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Reduced Cardiac Performance after Differential Pharmacological Stress in Streptozotocin-Induced Diabetic Rats

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Abstract

The development of heart failure including disturbed cardiac stress response is a main complication of diabetes mellitus (DM). In the present study we characterized in vivo the cardiac stress response in the often used streptozotocin (STZ) rat model. We analysed left ventricular (LV) performance of STZ-diabetic rats under basal and pharmacological stress conditions by recording pressure-volume loops using a microconductance catheter at two different time points. Under basal conditions, STZ induces after two weeks impaired LV systolic and diastolic dysfunction indexed by decreased LV pressure and dp/dtmax as well as decreased cardiac stiffness and dp/dtmin leading to decreased cardiac output. This cardiac phenotype behaved at least in part progressively up to six weeks after STZ injection. Intravenously infusion of dobutamine led to a dose-dependent depression of LV performance two and six weeks after STZ injection. Concordant with these findings, the maximum LV conductibility induced by adrenalin was significantly decreased at both two and six weeks after STZ injection. The STZ-diabetic rat is an adequate model for investigating disturbed cardiac stress response as a result of diabetic conditions.

Introduction

Diabetes Mellitus (DM) is a main risk factor for heart failure. A hallmark of this common complication is a disturbed conductibility of the left ventricle (LV). In this regard, diabetic cardiomyopathy is a significant entity, which could manifest as impaired cardiac performance in the absence of coronary artery disease, systemic hypertension or valvular heart disease that result from metabolic derangement present in diabetes [1]. Among others, structural changes in extracellular matrix and myocyte damage contain hallmarks of this disease. Abnormalities in these compartments may result in left ventricular dysfunction (LV).

The Application of streptozotozin (STZ) to rats is a well established model of type 1 DM. We previously showed in this model severe impaired LV function under basal conditions in a chronic stage of STZ-induced DM [2]. We further identified pathophysiological mechanisms, which could be responsible for this disturbed cardiac phenotype. This includes endothelial dysfuntion [3], cardiac fibrosis [4], inflammation and disturbed myocardial calcium regulation [5] as well as neurohumoral activation [6].

Whereas the cardiac phenotype under basal conditions in the chronic stage in STZ rats is well characterized, we analysed in the present study in vivo the time-dependent LV conductibility in this model. Therefore we measured LV function in STZ diabetic rats on two different time points under basal and under different pharmacological stress conditions using invasive LV microconductance catheter technique.

Materials and Methods

Animals and treatment

30 age-matched 6 weeks old Sprague Dawley rats were maintained on a 12:12-h light-dark cycle and fed with standard chow ad libidum. In 20 animals DM was induced by a intraperitoneally single injection of streptozotocin (STZ; 70mg/kg) diluted in 0.1 M sodium citrate buffer, pH 4.5 (Sigma, Munich, Germany), as described before [4, 7] and were randomized in two groups (STZ-2w and STZ-6w). Hyperglycemia was confirmed 48 h later by a reflectance meter (Acutrend, Hoffmann-La Roche, Grenzach-Wyhlen, Germany). All diabetic animals displayed a blood glucose level more than 550 mg/dl and severe polyuria and polydypsia and. 10 vehicle-treated animals (only citrate buffer) were used as controls (Co). All animals were kept in a 12 hour light/dark cycle. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Surgical procedures and assessment of pressure-volume loops

Two (STZ-2w) and six (STZ-6w) weeks after STZ injection, animals were anaesthetized with pentobarbital (60 mg/kg; i. p.), intubated and artificially ventilated.

