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Original article

Myocardial dysfunction identified by three-dimensional speckle tracking echocardiography in type 2 diabetes patients relates to complications of microangiopathy

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ABSTRACT

Background: The clinical effect of diabetic microangiopathy on left ventricular (LV) function is still uncertain. The purpose of this study was to assess the relation between diabetic microvascular complications and comprehensive myocardial deformation measurements using three-dimensional (3D) speckle tracking echocardiography.

Methods: Seventy-seven asymptomatic patients with type 2 diabetes mellitus (DM) and 35 age-matched healthy control subjects underwent 3D echocardiography. Patients with coronary artery disease or LV ejection fraction <50% were excluded. Presence of proliferative retinopathy, microalbuminuria as nephropathy, and decreased coefficient of variation of R-R intervals (CVRR) <3% as cardiac autonomic neuropathy were defined as diabetic microvascular complications.

Results: LV ejection fraction, LV mass index, and global radial strain did not differ between control and DM patients. However, global longitudinal and circumferential strain and endocardial area change ratio were lower in patients with DM than in the controls ($-12.0 \pm 3.0\%$ vs. $-16.2 \pm 1.9\%$, $-27.7 \pm 7.1\%$ vs. $32.2 \pm 5.7\%$, $-37.6 \pm 7.6\%$ vs. $44.0 \pm 6.2\%$, respectively, $p < 0.001$). In DM patients, longitudinal strain is related to CVRR ($R = 0.58$, $p < 0.001$), retinopathy stage, and nephropathy stage.

Conclusions: Diabetic microangiopathy and its accumulated effects significantly related to subclinical LV dysfunction are characterized by impaired longitudinal shortening.

Introduction

Diabetic cardiomyopathy, defined as left ventricular (LV) dysfunction occurring independently of coronary artery disease and hypertension [1], might be an important substrate for developing heart failure [2]. Although diabetic cardiomyopathy is thought to be a multifactorial disease, the pathophysiological significance of microvascular complications remains unclear [3]. Among the diabetic microangiopathies [4], cardiac autonomic neuropathy [5,6] is focused on because it has been reported to relate to adverse clinical outcomes [7] and is commonly observed in many diseases such as symptomatic heart failure, chronic kidney disease, myocardial infarction, hibernating myocardium, and in cardiac transplantation [8]. Furthermore, retinopathy [9,10] and nephropathy [11] show an apparent effect on the occurrence of heart failure and its outcome.

Two-dimensional (2D) speckle tracking echocardiography (STE) has revealed systolic, and not just diastolic [12], longitudinal dysfunction to be a sign of early mechanical damage in the diabetic heart [13] and poor prognosis [14]. Three-dimensional (3D) STE has been introduced as a promising quantitative technique allowing a more accurate and comprehensive evaluation of myocardial deformation than conventional cardiovascular imaging techniques of LV deformation [15]. Compared to 2D echocardiography, the 3D

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approach is not affected by cut-down views and performs tracking over time in all three dimensions, avoiding any potential out-of-plane motion of the ultrasonic speckles [16]. Accordingly, the aim of the present study was to reveal a complete picture of LV systolic deformation abnormality in asymptomatic patients with diabetes mellitus (DM) using 3D-STE comprehensively and to investigate the effect of the degree of DM microvascular disease on subclinical LV dysfunction.

Methods

Study population

We enrolled 77 hospitalized patients with type 2 DM requiring diabetes education in this study. Patients with coronary artery disease or LV ejection fraction (LVEF) <50%, other than sinus rhythm, significant valvular disease, and inadequate echocardiographic image quality for analysis were excluded. Patients with coronary artery disease were excluded by coronary computed tomography angiography or myocardial scintigraphy. Reasons for performing computed tomography or scintigraphy included carotid atherosclerosis, ischemic changes on electrocardiogram (ECG), positive exercise ECG test results, or LV wall motion abnormalities on echocardiography. ECG abnormalities, such as Q waves, ST-T changes, and negative T waves, positive exercise ECG test results, and LV wall motion abnormalities on echocardiography were considered to be suggestive of the presence of coronary artery disease. The control population consisted of 35 age-matched healthy subjects. Ethical approval was obtained from the local institutional review committee, and all patients provided written informed consent.

