Left Ventricular Dysfunction and Remodeling in Streptozotocin-Induced Diabetic Rats

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Background  It is not fully clarified how diabetes mellitus (DM)-induced cardiac dysfunction is associated with histopathological changes of the heart in a long lasting period of DM.

Methods and Results  Eighteen weeks after a streptozotocin injection was given to Wistar–Kyoto rats (D rats), echocardiography and hemodynamic studies including the dobutamine infusion test were performed. After perfusion fixation, immunofluorescent staining and histopathology of the heart were analyzed, and analysis with electron microscopy was also conducted. Systolic blood pressure in the conscious state and left ventricular (LV) ejection fraction by 2-dimensional echocardiography were reduced in D rats. LV mechanical responses to dobutamine assessed by maximal LV pressure derivative (+LVdP/dt) also decreased with higher dobutamine doses in D rats. Although LV and right ventricular (RV) wall thickness were smaller in D rats, there were increased RV volumes, indicating LV and RV dilatational remodeling in D rats. The cardiomyocyte transverse diameter and actin staining in cardiomyocytes in both the LV and RV were significantly reduced, and capillary tortuosity and type IV collagen were increased, indicating microangiopathy in D rats.

Conclusions  Advanced insulin-dependent DM incurred not only RV remodeling but also overt resting LV systolic dysfunction and decreased LV responsiveness to β adrenergic stimulation with dilatational remodeling, accompanied by pathological changes of capillaries and cardiomyocytes including actin filaments. (Circ J 2006; 70: 327–334)

Key Words: Actin filament; Cardiomyocyte; Diabetic cardiomyopathy; Left ventricular systolic dysfunction; Streptozotocin-induced diabetic rats

Epidemiological studies show a high incidence of diabetes mellitus (DM) in patients with chronic heart failure, suggesting that DM causes and/or promotes left ventricular (LV) dysfunction directly and/or indirectly via atherosclerotic coronary artery disease. Extensive investigations of LV functional and/or morphological abnormalities in experimental diabetic animals have suggested that DM alone induces latent LV systolic dysfunction, resulting in increased susceptibility to overt heart failure. Recently, it has also been reported that if the DM state persists for a long enough time, it induces cardiomyopathy, manifesting decreased resting LV ejection fraction (LVEF). According to Akula et al, the LV internal dimensions in systole as well as in diastole increased after only 12 weeks of diabetes, while systolic dysfunction with LV dilation was easily detected 5–6 weeks after streptozocin (STZ) treatment. Moreover, a depressed LV response to β adrenergic stimulation has been shown in a DM animal model whereas a preserved LV response is reported in the same DM model. Thus, there is controversy regarding the time-course of DM-induced LV dysfunction and LV responsiveness to β adrenergic stimulation. In addition, the reasons for cardiac dysfunction as well as cardiac remodeling in DM have not been fully clarified from a histopathological perspective, not only in the heart (right and left ventricles) but also in coronary vascular beds. The purpose of this study was to observe the severity of cardiomyopathy with overt resting global LV systolic dysfunction and LV remodeling induced in a longer DM state than investigated in previous studies, and whether right ventricular (RV) remodeling occurs as it does in the LV. In addition, we investigated whether there were any basal histopathologic changes of the heart and coronary arterial system in a dysfunctional diabetic heart.

Methods

Animals  Eight-week-old 170–190 g Wistar–Kyoto male rats (n=33) were used in this study (Life Science Center, Fukushima, Japan). They were randomly divided into 2 groups: diabetic (n=15) and control (n=15). This study conforms to the Guidelines on Animal Experiments from Fukushima Medical University (approval number 980098) and the Japanese Government Animal Protection and Management Law (No. 115).

Diabetic Model  DM was induced by using a bolus injection of STZ (50 mg/kg bodyweight; Sigma Chemicals, St Louis, MO, USA) into the tail vein, after rats were anesthetized with ether. Three days later, hyperglycemia of more than 400 mg/dl in tail vein blood was confirmed in all rats in the fasting state, by using a Glucose Analyzer (Daikin, Antsense II™, Osaka, Japan).
Experimental Protocols

