Left Ventricular Diastolic Dysfunction in Diabetic and Dysmetabolic Non-human Primates

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Abstract

Diabetes is one of the major risk factors for heart failure with reduced ejection fraction (EF), and is highly associated with left ventricular (LV) dysfunction. This study was designed to noninvasively assess LV function by using echocardiography in 89 cynomolgus monkeys with or without diabetes. Subjects were divided into 3 groups based on their blood glucose and other metabolic status. By using noninvasive echocardiography, the present study demonstrated for the first time that dysmetabolic and diabetic monkeys are associated with LV systolic (increased ESV, decreased EF, etc.) and diastolic (decreased EDV and E/A ratio, prolonged DT, etc.) dysfunctions similarly to that in diabetic patients. Thus, the spontaneous-diabetic monkey model is a highly translatable tool for studying human disease not only for the pathogenic mechanisms but also for testing the novel therapies for both cardiovascular and metabolic disorders.

Introduction

Diabetes mellitus is one of the most common chronic diseases in the world and is acquiring epidemic proportions. Its prevalence is growing in developed and developing countries. Echocardiography is used non-invasively to assess changes of cardiac structure, quantify ventricular function and detect non-perfused myocardium. It has shown to be an essential diagnostic tool in the critical assessment of ill patients, and is the most widely used method in the clinic because it is convenient, rapid, economical, and does not require radiation. Non-human primates (NHP) are particularly important models because the metabolic progression from insulin resistance through impaired glucose tolerance to overt diabetes, the pathological changes that occur in the pancreatic islets as diabetes develops, and the comorbidities that manifest as a consequence of disease progression are all comparable to characteristics of the disease in humans. Therefore, the aims of this study is (1) to establish an echocardiography method for non-invasive measurement of cardiac functions in the spontaneous T2D NHP; (2) to assess for similar pathogenetic characteristics and accompanying risk factors in LV, specifically LV diastolic dysfunction between human and NHP.

Methods

Studies were performed with a ProSound SSD-3500SX ultrasound system (Hltachl Aloka Medical, Ltd. Tokyo, Japan). We performed standard echocardiography examination in all subjects. Each monkey underwent a comprehensive transthoracic echocardiographic examination with two-dimensional, M-mode, Doppler echocardiography. The measurement of echocardiographic parameters was performed on 3-5 consecutive cardiac cycles and the average was used for the analysis. The LV end-systolic and end-diastolic dimensions (LVIDs and LVIDd) and wall thickness (LVSd) were measured using M-mode tracing from the parasternal long axis (PLAX) view. Additional heart rate was measured. From these parameters, fractional shortening (FS), ejection fraction (EF), end-diastolic and end-systolic volume (EDV and ESV), stroke volume (SV) and cardiac output (CO) were calculated. The LV diastolic function was assessed by Doppler echocardiography of trans-mitral flow velocities. Peak early (E) and late (A) diastolic velocities of mitral inflow and deceleration time of E wave (DT E) were measured using pulsed-wave Doppler with the sample volume at the tip of mitral valve. Left atrial (LA) maximal dimension was measured by M-mode echocardiography from PLAX view (LAD_{MAX}).

Table 1. Animals Characteristics

	Control	Pre-Diabetes	Diabetes
Number, n (%)	28 (31.5%)	20 (22.5%)	41 (46.1%)
Age (year)	11±1	12±2	18±1**##
Weight (kg)	9±1	9±1	8±1*
FBG (mg/dL)	66±4	99±3**	227±20**##
HbA1c (%)	4.7±0.6	5.2±0.6	9.1±0.8**##
CHO (mg/dL)	120±7	113±9	167±15**##
TG (mg/dL)	63±7	82±8	217±36**##
HDL (mg/dL)	54±4	48±4	48±5**
LDL (mg/dL)	41±4	41±6	69±9**##
CHO/HDL	2.2±0.5	2.3±0.1	3.5±1.8*#

Each value depicts mean ± SE. * & ** P<0.05 & 0.01 vs control, # & ## P<0.05 & 0.01vs pre-diabetes .