Echocardiographic examinations

Echocardiographic examinations were performed with an Aplio-Artida^{TM} (Toshiba Medical Systems Co., Tochigi, Japan) echocardiographic system with a multi-frequency transducer. LV diameters were measured on a 2D-guided M-mode image. The LV mass index was calculated from 2D echocardiographic measurements using the area-length formula at end-diastole and corrected for body surface area. LV volumes and LVEF were measured by biplane Simpson's method in apical 4- and 2-chamber views. The peak velocities of early (E) and late (A) mitral inflow, the ratio E to A (E/A), and the deceleration time of the E-wave were measured using pulsed Doppler echocardiography with the sample volume at the tip of the mitral valve leaflet. Using tissue Doppler imaging, the peak early diastolic velocities of (E′) at the basal septal and lateral mitral annulus were obtained in the apical 4-chamber view.

3D-STE

Full-volume ECG-gated 3D data sets were acquired from apical positions using a matrix array transducer (3 V). To obtain these data sets, 6 sectors were scanned and automatically integrated into a wide-angle (70×70 degrees) pyramidal data image covering the entire LV. The volume rate of each image was set at approximately 30 Hz. The data were stored and transferred to a computer (Inspiron 1300; Dell Inc., Round Rock, TX, USA) for off-line analysis. The images were analyzed for wall deformation with specialized software (3D Wall Motion Tracking, Toshiba Medical Systems Co.). First, the endocardial border of the 4-chamber image at end-diastole was traced manually, followed by manual tracing of the epicardial border. Then, the same tracing processes were repeated in the 2-chamber image. After these long-axis tracings were complete, 3D myocardial surfaces were automatically reconstructed, and fine adjustments were made to the traced borders on the short-axis images.

We identified the tracking quality by eye-ball based on both endo- and epicardial trace lines on multiplanar reconstruction images. Finally, 6 LV basal, 6 mid, and 4 apical segment measurements (total 16) of strain were calculated as strain = $[L(t) - L_0]/L_0$, where $L(t)$ is the segment length at time t and L_0 is the segment length at the end diastole. Then, the following parameters were obtained: global radial strain (GRS), global circumferential strain (GCS), global longitudinal strain (GLS), and area change ratio (ACR). GRS was measured based on both endo- and epicardial tracking, and GLS, GCS, and ACR were calculated based on endocardial surface deformation.

Reproducibility of 3D-STE

We selected 10 studies at random for assessment of intra- and interobserver reproducibility of speckle tracking analysis. To test intra-observer variability, a single observer analyzed the data twice. The second analysis was done 1 week after the first analysis. To test interobserver variability, a second observer analyzed the data without knowledge of the first observer's measurements. Reproducibility was assessed as the mean percent error (absolute difference divided by the mean of the two individual observations).

Complications of diabetes

We evaluated cardiac autonomic nervous system function by use of the coefficient of variation of R-R intervals (CVRR). Analysis of beat-to-beat fluctuations in heart rate provides a sensitive, quantitative, and noninvasive measure of the functioning of the principal rapidly reacting cardiovascular control systems: the sympathetic and parasympathetic nervous systems [17]. CVRR measurements were obtained based on previously reported methods [18]. First, the patients were kept at rest in a supine position for 15 min prior to monitoring by ECG. The R-R intervals were measured for 3 min on the ECG. The CVRR was obtained from the recorded R-R intervals by dividing their standard deviation (SD) by the mean. The normal value of CVRR of 40- to 50-year-old subjects is $3 \pm 1\%$. Therefore, an abnormal CVRR was defined as <3% in the present study.

The stage of diabetic retinopathy was diagnosed by ophthalmologists based on a modification of the Davis classification: simple retinopathy as class A and proliferative retinopathy as class B. The nephropathy stage was diagnosed according to the presence of urine albumin and estimated glomerular filtration rate (eGFR). Stage 1 was defined as no albuminuria and normal/high eGFR, stage 2 as microalbuminuria and normal/high eGFR, stage 3 as persistent proteinuria and decreased eGFR, stage 4 as persistent proteinuria and extremely decreased GFR, and stage 5 as patients receiving hemodialysis. Microangiopathy total burden was calculated as the sum of the following scores: CVRRs of the upper, middle, and highest tertile were scored as 0, 1, and 2, respectively; class A retinopathy was scored as 1 and class B as 2; and nephropathy stage 1 was scored as 1, and $\geq$ state 2 was scored as 2.

Statistical methods

All values are expressed as mean $\pm$ SD. The χ^2-test was used for categorical variables. Comparisons between two groups were performed using the Student t-test for continuous variables. Analysis of variance (ANOVA) was used to compare results among groups divided by the degree of microvascular complication, and post hoc analysis was performed using Scheffé's test. Scheffé's partial correlations for confounding variables were performed to evaluate the association among the nephropathy stage, retinopathy stage, and LV 3D-STE data. The data were analyzed using standard statistical