All STZ-induced diabetic rats and control rats were caged individually and received normal rat chow and tap-water ad libitum for 18 weeks in a constant environment (room temperature 23±1.5°C, room humidity 55±5%). The following study was performed at 18 weeks (ie, when rats were 26 weeks old), with both diabetic and control rats. On the day of the experiment, the blood pressure of the tail artery was measured with rats in the conscious state using an oscillometric method (Ueda, UR 5000™, Tokyo, Japan). Following this, rats were lightly anesthetized by using the intraperitoneal administration of sodium pentobarbital (25 mg/kg bodyweight). Two-dimensional echocardiography (2-DE) was performed when rats were in a prone position. After administration of additional sodium pentobarbital (50 mg/kg bodyweight in total), the chest was opened when rats were under artificial ventilation by using a rodent ventilator, and hemodynamic variables were measured and a dobutamine stress test was performed. After the experiment, perfusion fixation was performed and the heart was isolated from the aortic root for histopathological and immunohistochemical examinations.

Transthoracic 2-DE

LV end-diastolic (LVDd) and end-systolic diameters (LVDs) were measured by using 2-DE with a 10-MHz transducer (Hewlett-Packard, SONOS 100CF™, Andover, Mass, USA), and are shown as average values of 15 consecutive beats. The LVEF was calculated by using the cubic method with the following formula11: LVEF (%) = (LVDd3 – LVDs3)/LVDd3 × 100.

In Vivo Hemodynamics

After 2-DE, a 0.05 ml blood sample was taken from the rat’s tail vein for blood glucose measurement. Following this, the rat chest was opened at the fourth intercostal space while the rat was under artificial ventilation using a rodent respirator (SHINANO, MODEL-SN-480-7™, Tokyo, Japan). After a puncture at the LV apex was made with an 18-gauge needle, a polyethylene tube (Clay Adams, PE 50™, Parsippany, NJ, USA) was inserted into the left ventricle for the measurement of LV pressure with a pressure transducer (Nihon Kohden, TP4005™, Tokyo, Japan). The LV pressure, positive and negative LV dP/dt, and ECG were monitored continuously and measurements were recorded on a thermal array recorder (Nihon Kohden, Polygraph System™, Tokyo, Japan) at a paper speed of 100 mm/s as reported previously12.

Basal hemodynamic variables were recorded after a 15-min stabilization period following surgical preparation. Then, the left jugular vein was cannulated with a PE 50, which was connected to an infusion pump (Nihon Kohden, Syringe Pump CFV-2100™, Tokyo, Japan), and dobutamine infusion was started at a dose of 4 μg/kg bodyweight per min (μg). The dose was elevated by increasing the infusion rate every 2 min from 4 to 64 μg/6, 16, 32, and 64 μg. The LV pressure was recorded continuously and the LV peak systolic and diastolic pressures (LVSP, LVEDP) and maximal +/-LVdP/dt of the last 30 beats at each dose were measured and averaged.

Histopathology

After the experiment, perfusion fixation with a 4% paraformaldehyde solution at a perfusion pressure of 100 mmHg was conducted in 7 diabetic and 7 control rats (18 weeks after STZ administration), which were randomly selected from each group. The heart was isolated and the volumes of both ventricles were determined by measuring the quantity of physiological saline, which filled up each ventricle according to the method of Grover et al13; both atria were then removed. Both ventricles were cut transversely parallel to the atrio-ventricular groove at the equatorial plane and embedded in paraffin. Paraffin sections (4μm thick) were stained with hematoxylin-eosin (HE) and Azan stain (Mal- lory-Heidenhain) for interstitial fibrosis, and the thickness of the LV and RV walls was measured at 3 regions (anterior, lateral and posterior wall) by using a magnified photograph (×150) (Fig 2) and averaged. Using an ocular micro-meter disk with a linear scale, the transverse diameters of 30 cells containing nuclei were measured in the slices taken from each corresponding LV and RV wall and averaged. For a comparison of cardiomyocytes, prediabetic rats (0 weeks; 8-week-old rats; n=3) were used and paraffin sections were stained with HE and Azan.