As recently described [8], a 2 french microconductance-pressure catheter (Aria SPR 858; Millar Instruments, Inc., Texas, USA) was positioned in the LV for continious registration of LV pressure-volume (PV) loops [9,10] in a closed chest model. Calibration of the volume signal was obtained by hypertonic saline (10 %) wash-in technique [11]. Indices of cardiac function were derived from PV data obtained both at basal steady state and during transient preload reduction by occlusion of the abdominal vena cava. After the measurement under basal conditions, data were obtained at dose dependent response to dobutamine (Sigma) (0.75, 2.5 and 5 µg/kg/min) infused in the right vena jugularis to estimate the beta-adrenergic sensitivity. At these concentrations dobutamine is selective for beta receptors [12] . Data

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were measured three minutes after infusion of each dose. Furthermore, for assessment of maximum capacity of the LV we used adrenaline (suprarenin). At first a dose of 1.6 mg/kg was given intraperitoneally. This dose was enhanced if needed. Maximum capacity was defined at the state close to beginning of cardiac arrhythmia as a surrogat of cardiac decompensation. For the whole stress protocol next stress application was started when hemodynamic parameters reached basal level. All hemodynamic measurements were performed during apnoe. Load-dependent systolic function was quantified by LV end-systolic pressure (LVP), dP/dt max, ejection fraction (EF), endsystolic LV volume (ESV), stroke volume (SV), cardiac output (CO) and stroke work (SW). Load-independent LV inotropy was determined by slope of the end-systolic-pressure-volume relationship (ESPVR) [13]. Load-dependent diastolic function was measured by LV end-diastolic pressure (LVEDP), dP/dt min and the time constant of isovolumic pressure decline (Tau) as an index of early, active LV relaxation as well as the end-diastolic-PV-ratio (EDPVR, stiffness) as an index for load-independent diastolic function, determined from an exponential fit to the end-diastolic-pressure-volume points [9,10,14] and. Furthemore we determined the enddiastolic (ED) volume.

Statistical analyses

Statistical analysis was performed using SPSS Version 12.0. Data are expressed as the mean ± SEM. Statistical differences were assessed by using the Kruskal-Wallis test in conjunction with the Mann Whitney U post-hoc test. Differences were considered statistically significantly at a value of $P<0.05$.

Results

Basal systolic LV function

On basal conditions, systolic LV function was impaired two weeks after STZ treatment and behaved progressively at six weeks after DM induction (Table 1). Dp/dt max (STZ-2w: -23%; STZ-6w: -40%), LVP (STZ-2w: -15%; STZ-6w: -30%) and HR (STZ-2w: -32%; STZ-6w: -38%) were significantly reduced compared to the Co group. Also the load-independent index for contractility, the ESPVR, was significantly reduced in both diabetic groups (STZ-2w: -63%; STZ-6w: -56%) compared to the control group.

Basal diastolic LV function

The marker for active and load-dependent diastolic relaxation, dp/dt min and tau changed in the STZ-2w (-40%, +43%) and STZ-6w (-55%, +57%) groups compared to Co, whereas LVEDP did not change significantly (Table 1). The load-independent marker for myocardial stiffness and that for passive diastolic relaxation, the EDPVR, was in direction increased in the STZ-2w group (+44%) and statistically significantly increased in the STZ-6w group (+127%) compared to the Co group. The EDV did not differ between the animal goups indicating similar chamber sizes of the LV.

LV function under dobutamine stress

There was a dose-dependent enhancement of LVP and dp/dt max as systolic indices in the Co group as stress response to dose-dependent dobutamine infusion, whereas HR, Ped and dp/dtmin did not altered (Table 2 and Figure 1). Both the STZ-2w and the STZ-6w group displayed significantly impaired cardiac stress response due to

