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Left Atrial Volume Index

Relation to Long-Term Clinical Outcome in Type 2 Diabetes

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Objectives The study sought to determine the prognostic importance of left atrial (LA) dilation in patients with type 2 diabetes mellitus (T2DM) and no history of cardiovascular disease (CVD).

Background T2DM is associated with the development of CVD, and morphological changes in the heart may appear before symptoms arise.

Methods A total of 305 T2DM patients without known CVD referred to a diabetes clinic were included consecutively (age 58.6 ± 11.3 years, diabetes duration 2.0 [interquartile range: 0 to 6.0] years). Each patient underwent a comprehensive echocardiogram and a myocardial perfusion scintigraphy (MPS) at inclusion. Patients were divided according to left atrial volume index (LAVi) ≥32 ml/m^2. Patients were followed for median of 5.6 (interquartile range: 5.1 to 6.1) years for the occurrence of major cardiac events and death.

Results LAVi ≥32 ml/m^2 was found in 105 patients (34%). During follow-up, 60 patients (20%) experienced the composite endpoint, of whom 28 (9%) died. Patients with LAVi ≥32 ml/m^2 had a significantly higher cardiac event rate and death rate ($p < 0.001$ and $p = 0.002$, respectively). Univariate predictors of the composite endpoint were age, hypertension, left ventricular diastolic function, E/e'_{septum}-ratio and LAVi ≥32 ml/m^2; however, myocardial ischemia on MPS was not a predictor. When adjusting for age and hypertension, only LAVi ≥32 ml/m^2 was a predictor of the composite endpoint (hazard ratio: 1.82 [95% confidence interval: 1.08 to 3.07], $p = 0.024$).

Conclusions Increased LAVi was an independent and incremental predictor of cardiovascular morbidity and mortality in T2DM patients with no history of CVD. (Presence of Macrovascular Disease in Type 2 Diabetes Mellitus; NCT00298844). (J Am Coll Cardiol 2013;62:2416–21) © 2013 by the American College of Cardiology Foundation

The morbidity (1,2) and mortality (3) of type 2 diabetes mellitus (T2DM) is closely associated with development of cardiovascular disease (CVD). In T2DM, morphological changes suggestive of heart disease may appear before symptoms arise. The prevalence of left ventricular (LV) diastolic dysfunction has been shown to be increased among T2DM patients (4) and, further, to also predict outcome (5).

The evaluation of diastolic function requires multiple Doppler echocardiography variables (6). As these variables are influenced by pre- and after-load, they will reflect the instantaneous interaction of LV filling pressures and LV compliance (7). During ventricular diastole, left atrial (LA) and LV pressures will equalize. Factors causing LV filling pressure to rise will, therefore, also cause LA pressure overload and LA dilation (7,8). Thus, in the absence of LA volume overload, LA volume will reflect both the severity and duration of LV diastolic dysfunction (6,8,9). In agreement with this, LA size has proven to be a powerful predictor of outcome in several disease entities, including myocardial infarction, severe aortic valve stenosis, and heart failure (10–12). The importance of LA dilation in T2DM patients is, however, not known. On the basis of this, we hypothesized that left atrial volume index (LAVi) would predict long-term outcome in these patients.

Methods

Study group. The present single-center study has previously been described in detail (13). In brief, 431 consecutive T2DM patients without any medical history of CVD met the inclusion and exclusion criteria, of whom 126 declined participation; thus, 305 (71%) patients were enrolled after

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providing informed consent. The study was registered at www.clinicaltrials.gov (NCT00298844) and was approved by the local ethics committee.

Each patient underwent a single-day structured examination program including an echocardiogram, myocardial perfusion scintigraphy (MPS), and 1-point ^{51}Cr-EDTA clearance procedure.

Echocardiography. The echocardiograms were obtained on a Vivid 5 GE medical ultrasound machine with a 2.5 MHz transducer (GE Medical System, Horten, Norway). Blinded analysis of images was done using EchoPac 7.0, PC-08 (GE Medical System, Horten, Norway). For all Doppler and tissue Doppler recordings, a horizontal sweep of 100 mm/s was used, and the average of 5 consecutive beats was measured and averaged.

LV SYSTOLIC FUNCTION. LV ejection fraction and LV volumes were estimated using the biplane modified Simpson's method (14). LV dimensions were obtained from the parasternal long-axis view (14).