Immunohistochemical Staining

Five paraffin sections from each rat were deparaffinized, and after processing to alcohol, immunoperoxidase staining was conducted for all 7 rats in each group by the avidin-biotin-peroxidase complex method14. The sections were quenched for 30 min at room temperature in methanol containing 3% H2O2, washed in tap water for 5 min, and then incubated for 1 h with pepsin to activate antigenic sites. They were then incubated overnight at −20°C with specific type III collagen (for interstitial fibrosis) and type IV collagen and laminin (for basement membranes in the vessel wall) antisera (Fuji Chemical Industrial Co, Ltd, Tokyo, Japan; 300-fold with antibody diluting buffer). After washing with a phosphate-buffered saline (PBS), the sections were incubated at room temperature for 30 min with an anti-rabbit IgG biotinylated antibody (Nichirei, Tokyo, Japan), and visualized by incubation in 3,3′-diaminobenzidine solution for 5 min. They were counterstained for 3 min with Masson-modified hematoxylin. Negative control samples were created by replacing the primary antibody with non-immune rabbit serum.

The other 5 rats in each group were perfused with 8% paraformaldehyde solution and their hearts were isolated as described above and quickly frozen in a dry ice-acetone mixture for the immunofluorescent study of actin filaments. Five sections of 7μm thickness were sliced from the same 5 planes as above by using a cryostat. After incubation at room temperature with anti-actin antibody for 60 min, the sections were washed with PBS and incubated for 30 min at room temperature with tetramethylrhodamine B isothiocyanate-phalloidin (Sigma Chemicals, St Louis, MO, USA) and anti-rabbit IgG sheep serum. After washing with PBS, the sections were mounted on glass slides with PBS-glycerin, and actin fiber fluorescence was observed.

Evaluation of Immunohistochemical Staining

The extent and degree of fibrosis with Azan stain was subjectively graded in the RV and LV wall. Grade 0 signified no apparent collagen fiber proliferation except for small islets of fibrous tissue around the capillaries, as well as an intercellular single layer of collagenous tissue as in normal myocardium. Focal and minimal fibrosis was graded (1+) and the most prominent fibrosis, covering more than half of the area of the specimen, was classified as (4+). Grades (2+) and (3+) were intermediate, between...
The intensity of staining of type III and IV collagen, and laminin was graded on a semiquantitative scale, 0 (none) to 4+ (intense). Areas of actin fiber fluorescence of 30 cardiomyocytes in each slice were measured on magnified (×200) photographs of immunofluorescence by using an image analyzer (Mutoh, Dinigram Mode G™, Tokyo, Japan). The degree of actin fiber fluorescence was defined as the percent of total cardiomyocyte area stained.

**Electron Microscopy**

After the experiment, 3 rats in each group (18 weeks old) were fixed by perfusion with 1% osmium tetroxide for electron microscopic examination. The tissues were transferred through a graded alcohol series followed by propylene oxide and examined by using a transmission electron microscopy (JEOL-1200EX™) for the changes to cardiomyocytes and vessels.

**Data Analyses**

The data are presented as means±SD. The significant differences were determined by using Student's t-test.
differences of hemodynamic variables and 2-DE parameters between 2 groups of control and DM rats were assessed by an unpaired Student’s t-test. The difference between more than 2 groups was assessed by an analysis of variance, followed by Bonferonni’s test as a post-hoc test. A p value of <0.05 was considered to be significant.

### Results

#### General Features

Table 1 shows comparisons of the general characteristics and echocardiography findings between control and DM rats. The bodyweight of diabetic rats was significantly smaller than that of control rats (p<0.001). Blood glucose and serum cholesterol were higher; however, serum albumin was lower in diabetic rats compared to control rats (p<0.001 each). Systolic tail artery blood pressure in rats in the conscious state was slightly but significantly lower (p<0.01) in diabetic rats compared to control rats.

#### Echocardiography Findings

Comparisons of echocardiography findings are shown in Table 1. There was no significant difference in LVDd between control and DM, whereas the LVEF was slightly but significantly reduced in diabetic rats compared to control rats (p<0.005). Cardiac output estimated by 2-DE was significantly larger in control rats (99±11 ml/min) than in diabetic rats (81±11 ml/min; p<0.01). However, cardiac output normalized by bodyweight was significantly larger in diabetic rats (58±5 ml/min per 100 g) than in control rats (28±4 ml/min per 100 g; p<0.001).

#### Hemodynamic Differences in Thoracotomized Rats

Hemodynamic variables in rats that had open chests, and their responses to dobutamine infusion are shown in Fig 1a–d (LVSP, LVEDP, maximal +/– LVdP/dt). No significant differences were found in these variables between control and DM rats in the baseline state. However, in response to incremental dobutamine infusion, LVSP significantly increased in control rats, while there were no changes in diabetic rats. LVEDP was not different during dobutamine infusion or in the baseline state between the 2 groups. Maximal +LVdP/dt gradually increased in response to dobutamine infusion in control rats, but decreased at 64γ in diabetic rats compared to that at 8γ. Also, maximal –LVdP/dt increased with dobutamine infusion in control rats but not in diabetic rats.

