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Hemodynamics and Cardiac Contractile Function in Type 1 Diabetes

Aim	To study diastolic (DDF) and systolic (SDF) dysfunction in streptozotocin (STZ)-induced type 1 diabetes mellitus (DM).
Material and Methods	Cardiac hemodynamics was studied in Wistar male rats at one week following STZ administration (60 mg/kg) or at two weeks following the administration of STZ 30 mg/kg.
Results	In all rats, the concentration of blood glucose increased 5–6 times, to 27–31 mM. Echocardiographic data showed that approximately one third of diabetic animals had SDF and the rest of them had DDF with 1.5-fold prolonged isovolumic relaxation time. Left ventricular (LV) catheterization using a transducer that allowed simultaneous measurements of LV pressure and volume, detected a decrease in the minute volume by 25-31% and in the peak ejection velocity by 34–50%. However, the LV developed pressure, its maximal velocity of rise and blood pressure remained within the range of control values. Apparently, the decreases in peak ejection velocity in both groups were due to the increased arterial wall stiffness, since they showed a negative correlation (r=–0.70). DDF was observed in the hearts with a significantly lower (22%) diastolic volume compared to the hearts with SDF.
Conclusion	The decrease in LV volume allows preservation of a normal ejection fraction in type 1 DM.
Keywords	Diabetes mellitus; heart; contractility; diastolic volume; pressure
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Introduction

Cardiomyopathy of various origins figures prominently among various causes of chronic heart failure (CHF). Cardiomyopathies differ either in etiology (ischemia, doxorubicin, diabetes mellitus (DM)) or in form (hypertrophic, dilated, systolic, diastolic). Ischemic, doxorubicin-induced, isoproterenol-induced cardiomyopathy corresponds to the classical concept of cardiomyopathy as myocardial weakness. In these types of cardiomyopathies, CHF result from damage to mitochondria and disrupted energy metabolism of cardiomyocytes [1, 2]. Diabetic cardiomyopathy is characterized by the limited use of glucose, which causes the transition of energy metabolism almost exclusively to the use of fatty acids as the main source of energy [3]. Despite an adequate oxygen supply to the myocardium, systolic dysfunction (SD) and diastolic dysfunction (DD) naturally develop in DM with reduced heart rate (HR), maximum LV pressure and its change over time, and slowing of the relaxation [4–7]. However, it is still unclear what causes the development of CHF in the absence of ischemic damage to cardiomyocytes in the diabetic heart [2]. In this regard, the objective of this work was to study circulatory dynamics, contractile and pumping function of the heart in a model of DM type 1 characterized by very high levels of glucose in the blood.

Material and methods

Thirty male Wistar rats weighing 306–388 g were used in the study. The study was conducted following Directive 2010/63/EU of the European Parliament and the Council of Europe dated 22 September 2010 on the protection of animals used for scientific purposes. The administration of streptozotocin, which damages insulin-producing pancreatic cells, is classic DM type 1 model. After the first series of experiments (streptozotocin 60 mg/kg, experiment after 2 weeks), echocardiography showed that almost all rats had SD (reduced left ventricular ejection fraction (LVEF)) [8]. Two series (10 rats each) were carried out in this study to obtain DD, in one of which the experiments were performed in 1 week after the administration of the same dose of streptozotocin, and in the other series, the dose was reduced twice (30 mg/kg), but the period was extended to 2 weeks. At the same time, LVEF remained normal in most experiments, but slowing of LV relaxation characteristic of DD was observed. The results of these series were pooled; the control group was formed by 10 rats injected with isotonic sodium chloride solution.

All rats were subjected to transthoracic echocardiography using the FUJIFILM VisualSonic Vevo 1100 ultrasound system under zoletil anesthesia (5 mg/kg). A linear sensor 24–13 MHz with the maximum location depth of 30 mm

was used. In the acute experiment, LV catheterization was performed under the same anesthesia with FTH-1912B-8018 PV catheter inserted in the LV through the right carotid artery and ADV500 system (Transonic, Canada). The animals were then transferred to inhaled isoflurane (0.1–0.5%) anesthesia using the SomnoSuite Kent Scientific system to better control the depth of anesthesia and heart rate. Physiological parameters were further measured under this anesthesia.

