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Clinical Implications of Echocardiographic Phenotypes of Patients With Diabetes Mellitus

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ABSTRACT

BACKGROUND Type 2 diabetes mellitus (T2DM) may alter cardiac structure and function, but obesity, hypertension (HTN), or aging can induce similar abnormalities.

OBJECTIVES This study sought to link cardiac phenotypes in T2DM patients with clinical profiles and outcomes using cluster analysis.

METHODS Baseline echocardiography and a composite endpoint (cardiovascular mortality and hospitalization) were evaluated in 842 T2DM patients from 2 prospective cohorts. A cluster analysis was performed on echocardiographic variables, and the association between clusters and clinical profiles and outcomes was assessed.

RESULTS Three clusters were identified. Cluster 1 patients had the lowest left ventricular (LV) mass index and ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e′) ratio, had the highest left ventricular ejection fraction (LVEF), and were predominantly male with the lowest rate of obesity or HTN. Cluster 2 patients had the highest strain and highest E/e′ ratio, were the oldest, were predominantly female, and had the lowest rate of isolated T2DM (without HTN or obesity). Cluster 3 patients had the highest LV mass index and volumes and the lowest LVEF and strain, were predominantly male, and shared similar age and rate of obesity and HTN as cluster 1 patients. After follow-up of 67 months (interquartile range: 40 to 87), the composite endpoint occurred in 56 of 521 patients (10.8%). Clusters 2 (hazard ratio: 2.37; 95% confidence interval: 1.15 to 4.88) and 3 (hazard ratio: 2.19; 95% confidence interval: 1.00 to 4.82) had a similar outcome, which was worse than cluster 1.

CONCLUSIONS Cluster analysis of echocardiographic variables identified 3 different echocardiographic phenotypes of T2DM patients that were associated with distinct clinical profiles and highlighted the prognostic value of LV remodeling and subclinical dysfunction. (J Am Coll Cardiol 2017;70:1704–16) © 2017 by the American College of Cardiology Foundation.

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Insulin resistance and glycemic dysregulation are associated with subtle and progressive modifications in cardiac structure and function. Such a "metabolic exposome" results in left ventricular (LV) remodeling (1-3) and impaired LV systolic and diastolic function (4,5). More specifically, type 2 diabetes mellitus (T2DM), an independent risk factor for heart failure (HF) (6), can induce a diabetic cardiomyopathy (7-9). In T2DM, early cardiac modifications include LV hypertrophy (10), diastolic dysfunction (11), and decreased myocardial strain (12-14), which are precursors for the development of LV remodeling (15) and adverse outcomes, including HF (16) and all-cause mortality and hospitalization (17).

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Obesity and hypertension (HTN) are frequent comorbidities of T2DM (18-20), and many of the abnormalities found in diabetic cardiomyopathy are analogous to those described in both obese (21) and hypertensive patients (22,23). Moreover, parameters such as age (1,24) and sex might also influence early cardiac geometry and functional changes. The specific contribution of these causative factors is unclear, as is their synergistic contribution to cardiac dysfunction in T2DM. Whereas classic statistical analyses are built on a priori hypothesis, cluster analysis might improve cardiac phenotyping and provide new insights in heterogeneous patient groups, such as those with T2DM, by providing an innovative exploratory analysis (25). Therefore, we hypothesized that cluster analysis might allow identification of T2DM patient groups (clusters) with common cardiac phenotypes based on ultrasound data and that those cardiac phenotypes are associated with distinct clinical profiles and different prognosis.

METHODS

This analysis used data from 2 large prospective cohorts (453 from Lyon, France, and 389 from Brisbane, Australia) of asymptomatic T2DM patients free of overt heart disease. Although similar inclusion criteria were shared between the 2 cohorts in terms of age, T2DM, and absence of overt cardiac disease, the different characteristics of the 2 populations, especially the prevalence of obesity and HTN, provided a heterogeneity suitable for cluster analysis (Online Table 1).

Inclusion criteria were T2DM with normal left ventricular ejection fraction (LVEF; >50%) and taking oral hypoglycemic or insulin treatment (12,15,26). Exclusion criteria were type 1 diabetes mellitus; symptoms, signs (clinical or electrocardiographic), or history of heart disease; presence of regional LV wall motion abnormalities; absence of sinus rhythm; history of cardiomyopathy, coronary artery disease, or valvular heart disease; severe renal failure (defined as creatinine clearance <30 ml/min); echocardiographic images unsuitable for quantification; severely uncontrolled diabetes (glycosylated hemoglobin [HbA_{1c}] >12% or glycemia >3 g/l); and uncontrolled resting blood pressure (>180/100 mm Hg). Silent ischemia and/or coronary artery disease was excluded by a negative stress electrocardiogram, echocardiogram, or myocardial perfusion scintigraphy, and/or by normal coronary angiogram.

Ethics committee approval was obtained from both institutions, and all subjects provided informed consent to participate.

CLINICAL AND BIOLOGICAL DATA. All patients underwent physical examination, echocardiography, and biochemical analysis on the same day at inclusion. Clinical data were collected regarding the age, sex, diabetes duration, height, weight, smoking status, and medication use of subjects. A complete physical examination was performed. Hemodynamic parameters, including heart rate and blood pressure, were measured. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Diagnosis of HTN was based on medical history and the use of antihypertensive medications and/or office blood pressure measurement confirmed by ambulatory blood pressure monitoring (27).

The presence or absence of diabetic retinopathy was assessed by dilated eye examination performed by an ophthalmologist (7). The diagnosis of neuropathy was determined based on interview and physical examination. Blood samples were taken for biochemical analysis of creatinine, cholesterol, triglyceride, HbA_{1c}, and brain natriuretic peptide

ABBREVIATIONS AND ACRONYMS

A = peak late diastolic velocity

BMI = body mass index

CI = confidence interval

E = peak early diastolic velocity

e′ = mitral annular early diastolic velocity

e′ lateral = early diastolic velocity at the lateral site of the mitral annulus

e′ septal = early diastolic velocity at the septal site of the mitral annulus

HbA_{1c} = glycosylated hemoglobin

HF = heart failure

HR = hazard ratio

HTN = hypertension

LA = left atrium

LV = left ventricle

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

LVMi = left ventricular mass indexed to body surface area

T2DM = type 2 diabetes mellitus

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