LV DIASTOLIC FUNCTION. Mitral inflow was assessed with pulsed-wave Doppler obtained with the transducer in the apical 4-chamber view, with the Doppler beam aligned perpendicular to the plane of the mitral annulus. The Doppler sample volume was placed between the tips of the mitral leaflets during diastole. Pulsed-wave tissue Doppler was used at the septal and lateral mitral annulus to measure the mitral plane movement. LV filling was divided into 4 distinct filling patterns (normal, impaired relaxation, pseudonormal, and restrictive filling) on the basis of a combination of mitral inflow and tissue Doppler measurements of the mitral plane movement (6).

LAVI. LAVi was estimated by the biplane area-length method, using measurements at the apical 4- and 2-chamber views at end-systole and indexed by body surface area (14). LAVi $\geq$32 ml/m^2 was considered abnormally increased. The absolute interobserver agreement between 2 observers obtained in 20 randomly-selected study patients on LV diastolic filling pattern and LAVi over or below 32 ml/m^2 was 95% (kappa = 0.91) and 85% (kappa = 0.70), respectively.

MPS. MPS examinations were performed using electrocardiogram-gated single photon emission computed tomography with ^{99m}technetium sestamibi. Whenever a potential stress-induced perfusion defect was observed, an additional rest study was carried out to evaluate the degree of reversibility. A semiquantitative visual interpretation was made by 2 observers using a 20-segment model. A summed stress score (SSS) was calculated. Myocardial ischemia was defined as a regional perfusion abnormality with a total SSS $\geq$4 and at least 1 segment with an SSS $\geq$2. The diagnostic accuracy has been reported previously (15).

Clinical follow-up. The primary endpoint was a composite endpoint of death from all causes or the appearance of the first-occurred cardiovascular event during follow-up. Major adverse cardiovascular events (MACE) were nonfatal myocardial infarction, unstable angina, acute heart failure, ischemic stroke, and coronary or peripheral revascularization using the criteria from the DIAD (Detection of Ischemia in Asymptomatic Diabetics) trial (16). The secondary endpoint was death from all causes.

Overall mortality and MACE were recorded from the Danish Personnel Register and from discharge notes available in the Danish Admission Registry on October 1, 2012. In case of ambiguous information, original patient charts were reviewed.

Abbreviations and Acronyms

CVD = cardiovascular disease
LAVi = left atrial volume index
LV = left ventricular
MACE = major cardiovascular event(s)
MPS = myocardial perfusion scintigraphy
SSS = summed stress score
T2DM = type 2 diabetes mellitus

Statistics. Continuous variables are presented as mean ± SD and variables with a non-Gaussian distribution as median (interquartile range). Categorical variables are presented as numbers and percentages. The Student *t* test and Mann-Whitney 2-sample tests were used to test for between-group differences in independent continuous parametric and nonparametric variables. The chi-square test was used to test for differences between categorical variables.

Overall mortality and event rates were calculated using the product limit method and presented in Kaplan-Meier plots. Event rates were compared using the log-rank test. Further, estimation of hazard ratios was performed using Cox proportional hazards models. Comparison of each model's predictive capability was performed by comparing the C-statistic derived from the area under the receiver-operating characteristic curves using the generalized *U* statistic. A p value <0.05 was considered significant using STATA/SE 12.0 (StataCorp, College Station, Texas).

Results

The study included 305 consecutive T2DM patients who were followed for a median 5.6 (5.1 to 6.1) years, with complete follow-up data for all patients. Patient and echocardiographic characteristics are presented in Tables 1 and 2.

During follow-up, 60 patients (20%) experienced the composite endpoint, and 41 (15%) experienced a MACE. At follow-up, patients with LAVi $\geq$32 ml/m^2 had significant higher event rates ($p < 0.001$) (Fig. 1). Finally, during follow-up 28 patients (9%) died (Table 3), and further patients with LAVi $\geq$32 ml/m^2 had lower overall survival ($p = 0.002$) (Fig. 1). Finally, the 5-year event rates increased with increasing LAVi (Fig. 2). Univariate and multivariate predictors of the composite endpoint are presented in Table 4. When adjusting for age and hypertension, only LAVi $\geq$32 ml/m^2 was a predictor of the composite endpoint (Table 4). Finally, the incremental value of LAVi assessed in 4 modeling steps is shown in Figure 3. The addition of LAVi $\geq$32 ml/m^2 increased the area under the