Signals were analyzed at baseline in a fragment with multiple (600 to 2,000 times) records of parameters, which were used to automatically calculate the mean values of the parameters characterizing LV function in LabChart 8.1. The fasting levels of glucose in the tail vein blood was measured with a OneTouch Select Plus Flex glucose meter before the injection of streptozotocin and 1 and 2 weeks after the injection.

The findings were statistically processed using computational algorithms available in GraphPad Prism (version 9.1.0). This statistical software suite allows an effective analysis of the results of multiple comparisons using both analysis of variance (ANOVA) with F-test and Brown-Forsythe test and the evaluation of significance of differences in mean values of the measured parameters, including considering the multiplicity of comparisons. The results are expressed as M±SE (mean and standard error of mean). Dannet's T3 test was used to compare parameters between all three experimental groups. The normality of distribution of the parameters measured was confirmed by using the Kolmogorov-Smirnov and D'Agostino-Pearson tests.

Results

The baseline fasting blood glucose levels were 5.1–5.5 mmol/L. It was 27.0±1.8 mmol/L in streptozotocin rats in a week and 31.2±1.5 mmol/L in two weeks, however, it did not change in control rats. Body weight of rats was 368±9 g after 1 week of administering streptozotocin 60 mg/kg, and 306±8 g after two weeks of 30 mg/kg. Body weight of the control rats was 380±9 g.

LV echocardiography showed approximately two thirds of rats had LVEF and LV end-diastolic volume at the control levels (Table 1), but differed from the control animals by a significant slowing of relaxation, which is typical of DD.

LV catheterization revealed heart failure with reduced cardiac output and stroke work by 26–31% and increased LV diastolic pressure in all diabetic rats (Table 2, 3). At the same time, the indicators of LV contractility in rats with normal or reduced LVEF (maximum change in LV pressure over time and contractility index calculated as a quotient of the maximum change in pressure over time divided by the value of pressure at the time of the peak velocity (Table 2, 3) did not differ from the control values, and a decrease in the maximum LV ejection rate by 34% can be explained by a 32% increase in arterial wall stiffness. The calculation of the ratio between these indicators in all experimented groups showed negative feedback with a correlation coefficient of –0.70 (Figure 1). One experiment was unsuccessful in the DD group, the animal's heart fibrillated when a catheter was inserted, and resuscitation was unsuccessful.

The main hemodynamic indicators of the hearts with SD (cardiac output, stroke work, developed pressure, arterial wall elasticity) did not differ from the similar values in the DD group. The main difference between these groups, which differed in LVEF, was in end-diastolic volume. In the SD group, it was comparable with the control, and in the DD group, it was significantly lower not only compared to the SD group, but also to the control, by 16% (Figure 2; Table 2).

Discussion

The results of our study are generally consistent with the findings of other researchers. In one of the studies on conscious rats, HR, LV systolic pressure and maximum changes in pressure over time were the same in 1 week, but decreased in 4 weeks [4], and in another study, a decrease in these indicators was observed in 2 weeks [5]. This period allows determining the actual pathogenetic factors, while the mechanisms of long-term adaptation will be implemented in 2–3 months.

