Dobutamine Stress Echocardiography Unmasks Early Left Ventricular Dysfunction in Asymptomatic Patients with Uncomplicated Type 2 Diabetes: A Comprehensive Two-Dimensional Speckle-Tracking Imaging Study

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Background: Discrepancies are present in the literature on resting myocardial mechanics in patients with uncomplicated type 2 diabetes mellitus (T2DM). Data are noticeably sparse regarding circumferential function and torsional mechanics. Resting deformation imaging may not be sensitive enough to detect subtle dysfunctions. The aim of this study was thus to comprehensively evaluate myocardial mechanics in patients with T2DM at rest and to investigate whether dobutamine stress echocardiography could unmask functional alterations that would remain otherwise subtle at rest.

Methods: Forty-four patients with T2DM and 35 healthy control subjects of similar age and sex were prospectively recruited. After conventional echocardiography, myocardial mechanics was evaluated at rest and during low-dose dobutamine stress echocardiography (target heart rate, 110 beats/min).

Results: Patients with T2DM presented with altered global diastolic function but preserved systolic function. Deformation imaging indexes were similar between groups at rest, but significant differences were noticed under dobutamine infusion for longitudinal strain ($-21.2 \pm 2.4\%$ vs $-24.2 \pm 2.5\%$, $P < .001$), circumferential strain (apex, $-32.3 \pm 5.3\%$ vs $-36.3 \pm 5.3\%$, $P = .002$; papillary muscle, $-25.6 \pm 3.2\%$ vs $-28.0 \pm 3.6\%$, $P = .001$; base, $-23.2 \pm 3.6\%$ vs $-25.3 \pm 3.8\%$, $P = .03$), apical ($11.2 \pm 4.4^\circ$ vs $14.1 \pm 6.3^\circ$, $P = .020$) and basal ($-12.2 \pm 3.3^\circ$ vs $-14.3 \pm 3.9^\circ$, $P = .021$) rotation, and twist ($21.9 \pm 5.9^\circ$ vs $26.8 \pm 8.3^\circ$, $P = .007$). Multivariate analysis identified epicardial fat, dyslipidemia, and fasting glycaemia as significant contributors to the changes from rest to dobutamine.

Conclusions: These findings demonstrate the usefulness of dobutamine stress echocardiography in establishing impairments in myocardial mechanics in patients with uncomplicated T2DM. Systemic metabolic disturbances and epicardial fat act as the main contributors to the blunted response to dobutamine stress in these patients. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Uncomplicated type 2 diabetes, Asymptomatic patients, Dobutamine stress echocardiography, Speckle-tracking imaging, Regional myocardial function, Epicardial adipose tissue

Type 2 diabetes mellitus (T2DM) is a worldwide epidemic that is increasing constantly.[1] The leading cause of morbidity and mortality, as well as the most frequent complication observed in patients with T2DM, is diabetic cardiomyopathy (DMCM).[2] DMCM develops independently from hypertension or coronary artery disease (CAD), and its pathogenesis is thought to begin shortly after the onset of T2DM, emphasizing the importance of early diagnosis.[2]

Largely on the basis of standard echocardiography, the earliest stages of DMCM have long been defined as a diastolic dysfunction with preserved systolic function, as evidenced by a normal left ventricular (LV) ejection fraction. However, the latter is not a sensitive marker for the detection of subclinical systolic dysfunction. The emergence of techniques for analyzing myocardial wall deformation that are sensitive to subtle myocardial impairment made it possible to reveal preclinical LV regional systolic abnormalities[3-5] in T2DM patients with normal

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Abbreviations

σ_{ES} = Systolic meridional wall stress

2D = Two-dimensional

BMI = Body mass index

BP = Blood pressure

CAD = Coronary artery disease

CRPus = Ultrasensitive C-reactive protein

CS = Circumferential strain

DB = Dobutamine

DMCM = Diabetic cardiomyopathy

DSE = Dobutamine stress echocardiography

DTI = Doppler tissue imaging

EAT = Epicardial adipose tissue

HR = Heart rate

LS = Longitudinal strain

LV = Left ventricular

SI-DI = Strain imaging diastolic index

STE = Speckle-tracking echocardiography

T2DM = Type 2 diabetes mellitus

conventional echocardiography. However, this finding has not been uniformly reported,[6,7] especially in uncomplicated T2DM. Those discrepancies may likely arise from differences in study populations (e.g., glycemic control, presence of extracardiac complication and comorbidities, insulin therapy).