#### Morphological Findings

Following 18 weeks of observation, both bodyweight and heart weight were remarkably smaller in diabetic rats than in control rats (Table 1), however, the LV volume obtained from excised hearts was not different between the 2 groups (Table 2; Fig 2). In contrast, the RV volume was significantly greater in diabetic rats than in control rats (p<0.05). As
shown in Table 2 and Fig 2, the LV and RV wall thickness was smaller (p<0.01) in diabetic rats than in control rats. A transverse diameter of cardiomyocytes observed in the LV and RV was smaller (p<0.05) in diabetic rats (7.8±0.8 μm, 7.6±0.8 μm, bodyweight 144±36 g) than in control rats (11.6±1.6 μm, 11.1±1.5 μm, bodyweight, 383±24 g). In contrast, the diameter of cardiomyocytes in prediabetic rats (0 weeks: bodyweight, 179±4 g; heart weight, 680±40 mg; heart weight/bodyweight ratio (×10−3), 3.7±0.4) was RV: 10.4±1.2 μm, LV: 10.2±1.0 μm. The diameter of cardiomyocytes in control rats at 0 weeks and 18 weeks was almost the same, although the bodyweight or heart weight was significantly different at the 2 ages. Thus, the transverse diameter of cardiomyocytes was not dependent on bodyweight or heart weight, suggesting that the smaller transverse diameter of diabetic rat cardiomyocytes observed when rats had similar bodyweights or heart weights of 0-week-old rats was due to the remodeling of cardiomyocytes in rats in the diabetic state.

The quantities of interstitial fibrosis evaluated by Azan staining (Fig 3a) and type III collagen evaluated by immunohistochemical staining did not differ between control and DM rats (Table 2). Laminin and type IV collagen, which constitutes the capillary basement membrane, were increased in diabetic capillary vessels compared with those of the controls (Table 2). Capillary tortuosity was evident in diabetic rats (Fig 3b), but significant pathological changes such as intimal and medial thickening were not observed in vascular beds from the epicardial conduit artery to arterioles (Fig 3a). Actin immunofluorescent staining decreased in diabetic rats (Table 2; Fig 4), suggesting that the myocardial contraction system is impaired during long-lasting DM.

Fig 3. Histology of small coronary arteries and capillaries. Intimal or medial thickening was not observed in small conduit coronary arteries, and interstitial fibrosis did not increase in diabetic rats (Lower panel), compared with control rats (Upper panel). (a) Azan staining, ×20. In contrast, capillary tortuosity and increase in type IV collagen (b, type IV collagen staining, ×100) were evident in diabetic rats (Right panel) compared with control rats (Left panel).

Fig 4. Representative immunofluorescent staining of actin in control and diabetic rats. Fluorescence of actin filament in cardiomyocytes was significantly reduced in diabetic rats (Lower) compared with control (Upper) rats. This decreased actin fluorescence was consistently observed in diabetic rats.
Electron Micrographical Findings

Electron micrographs showed thickened capillary basement membrane, transformation of the nucleus, and derangement and decrease of myofibers and mitochondria in cardiomyocytes in STZ rats compared with control rats as shown in Fig 5.

Discussion

In the present study, no significant pathological changes were observed by light microscopy in coronary arterial trees of DM rats, whereas capillary tortuosity and type IV collagen constituting vascular basement membrane were found to be significantly increased. These results strongly suggest that insulin-dependent DM would induce cardiomyopathy with slightly decreased LVEF and dilatational remodeling in both ventricles, which was indicated by an enlarged ventricular volume normalized by heart weight, even without coronary macroangiopathy and hypertension. Decreased LV pump function in the basal state or following β-adrenergic stimulation may be partly attributable to the reduced transverse diameter of cardiomyocytes and a decrease and/or change in actin filaments.

