Impact of Diabetes and Increasing Body Mass Index Category on Left Ventricular Systolic and Diastolic Function

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Background: Diabetes and obesity are both worldwide growing epidemics, and both are independently associated with increased risk for heart failure and death. The aim of this study was to examine the additive detrimental effect of both diabetes and increasing body mass index (BMI) category on left ventricular (LV) myocardial systolic and diastolic function.

Methods: The present retrospective multicenter study included 653 patients (337 with type 2 diabetes and 316 without diabetes) of increasing BMI category. All patients had normal LV ejection fractions. LV myocardial systolic (peak systolic global longitudinal strain and peak systolic global longitudinal strain rate) and diastolic (average mitral annular e′ velocity and early diastolic global longitudinal strain rate) function was quantified using echocardiography.

Results: Increasing BMI category was associated with progressively more impaired LV myocardial function in patients with diabetes ($P < .001$). Patients with diabetes had significantly more impaired LV myocardial function for all BMI categories compared with those without diabetes ($P < .001$). On multivariate analysis, both diabetes and obesity were independently associated with an additive detrimental effect on LV myocardial systolic and diastolic function. However, obesity was associated with greater LV myocardial dysfunction than diabetes.

Conclusion: Both diabetes and increasing BMI category had an additive detrimental effect on LV myocardial systolic and diastolic function. Furthermore, increasing BMI category was associated with greater LV myocardial dysfunction than diabetes. As they frequently coexist together, future studies on patients with diabetes should also focus on obesity. (J Am Soc Echocardiogr 2018;31:916-25.)

Keywords: Cardiomyopathy, Diabetes mellitus, Obesity, Ventricles

There is currently a worldwide epidemic of obesity and type 2 diabetes. The latest projection by the World Health Organization estimated that globally in 2005, approximately 1.6 billion adults >15 years of age were overweight, and at least 400 million adults were obese. Because of the obesity epidemic, there is a concomitant increase in the prevalence of type 2 diabetes. In 2000, the World Health Organization estimated that more than 170 million people worldwide had diabetes, and the prevalence was projected to double in the next 20 years.[1] Both obesity and diabetes are independently associated with increased risk for heart failure.[2] Although the pathophysiologic mechanisms underlying obesity and diabetic cardiomyopathy are not identical, the combination of insulin resistance, hyperinsulinemia, and hyperglycemia leads to inflammation, neurohormonal activation of the renin-angiotensin-aldosterone system, and eventual myocardial structural and functional changes.[3-8] Despite previous studies showing obesity to be an independent risk factor for subsequent development of diabetes and heart failure,[2,9,10] few have examined the simultaneous impact of increasing body mass index (BMI) category and concomitant diabetes on changes in left ventricular (LV) myocardial function. We hypothesized that both increasing BMI

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Abbreviations

2D = Two-dimensional

ANOVA = Analysis of variance

BMI = Body mass index

BSA = Body surface area

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVESV = Left ventricular end-systolic volume

category and diabetes are independently associated with progressive impairment of LV myocardial systolic and diastolic functions and that the association is additive and not synergistic. Thus, we conducted a multicenter retrospective study (Leiden University Medical Center, The Netherlands, and Liverpool Hospital, Australia) whereby both patients with diabetes and those without diabetes without coronary artery disease were evaluated in order to (1) examine the impact of increasing BMI category on LV myocardial systolic (peak systolic global longitudinal strain and peak systolic global longitudinal strain rate) and diastolic function (average mitral annular e′ velocity and early diastolic global longitudinal strain rate) as quantified by echocardiography in patients with type 2 diabetes, (2) compare LV myocardial systolic and diastolic function with increasing BMI category between patients with diabetes and those without diabetes, and (3) determine the independent and additive detrimental effect of increasing BMI category and diabetes on LV myocardial systolic and diastolic function.