	LVP (mmHg)	Dp/dtmax (mmHg/s)	ESPVR (mmHg/µl)	LVEDP (mmHg)	Dp/dtmin (mmHg/s)	Tau (ms)	PHT (ms)	Stiffness (mmHg/µl)	Heart rate (min^{-1})	Ved (µl)	Ves (µl)	CO (µl/min)	EF (%)
SD	112±2	7142±371	0.32±0.06	4±1	-6458±173	14±1	8±0.5	0.0059±0.001	373±9	500±56	253±36	94544±11246	52±4
STZ 2weeks	95±4*	5523±253*	0.12±0.01*	5.5±1	-3871±186*	20±1*	13±1*	0.0085±0.0008	255±8*	450±67	264±48	50657±9299*	45±4
STZ 6weeks	78±4*#	4254±212*#	0.14±0.01*	6±1	-2921±185*#	22±1*	14±1*	0.0134±0.002*	232±8*	479±52	260±39	53847±4413*	52±4

*=P<0.05 vs. SD, #=P<0.05 vs. SD and STZ 2 weeks

Table 1: Cardiac performance under basal conditions. This table shows systolic and diatolic LV parameter derived from conductance measurement under basal conditions. Data are depicted as mean±S.E.M.

	LVP (mmHg)	LVEDP (mmHg)	Tau (ms)	PHT (ms)	Heart rate (min^{-1})
SD					
Dob 1	160±14	4±1	19±1	11±2	359±11
Dob 2	176±15	3±1	19±2	9±1	380±13
Dob 3	206±19	4±0.4	18±1	9±1	391±13
STZ 2 weeks					
Dob 1	115±7*	12±1*	19±1	12±1	271±9*
Dob 2	136±10*	11±2*	21±3	13±1	293±10*
Dob 3	135±8*	11±1*	21±2	13±1	305±7*
STZ 6 weeks					
Dob 1	Dob 1 94±5*	7±1	19±1	12±0.3	240±8*
Dob 2	102±5*	6±1	19±2	12±1	254±7*
Dob 3	107±5*	6±1	21±3	13±1	269±7*

*=P<0.05 vs. SD, #=P<0.05 vs. SD and STZ 2 weeks. SD = Sprague Dawley, STZ = Streptozotozin

Table 2: Cardiac performance under dobutamine-stress. This table shows systolic and diatolic LV parameter derived from conductance measurement under dobutamine-stress (0.75, 2.5 and 5 µg/kg/min). Data are depicted as mean±S.E.M.

	LVP (mmHg)	Dp/dtmax (mmHg/s)	LVEDP (mmHg)	Dp/dtmin (mmHg/s)	Tau (ms)	PHT (ms)	Heart rate (min^{-1})
Adrenaline							
SD	220±12	16524±959	8±2	-9105±898	16±2	8±1	390±13
STZ 2 weeks	180±5*	13567±498*	9±1	-6678±366*	22±2	14±1*	301±7*
STZ 6 weeks	148±6*	10145±367*	9±1	-4972±544*	21±2	17±3*	265±12*

*=P<0.05 vs. SD, #=P<0.05 vs. SD and STZ 2 weeks. SD = Sprague Dawley, STZ = Streptozotozin.

Table 3: Cardiac performance under adrenaline-stress. This table shows paramters of the maximum systolic and diatolic LV function derived from conductance measurement under adrenaline-stress stress. Data are depicted as mean±S.E.M.

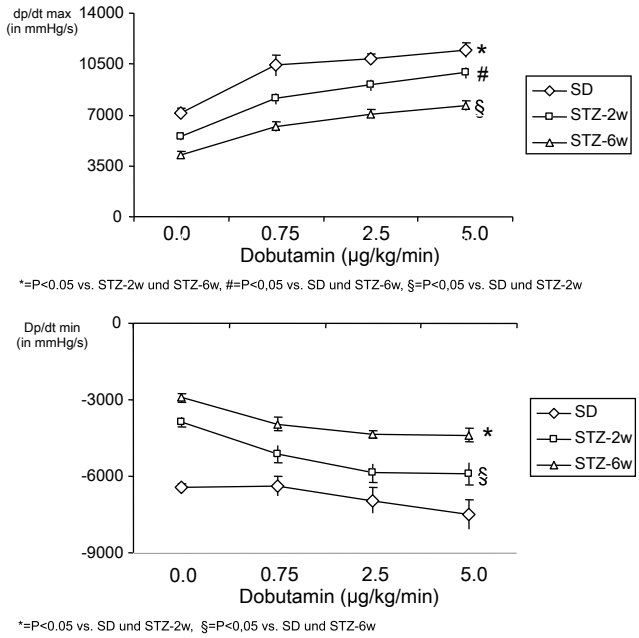

Figure 1: Dp/dtmax and dp/dt min under dobutamine-stress.

