliptin
Basal
Sitagliptin
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
Sitagliptin
Basal
Sitagliptin
Control
DM
D
LV +dP/dtmax
mmHg
4000
3000
2000
1000
0
*
*
Basal
Sitagliptin
Basal
Sitagliptin
Control
DM
E
LV -dP/dtmin
mmHg
2500
2000
1500
1000
500
0
*
*
Basal
Sitagliptin
Basal
Sitagliptin
Control
DM
F
RPP
mmHg.beat/min
25000
20000
15000
10000
5000
0
*
*
Basal
Sitagliptin
Basal
Sitagliptin
Control
DM


A
Heart rate
beat/min
250
200
150
100
50
0
*
*
Basal
Glimepiride
Basal
Glimepiride
Control
DM
B
LVDP
mmHg
150
100
50
0
Basal
Glimepiride
Basal
Glimepiride
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
Glimepiride
Basal
Glimepiride
Control
DM
D
LV +dP/dtmax
mmHg
4000
3000
2000
1000
0
*
*
Basal
Glimepiride
Basal
Glimepiride
Control
DM
E
LV -dP/dtmin
mmHg
2500
2000
1500
1000
500
0
*
*
Basal
Glimepiride
Basal
Glimepiride
Control
DM
F
RPP
mmHg.beat/min
25000
20000
15000
10000
5000
0
*
*
Basal
Glimepiride
Basal
Glimepiride
Control
DM


A
Heart rate
beat/min
300
200
100
0
*
*
Basal
Pioglitazone
Basal
Pioglitazone
Control
DM
B
LVDP
mmHg
150
100
50
0
Basal
Pioglitazone
Basal
Pioglitazone
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
Pioglitazone
Basal
Pioglitazone
Control
DM
D
LV +dP/dtmax
mmHg
4000
3000
2000
1000
0
*
*
Basal
Pioglitazone
Basal
Pioglitazone
Control
DM
E
LV -dP/dtmin
mmHg
2500
2000
1500
1000
500
0
*
*
Basal
Pioglitazone
Basal
Pioglitazone
Control
DM
F
RPP
mmHg.beat/min
30000
20000
10000
0
*
*
Basal
Pioglitazone
Basal
Pioglitazone
Control
DM


A
Heart rate
beat/min
300
200
100
0
*
*
Basal
Metformin
Basal
Metformin
Control
DM
B
LVDP
mmHg
150
100
50
0
Basal
Metformin
Basal
Metformin
Control
DM
C
LVEDP
mmHg
10
8
6
4
2
0
Basal
Metformin
Basal
Metformin
Control
DM
D
LV +dP/dtmax
mmHg
4000
3000
2000
1000
0
*
*
Basal
Metformin
Basal
Metformin
Control
DM
E
LV -dP/dtmin
mmHg
2500
2000
1500
1000
500
0
*
*
Basal
Metformin
Basal
Metformin
Control
DM
F
RPP
mmHg.atım/dk
30000
20000
10000
0
*
*
Basal
Metformin
Basal
Metformin
Control
DM