METHODS

Patient Population

The overall patient population consisted of 653 patients recruited from two institutions (104 from Liverpool Hospital and 549 from Leiden University Medical Center). All patients were identified over a 10-year period from the Australian and Dutch departmental combined echocardiographic and clinical databases. Of these, 337 had type 2 diabetes, which was diagnosed according to World Health Organization criteria.[11] Although BMI does not take into account the wide variation in body fat distribution, it is the most useful population-level measure of obesity and is recommended by the World Health Organization to define overweight and obesity within a population and the risks associated with it.[12] Furthermore, several multicenter and epidemiologic studies have demonstrated the independent prognostic value of BMI as a measure of general obesity for predicting all-cause mortality.[13-15] As there were only two patients with diabetes with BMI < 20 kg/m^2 measured at the time of echocardiography, all 337 patients with diabetes were divided into three categorical groups: 80 lean patients with diabetes (BMI < 25 kg/m^2), 139 overweight patients with diabetes (BMI 25–29.9 kg/m^2), and 118 obese patients with diabetes (BMI ≥ 30 kg/m^2).

Patients with type 2 diabetes were compared against 316 patients without diabetes of similar age, gender, and BMI. All patients without diabetes were clinically referred for assessment of LV and/or valvular function and had structurally normal hearts on echocardiography. Similarly, as there were only five patients without diabetes with BMI < 20 kg/m^2, all 316 patients without diabetes were divided into three categorical groups: 89 lean patients without diabetes (BMI < 25 kg/m^2), 134 overweight patients without diabetes (BMI 25–29.9 kg/m^2), and 93 obese patients without diabetes (BMI ≥ 30 kg/m^2).

The exclusion criteria for all patients with diabetes and without diabetes included age < 18 years, rhythm other than sinus rhythm, LV ejection fraction (LVEF) $< 50\%$, moderate or severe valvular stenosis or regurgitation, and congenital heart disease. To avoid coronary artery disease as a potential confounding factor for any changes observed in myocardial function, all patients with known significant underlying coronary artery disease, previous myocardial infarction, previous coronary artery bypass surgery or percutaneous coronary intervention, presence of segmental wall motion abnormalities on echocardiography, or positive results on stress testing were excluded.

All patients underwent history, physical, biochemical, and transthoracic echocardiographic examinations. Baseline biochemical analyses included hemoglobin level, glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula as recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guidelines[16] and glycated hemoglobin level. The definition of hypertension was different between patients with and those without diabetes. In patients with diabetes, the cutoff was >130/80 mm Hg on two separate occasions after >5 min of rest. In patients without diabetes, the cutoff was >140/90 mm Hg on two separate occasions after >5 min of rest. All clinical and biochemical variables were collected by an independent observer blinded to the echocardiographic results.

The impact of increasing BMI categories on LV structure (LV volumes and mass) and function was initially assessed in the patients with type 2 diabetes. LV myocardial function within each BMI category (lean, overweight, and obese) in the diabetic population was then compared against patients without diabetes. Finally, to determine the independent and additive detrimental effect of increasing obesity and diabetes on LV myocardial function, multivariate analysis was performed with BMI categories and the presence or absence of diabetes entered as covariates, adjusted for baseline age, gender, systolic blood pressure, heart rate, LV mass, and LV volume. Echocardiographic analyses for all patients with and without diabetes, including two-dimensional (2D) speckle-tracking, were performed offline. Therefore, the present evaluation does not tabulate the results summarized in clinical reports.

The institutional review boards approved the study. The institutional review board of the Leiden University Medical Center waived the need to obtain patient written informed consent for retrospective analysis of clinically acquired data anonymously handled.

Echocardiography

Transthoracic echocardiography was performed in all subjects at rest using commercially available ultrasound systems (Vivid 7 and E9, GE Vingmed Ultrasound, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5; GE Vingmed Ultrasound). A complete 2D, color, pulsed, and continuous-wave Doppler echocardiographic examination was performed according to standard techniques.[17,18] LV end-diastolic volume and LV end-systolic volume (LVESV) were calculated using the Simpson biplane method of disks. LVEF was calculated and expressed as a percentage. LV mass was calculated from the formula as recommended by the American Society of Echocardiography.[19]

Transmitral inflow velocities were recorded using conventional pulsed-wave Doppler echocardiography in the apical four-chamber view using a 2-mm sample volume. Transmitral early (E-wave) and late (A-wave) diastolic velocities as well as deceleration time were recorded at the mitral leaflet tips. Average mitral annular e′ velocity and average E/e′ ratio were obtained from the septal and lateral annulus as recommended by current guidelines.[20] Maximal left atrial volume was calculated using the Simpson biplane method of discs in the four- and two-chamber views.