dobutamin stimulation indexed by LVP, dp/dtmax, dp/dt min and HR. The LVEDP did not differ in the STZ-6w group when compared with the Co group. In contrast, this parameter for diastolic function was at least at higher dobutamine doses significantly increased in the STZ-2w group compared to controls (Table 2).

LV function under adrenalin-stress

To assess maximum possible response to symphatomimetic stimulation adrenaline was used. After application of adrenalin in the Co group LVP and dp/dt max as systolic indices were significanlty enhanced (+96% and 131%) compared to baseline (Table 1 and 3). In addition, the diastolic parameter for active relaxation was also significanlty increased (+41%) under these conditions. The diastolic parameter for passive relaxation, the LVEDP, did not changed in the Co group after adrenalin application. Both STZ-2w and STZ-6w showed impaired parameters of systolic function and active diastolic relaxation in response to adrenalin stimulation, whereas the LVEDP did not change among the groups.

Discussion

The present study demonstrates in vivo impaired cardiac stress response in an early and in a late stage of STZ-induced DM. The LV function of the STZ diabetic rat in the chronic stage under basal conditions is well known and both its pathophysiological mechanisms and treatment strategies are subject of intense current investigations. The goal of the present study was to investigate in vivo the cardiac stress response to two different stimuli.

We and others previously showed disturbed LV dysfunction in a chronic stage of STZ-induced DM. LV function with impaired dp/dt max and Pes demonstrates clearly systolic LV dysfunction. This is in agreement with our previous studies [5,15] in the same model of DM. To define changes in contractility, more parameters are necessary because contractility is per definition independent of loading conditions [16]. The assessment of contractility is important to separate effects of a primary changing in loading conditions from an intrinsic change in the force of contraction. Because of the load dependency of dp/dt max, the determination of load-independent systolic indices like ESPVR is necessary to quantify LV contractility. ESPVR was significantly reduced at both time points of DM and indicates impaired contractility in this model. In contrast, stroke volume and stroke work were not altered under diabetic conditions. These unexpected findings can be explained by loading conditions. Because of the severe dehydration of diabetic rats resulting mostly from osmotic diurese in DM, afterload is decreased. However, Ea as a surrogate for afterload was not significantly changed, but there was a tendency. In summary, less LV contractility is necessary to preserve stroke volume under diabetic conditions causing by a reduction of afterload. Other investigators found controversially data. In nearly the same STZ protocol despite another rat strain they found decreased SV 6 weeks after T1D induction [17]. Data was assessed by magnetic resonance imaging, which is not widely used for determination of cardiac performance in very small animals like rats. So a final validation of this method is absent. Another reason for this discriminative data could be the use of different rat strains. Al-Shafei et al. [17] used Wistar rats whereas Sprague Dawley rats were used for the present study. However, large differences were observed between different strains of murines, for example, the susceptibility of coxsackievirus infection in different strains of mices [18].