Most studies performing speckle-tracking echocardiography (STE) in patients with T2DM have focused on longitudinal deformation. However, because of myocardial fiber architecture and geometry, LV function results from a complex interplay between multidirectional (longitudinal, circumferential, and radial) deformations and torsional mechanics. Longitudinal strain (LS) is thus principally governed by the subendocardial layer, whereas midmyocardial and subepicardial fibers are mainly responsible for circumferential strain (CS) and torsional mechanics. Investigating all components of LV regional myocardial function is therefore essential to estimate the transmural impact of T2DM and to provide a pathophysiologic overview of the mechanisms of LV dysfunction.[8] However, current data regarding CS and rotational mechanics are noticeably sparse and conflicting, emphasizing the need for further investigations.[3-5,9]

Most studies of T2DM have been conducted at rest, and consequently, it might be possible that resting deformation imaging is not sensitive enough to detect subtle dysfunction, especially in uncomplicated T2DM. Dobutamine stress echocardiography (DSE) is usually performed when CAD is suspected, allowing wall motion abnormalities undetectable at rest to be revealed.[10] In T2DM, DSE has already been used in previous studies using Doppler tissue imaging (DTI) and has enabled researchers to unveil LV longitudinal myocardial alterations that remained otherwise subtle at rest.[11,12] However, such an approach exhibits shortcomings. As a result of angle dependency, DTI restricts the evaluation of myocardial deformation to basal and mid segments of the left ventricle in its longitudinal axis only, failing to take into account the complex three-dimensional mechanics of myocardial wall motion.[13] The use of STE attenuates those limitations[14] and, more important, enables the assessment of CS and torsional mechanics, two key components of the myocardial adaptive response to increased workload.[15-17] Using STE during DSE could thus provide a more reliable and comprehensive assessment of the early alterations of the diabetic heart.

Among the different factors that have been linked to LV dysfunction in patients with metabolic diseases, growing evidence suggests that epicardial adipose tissue (EAT) may play a substantial role.[18,19] Because of its tight relationship with the myocardium, EAT actually influences cardiomyocyte function, being cardioprotective in normal circumstances but becoming a source of proinflammatory cytokines and oxidative stress in a pathologic context.[20,21] However, to our knowledge, no previous study has explored the link between EAT and LV myocardial function in response to DSE in patients with T2DM.

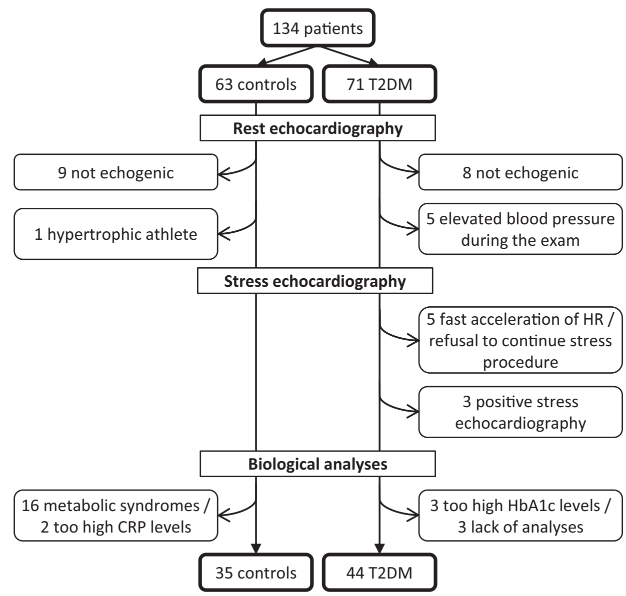

Figure 1 Flowchart of patient recruitment.

Thus, our aims were, first, to comprehensively study LV longitudinal and circumferential deformation, as well as rotation and twist mechanics, in asymptomatic patients with uncomplicated T2DM at rest and, second, to evaluate whether DSE can unmask functional alterations that would remain subtle at rest. Finally, the third aim of this study was to assess the association between EAT and LV regional myocardial function during DSE.

METHODS

Study Population

Patients were prospectively recruited from our cardiology department from January 2015 to July 2016. The exclusion criteria for both populations included severe obesity, insulin therapy, LV ejection fraction < 55%, known cardiovascular diseases, and T2DM-related complications, including moderate to severe autonomic neuropathy, proliferative retinopathy, and nephropathy. An additional exclusion criterion was poor echogenicity. The control subjects were referred for routine checkups, and all had normal physical examination and echocardiographic findings. All subjects were free of epicardial CAD, attested by negative findings on high-dose DSE (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or coronary angiography when appropriate. Patients with hypertension but well-controlled blood pressure (BP) were included. After application of the inclusion and exclusion criteria, a total of 44 patients with T2DM and 35 healthy control subjects of similar age and sex were enrolled (see flowchart, Figure 1). The study was approved by the local human ethics committee (IRB-15/05.01), and all subjects gave written informed consent.

Clinical and Biologic Assessments

Patients underwent medical examinations, during which ongoing treatments and existence of risk factors were noted. Blood samples were then collected, and fasting glycemia, glycated hemoglobin,