Diabetic Cardiomyopathy and Nutrition

There are ECG abnormalities and pathologic evidence supporting LV hypertrophy in DM patients regardless of the type of DM. In the present study, heart weight as well as bodyweight were much lower in DM rats compared with control rats. Such a significant weight loss has also been observed in previous studies using experimentally-induced, insulin-dependent diabetic animals, and pathological and functional similarities between undernourished and diabetic hearts have been suggested. Food restriction associated with weight loss can also produce cardiac dysfunction. However, calorie deprivation resulted in heart atrophy with a decrease in LV cavity and normal concentration of actinomyosin in contrast to the dilatational remodeling accompanied by the structural change in actin filaments in the present study. Moreover, the nutritional state of diabetic rats seemed to be much different from rats in a food-restricted malnourished state because serum albumin decreased slightly but serum cholesterol increased in the present study, showing a negative correlation between serum cholesterol and albumin in the diabetic rats (data not shown). However, metabolic disturbances in DM rats, in which energy production is shifted from glucose utilization towards β-oxidation of free fatty acids, might have led to calorie deprivation and then to diabetic-related myocardial dysfunction.

LV Function and Structures

There is still controversy regarding the severity or time of appearance of cardiac impairment following the appearance of DM. In the present study, LVEF in rats in the resting state was significantly reduced and maximal +dP/dt worsened with the higher dobutamine dose, suggesting deterioration of LV pump function. Cardiac output normalized by bodyweight increased approximately 2-fold, and the systolic blood pressure decreased or tended to decrease, suggesting a decrease in peripheral vascular resistance as previously reported. This decreased peripheral vascular resistance, resulting in a high output state, might partly contribute to volume overload-type dilatational remodeling in both ventricles.

It is known that coronary flow reserve related to nitric oxide is reduced in type 1 DM in animals and in humans. In addition, the oxygen diffusion distance between coronary capillaries and cardiomyocytes is increased because of coronary microangiopathy and interstitial fibrosis. Thus, there may be a physiological susceptibility to myocardial ischemia under cardiac stress in type 1 DM. In contrast, the β receptor density is decreased in type 1 DM and also the β receptor-coupled G protein-adenylate cyclase signal pathway is impaired in this type of DM, resulting in an adrenergic hyporesponsiveness. Thus, we assume that a mechanical hyporesponsiveness of our model to dobutamine-stress may be due to impaired signal transduction as well as a possibility of induction ischemia. Further study is necessary to clarify these possibilities.

There are no absolute increases (only relative increases) in the LV diameters in our DM model compared to those in sham rats. However, for the reasons discussed above including nutritional problems related to an insulin depletion, we assume that our DM model is in the process of ventricular dilatational remodeling, although absolute enlargement of LV structures is suboptimal.

RV Function

Only a few reports have assessed RV dysfunction or structural abnormality in diabetic cardiomyopathy. Moreover, RV systolic and diastolic functions remain to be clar-
Cardiac Compliance

A decrease in LV diastolic compliance has been described in a diabetic heart model and was attributed to interstitial collagen accumulation in the alloxan-induced DM dog25 or STZ-induced DM rat26 as well as in human type 2 DM.27 Moreover, interstitial collagen accumulation and diastolic filling abnormalities were evident only in the pre-diabetic stage, but not in the diabetic stage in a type 2 diabetic rat model.12,28 Therefore, there are different data concerning this issue, and species differences in addition to different types or phases of DM are probably contributory. Further study is necessary to clarify this issue. LV relaxation estimated from maximal negative dP/dt did not deteriorate in the basal condition in the present study, but previous reports6,28 showed results relating to impaired relaxation. The reason for these differences is also unclear, as mentioned above with respect to the issue of diastolic compliance.

Histopathological Changes

LVDD by 2-DE and LV volume after perfusion fixation were not different between the control and diabetic rats, whereas the heart weight was significantly lower, and there were decreases in both LV wall thickness and transverse diameters of cardiomyocytes in diabetic rats, suggesting LV dilatational remodeling. Heart weight and body-weight in prediabetic rats (at 0 weeks) were similar to that found in diabetic rats (18 weeks), but the transverse diameters of cardiomyocytes were larger than that found for DM rats, suggesting that a long-lasting diabetic state itself, but not the reduction of heart or body size, induces cardiomyocyte diameter reduction. The mechanism of the cellular remodeling of diabetic rats, that is, reduction of transverse diameter in cardiomyocytes, and decrease of mitochondria and myofibers, remains unknown. Mechanical stretch did not seem to be significantly involved in cellular remodeling because LV systolic and filling pressures did not increase in diabetic rats. Therefore, further study is needed to clarify this issue.