Our findings showed that cardiac dysfunction in DM is fundamentally different from isoproterenol-induced [1] or doxorubicin-induced [2] cardiomyopathy. These factors

Table 1. Echocardiographic indicators of diabetic heart after 1–2 week administration of streptozotocin

Parameter	Control	DD	SD
Number of experiments	10	13	7
HR, bpm	444±37	420±13	443±60
LVEDV, mL	0,43±0,08	0,40±0,09	0,46±0,07
LVEF, %	74±7	70±5	54±4**
Isovolumic relaxation time, ms	14±1	20±3**	22±5*

* – p<0.05, ** – p<0.01 versus the control. DD, diastolic dysfunction; SD, systolic dysfunction;
HR, heart rate; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

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Table 2. Circulatory dynamics of the heart after 1–2 week administration of streptozotocin

Parameter	Control	DD	SD
Number of animals	10	9	10
Cardiac output, mL/min	112±17	84±21*	77±15**
HR, bpm	351±21	327±25	338±22
LVEDV, mL	0.43±0.07	0.36±0.07*	0.46±0.11#
LVESV, mL	0.15±0.05	0.10±0.02*	0.23±0.09*.##
LVEF, %	70±7	71±5	52±9*.#
Peak ejection rate, mL/s	11.5±2.1	7.6±1.5*	5.8±1.3**.#
Stroke work, mm Hg·mL	36.3±5.6	30.0±2.5	26.8±7.1*
Maximum LV pressure, mm Hg	128±8	122±12	122±15
Peak LV filling velocity, mL/s	11.0±2.4	9.0±2.3	7.6±2.4
Ea, mm Hg/μL	0.37±0.06	0.49±0.13*	0.56±0.09**
P (dP/dt max), mm Hg	91±10	86±12	89±13

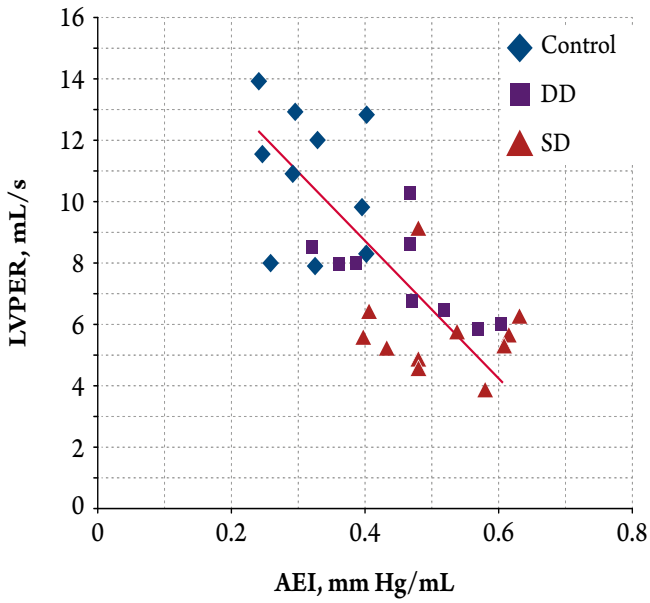
* – $p < 0.05$, ** – $p < 0.01$ versus the control; # – $p < 0.05$; ## – $p < 0.01$ versus DD. DD, diastolic dysfunction; SD, systolic dysfunction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

Table 3. Left ventricular contractility after 1–2 week administration of streptozotocin

Parameter	Control	DD	SD
Number of animals	10	9	10
Maximum rate of LV pressure rise, mm Hg/s	11010±2280	9770±2520	10210±2510
Contractility index, s^{-1}	116±21	113±26	118±23
Maximum rate of LV pressure decrease, mm Hg/s	9360±1280	9740±2920	8370±3040
Relaxation time constant (tau), ms	7.6±1.4	7.9±1.5	8.7±1.8
Minimum LV pressure, mm Hg	0.4±1.0	2.2±2.0*	3.2±2.2**
LVEDP, mm Hg	3.3±1.2	4.9±1.8*	6.6±2.9**