Results

Figure 1. Left Ventricular Systolic Function in Different Groups.

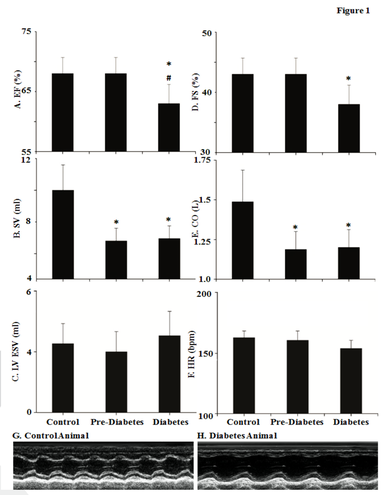


Table 2. Echocardiography parameters

	Control	Pre-Diabetes	Diabetes
LV dimensions			
LVSd (mm)	3.7±0.2	3.9±0.1	3.4±0.2
LVIDd (mm)	21.4±0.4	19.9±0.4	19.3±0.4
LVPWd (mm)	4.8±0.1	5.0±0.1	4.6±0.4
LVIDs (mm)	11.9±0.1	11.6±0.2	11.9±0.1
Mitral Valve parameters			
MVA (cm^2)	1.1±0.1	1.1±0.1	0.9±0.1
MaxVMV(cm/sec)	83±4	79±4	84±4
MV ΔP (mmHg)	2.6±0.3	2.6±0.3	3.0±0.4*##

Each value depicts mean ± SE. * & ** P<0.05 & 0.01 vs control, # & ## P<0.05 & 0.01vs pre-diabetes .

Figure 2. Left Ventricular Diastolic Function in Different Groups.

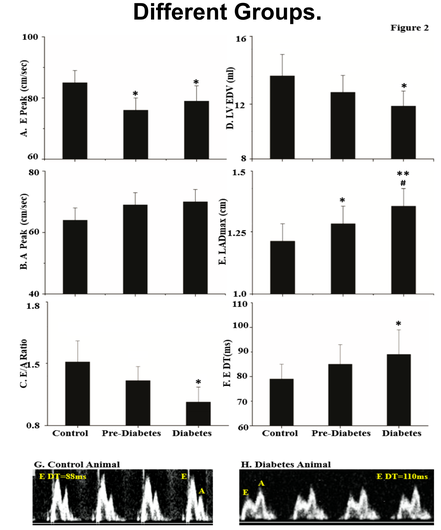
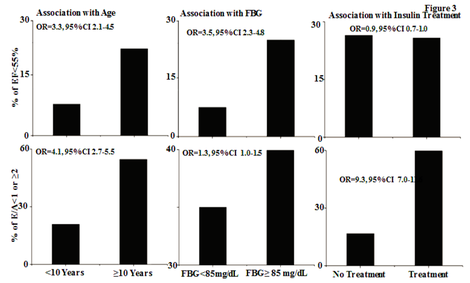


Figure 3. Personal characteristics associated with LV dysfunction



Summary

In summary, the present study demonstrated for the first time that dysmetabolic and diabetic NHPs are associated with LV systolic (increased ESV, decreased EF, etc.) and diastolic (decreased EDV and E/A ratio, prolonged DT, etc.) dysfunctions similarly to that in diabetic patients by using noninvasive echocardiography. In addition, the similar pathogenetic characteristics and accompanying risk factors observed in both humans and NHPs make NHPs unique models for studying early development and environmental factors that affect obesity and diabetes and for studying potential pharmacological interventions. The spontaneous-diabetic NHP model is a highly translatable tool for studying human disease not only for studying pathogenic mechanisms but also for testing the novel therapies for both cardiovascular and metabolic disorders.