The present data indicate an early diastolic dysfunction, which behaved progrediently. Both active and passive relaxation during the diastole is affected by STZ-T1D. Dp/dt min and Tau as a surrogate for active relaxation of the LV are significantly impaired 2 weeks after DM induction, whereas the LV stiffness index as a marker for passive relaxation performance was after 2 weeks enhanced in direction and after 6 weeks significantly enhanced. The earlier development of impaired active relaxation might be induced by quickly inflammatory response induced by hyperglycemia. In a preceding study we found an activation of myocardial inflammation induced by STZ-T1D and an association with impaired LV systolic performance [19]. At the 6 week time point of STZ-T1D we shown in addition to the inflammatory response changes in extracellular matrix, determined by collagen type I, III and IV compared to normoglycemic control rats [4]. Collagen I, III, IV and VI in addition to type V collagen and elastin, constitute the main components of extracellular cardiac matrix. Changes in the extracellular cardiac matrix, especially in the collagen components, decisively influence the passive mechanical properties of the myocardium and thus are important for cardiac hemodynamic [20], especially for LV diastolic passive filling.

However, the assessed diatolic performance of this study is in agreement with pathophysiological changes of the LV we showed in the past. The Ped behaved unespectively. In the early state of both STZ-T1D and STZ-T2D we found no significant increase of Ped. This is most likely a result from chronic dehydration, which in turn leads to decreased afterload. This study shows further an unaffected EDV under T1D. Riva et al. found controversial data [21]. They found a decreased enddiastolic volume in a STZ model. Despite of the fact, that the STZ dose was lower (60 mg/kg) and the earliest time point was 4 month, data was assessed by an in vitro perfusion method. Filling characteristics of the LV are highly dependent of loading conditions. Perfusion models naturally have not physiologically loading conditions. Furthermore the perfusate in this study was the same among diabetic and normoglycemic groups even through under in vivo conditions both groups have different perfusate (circulating blood).

The pharmacological stress induction with different doses of dobutamine was used to evaluate the beta sensitivity of the LV under T1D conditions during the course of time. Dobutamine stimulation is also a common clinical setting in patients who underwent stress echocardiography. Systolic performance dependent on doputamine infusion was impaired in all stress levels compared to normoglycemic controls. Heart rate, contractility and Pes were reduced at the 2 week time point and behaved progressively. These findings confirm with other studies. Nishio et al. found a decreased number of beta-receptors in diabetic myocytes [22] which may blunt the rise in intracellular calcium during beta-adrenergic stimulation In contrast, diastolic indices such as dp/dt min, tau did not differ compared to Co. Especially the Ped, which was unaffected under basal diabetic conditions six weeks after T1D induction, was also not enhanced during dobutamine stress.

Adrenalin was used to stimulate the LV maximally. We found a significant decreased capacity of diabetic hearts up to two weeks T1D indexed by decreased contractility and HR compared to stimulated control LV. In the same way like the dobutamine stress a new behaviour of systolic and diastolic indices was not found compared to basal data. Especially the Ped was also not enhanced after application adrenalin.

Diabetic rats displayed LV dysfunction even up to two weeks after STZ injection. This dysfunction leads not to a significant decreased SV or SW. Interestingly, CO is even though decreased under diabetic conditions despite of preserved SV along with markedly decreased heart rate. Furthermore, end-systolic and end-diastolic volume was also not affected by STZ-induced DM. In other words, the present STZ-model does not result in a dilation of the LV such a state of classical dilatative cardiomyopathy as also indicated by unchanged LVEDd derived from echocardiographic measurements. The present data about beta-receptor-dependent and maximum possible response to sympathetic stimulation in this model shows, that the LV performance behaved equally compared to the results derived from basal measurement. Therefore it gives no new information about the behavior of systolic and diastolic indices under STZ-diabetic conditions. But it clearly demonstrates a severe impaired response to both alpha and beta receptors at early and late state of DM.

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In conclusion, our study demonstrates that STZ-diabetic rats display severe heart failure. This includes reduced left ventricular function under basal conditions and further, early reduced stress response to adrenaline and dobutamine. The relation between systolic and diastolic cardiac performance and CO which results from both evaluated in this study may help us to answer more precise questions regarding pathophysiology and development of diabetic cardiomyopathy.

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Disclosures

All authors have no conflict of interest.

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