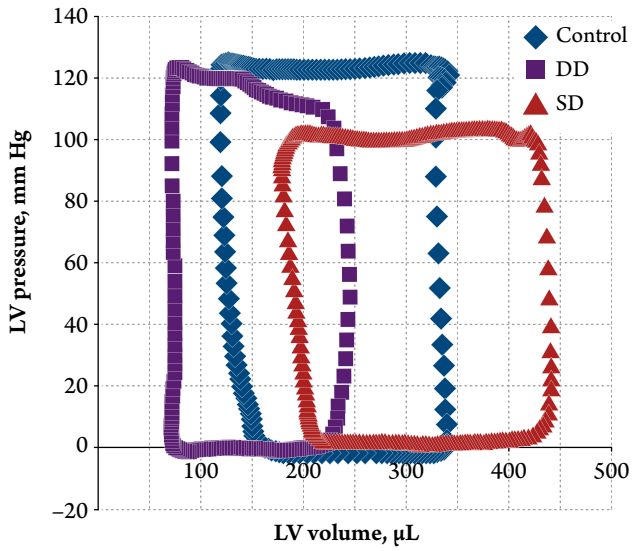
* – $p < 0.05$, ** – $p < 0.01$ versus the control. DD, diastolic dysfunction; SD, systolic dysfunction; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure.

Figure 1. Ratio between arterial elasticity index (AEI) and the left ventricular peak ejection rate (LVPER). Correlation coefficient r = –0.70



DD, diastolic dysfunction; SD, systolic dysfunction

Figure 2. Typical cardiac cycles in the control group and in various forms of diabetic CHD



DD, diastolic dysfunction; SD, systolic dysfunction; left ventricular ejection fraction 65 % (in the control group), 65% (DD), and 54% (SD).

primarily disrupt the energy metabolism of cardiomyocytes, which naturally reduces their contractility. Under these conditions, the circulatory system uses means that increase LV filling and facilitate LV ejection: increased pressure in the pulmonary circulation, increased myocardial compliance and decreased in peripheral resistance (arterial pressure and arterial wall elasticity) [2]. In DM type 1, the virtual lack of glucose use for ATP synthesis in cardiomyocytes is fully compensated by increased consumption of fatty acids [3], and myocardial contractility remains normal. Therefore, the use of the term «diabetic cardiomyopathy» in this model is inadequate, since «cardiomyopathy» is primary myocardial weakness. A situation similar to the one observed occurs, for example, in valve defects, when LV pumping function is impaired due to causes external in relation to the myocardium.

Our findings suggest that the reduced LV pumping function is caused in the DM group by increased arterial wall elasticity. It develops almost immediately due to hyperglycemia – when an isolated heart is perfused with a high-glucose solution (33 mM), the tone of coronary vessels increases significantly [9], which is likely to be due to significantly increased levels of reactive oxygen species [9, 10]. In constant hyperglycemia, endothelial function is impaired and the sensitivity of the contractile apparatus of smooth muscle cells to Ca^{2}+ increases [11]. As a result, the increased vascular tone is stabilized, which hampers ejection from the heart. Coronary vessel calcification occurs in the heart and their reactivity decreases [12], which is manifested in reduced coronary reserve [13]. Our findings showed that increased vascular stiffness is an important pathogenetic factor of CHF in DM type 1.

DM-associated DD has specific features: it develops secondary to reduced diastolic volume, and this occurs as soon as a week after the onset of streptozotocin effect. Decreased LV volume is most likely to be a result of increased rigidity of connectin (titin), a protein that determines myocardial compliance [14]. Special study is necessary to find out whether reduced size of the heart is a compensatory factor. Our findings showed that, regardless of the mechanism, LVEF can remain within normal range despite an obvious decrease in pumping function of the heart. This circumstance suggests that LVEF does not always characterize myocardial contractility, but rather reflects the relationship between the ventricle and arterial resistance.

Conclusions

1. Decreased pumping function of the heart in diabetes mellitus type 1 is observed with normal myocardial contractility but increased arterial wall elasticity, which hampers the ejection.
2. Increased vascular stiffness is an important pathogenetic factor of chronic heart failure in diabetes mellitus type 1.
3. Diastolic dysfunction develops in diabetes mellitus type 1 secondary to decreased left ventricular diastolic volume.

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