Increased βmyosin heavy chain29 and depressed cardiac myofibrillar adenosine triphosphate activity30 are well known to play significant roles in contraction and relaxation abnormalities in models of diabetic heart, however, less is known about the role of actin. The staining of actin filaments was decreased in insulin-dependent diabetic rats, indicating a quantitative decrease or qualitative change in actin cytoskeleton filaments. This change, as well as the parallel decrease of myofiber and mitochondria by electron microscopy was observed not only in the left ventricle but also in the right ventricle. As far as we know, this is the first report to document an actin filament abnormality in a diabetic heart model. The actin cytoskeleton is involved in propagating the effects of insulin on glucose transport, and insulin reorganizes the actin cytoskeleton of a cell.31 In the absence of insulin, actin disassembly caused a reduction in the amount of glucose transporters in intracellular membrane fractions.32 The cardiomyocyte cytoskeleton is also known to influence myocardial function dynamically. It was reported recently that dilated cardiomyopathy causing systolic heart failure and dilatational hypertrophy may result from mutations in actin genes leading to the defective transmission of force in cardiomyocytes.33 It is probable in DM that insulin deficiency, which decreases protein synthesis and promotes protein degradation,33 defective mitochondrial function,34 or altered lysosomal enzyme activity35 might reduce the quantity of actin, resulting in cellular remodeling. However, in contrast to our results obtained 18 weeks after STZ injection, contractile myofilaments and associated structures were not greatly altered even 8 months after STZ treatment.36 Thus, further study is also needed to clarify these discrepancies.

Myocardial Changes Before Appearance of Cardiac Dysfunction

The appearance of histopathological changes such as cardiomyocyte necrosis detected by light microscopy may be adjacent to that of LV dysfunction.16 In contrast, changes in gene expressions on energy metabolism precede LV functional and structural changes.37 Namely, transcription of glucose transporters 1 and 4, and a carnitine palmitoyltransferase 1 activity decrease, followed by changes in mRNA expression of myosin heavy chain isoform from α to β, a decrease in the α-actin mRNA expression, and a decrease in sarcoplasmic Ca-ATPase activity, as early as 1 week after STZ administration when the features of cardiomyopathy are absent. These reports confirm that metabolic alteration-induced cardiac genetic and biochemical changes are involved in the pathogenesis of cardiomyopathy derived from type 1 DM.

Myocardial Perfusion

Microvascular lesions expected from capillary tortuosity were found in this long lasting rat DM model. However, atherosclerotic changes in coronary arterial trees from the epicardial conduit artery to arterioles were not observed in these STZ-induced diabetic rats, at least by light microscopy. In contrast, atherosclerosis in coronary arteries or aorta of type 2 DM models13,12 has been reported. From the present results, coronary macroangiopathy was unlikely to be a cause of pathological and functional cardiac changes in this DM model, although the possibility of a causal link between microangiopathy and LV functional and pathological changes has not been determined.

Clinical Implication

The fact that most human DM belongs to type 2,4,12 greatly influences the results of many of the clinical studies on diabetic cardiomyopathy. In contrast, there are few studies, as long as we acknowledged, which investigated human...
type 1 DM-induced cardiomyopathy in detail. Therefore, there is a limitation in simply applying the results of the present experimental study to diabetic cardiomyopathy in humans. However, the present study may at least contribute to investigating the pathophysiological aspects of a subtype of human cardiomyopathy caused by type 1 DM. In addition, a relative or absolute decrease in insulin secretion sometimes appears in the advanced stage of type 2 DM, in which fasted blood sugar levels are elevated. In such a situation, cardiomyopathy induced by type 2 DM might be further modified. Thus, our experimental study may also contribute to the investigation of such aspects of insulin depletion-related cardiac morbidity.

Conclusion

In a long-standing STZ-induced diabetic model, that is, a severe type of insulin-dependent diabetic model, a slight LV systolic dysfunction in the basal state as well as decreased responsiveness to β-adrenergic stimulation were shown to be associated with cellular and LV dilatational remodeling. In addition, although RV function was not investigated in the present study, RV dilatation was observed simultaneously, indicating that DM itself may induce overall cardiomyopathy. Microvascular disorder and changes in contractile protein might be partly attributable to cardiac dysfunction with dilatational remodeling in both ventricles.

References