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Relationship between increased left atrial volume and microvascular complications in patients with type 2 diabetes

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ABSTRACT

Aims: We assessed whether left atrial volume index (LAVI) was associated with the presence of microvascular complications in patients with type 2 diabetes, and whether this association was independent of hemodynamic and non-hemodynamic factors.
Methods: We studied 157 consecutive outpatients with type 2 diabetes with no previous history of ischemic heart disease, chronic heart failure and valvular diseases. A transthoracic echocardiography and myocardial perfusion scintigraphy were performed in all participants. Presence of microvascular complications was also recorded.
Results: Overall, 51 patients had decreased estimated glomerular filtration rate and/or abnormal albuminuria, 24 had diabetic retinopathy, 22 had lower-extremity sensory neuropathy, and 67 (42.7%) patients had one or more of these microvascular complications (i.e., combined endpoint). After stratifying patients by LAVI, those with LAVI ≥ 32 ml/m^2 had a greater prevalence of microvascular complication, lower left ventricular (LV) ejection fraction, higher LV mass index and higher E/e' ratio than those with LAVI <32 ml/m^2. Logistic regression analyses revealed that microvascular complications (singly or in combination) were associated with increased LAVI, independently of age, sex, diabetes duration, hemoglobin A1c, hypertension, LV-ejection fraction, LV mass index and the E/e' ratio.
Conclusions: These results indicate that microvascular diabetic complications are associated with increased LAVI in well-controlled type 2 diabetic patients with preserved systolic function and free from ischemic heart disease, independently of multiple potential confounders.

1. Introduction

Several epidemiological studies have demonstrated that type 2 diabetes is a powerful risk factor for cardiovascular diseases (CVDs), including the development of heart failure (HF) (Seshasai et al., 2011).

The mechanisms leading to the increased risk of HF in people with type 2 diabetes remain uncertain and are likely multifactorial. Possible pathogenic factors include coronary atherosclerosis, hypertension and other established CVD risk factors. However, a number of studies have suggested that type 2 diabetes may affect cardiac structure and function, independent of established CVD risk factors, consistent with the presence of a distinct diabetic cardiomyopathy (Boudina & Abel, 2007; Fang, Prins, & Marwick, 2004; Galderisi, Anderson, Wilson, & Levy, 1991; Rubler et al., 1972). Efforts to understand risk factors contributing to the increased burden of HF in people with type 2 diabetes are critical in reducing the morbidity and mortality attributed to this disease.

Left atrial (LA) enlargement is thought to be a sensitive marker of chronic left ventricular (LV) diastolic dysfunction (Tsang, Barnes, Gersh, Bailey, & Seward, 2002) and provides prognostic information incremental to both clinical parameters and conventional measures of LV function in various pathological conditions (Abhayaratna et al., 2006). The Framingham Heart Study investigators reported that after multivariable adjustment, LA enlargement was a strong predictor of incident stroke in men and mortality in both sexes (Benjamin, D'Agostino, Belanger, Wolf, & Levy, 1995). Other investigators reported that LA volume index (LAVI) ≥ 32 ml/m^2 was independently associated with an increased incidence of CVD and HF in a cohort of elderly individuals with preserved LV systolic function (Takemoto et al.,

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2005; Tsang et al., 2003). Again, increased LAVI predicted independently the risk of CVD mortality in patients with acute myocardial infarction (Moller et al., 2003), in those with dilated cardiomyopathy (Rossi et al., 2002), in those with chronic HF and preserved systolic function (Rossi et al., 2006, 2014), and in patients with chronic kidney disease (Hee et al., 2014).

For several years, most studies in type 2 diabetes were focused mainly on LV structural and functional abnormalities (Fang et al., 2003; Galderisi, 2006; Jarnert et al., 2008; Poulsen et al., 2010; Shishehbor et al., 2003). In recent years, however, there has been a growing scientific interest in exploring the functional and structural changes of the LA as well as the prognostic impact of LA enlargement on CVD outcomes in this patient population (Kadappu et al., 2012; Poulsen et al., 2013; Tadic & Cuspidi, 2015).

Recent data from the Atherosclerosis Risk in Communities study also demonstrated an independent association between diabetic retinopathy and the development of HF in patients with type 2 diabetes without a history of CVD (Cheung et al., 2008). Additionally, Aguilar et al. (2009) reported that more severe diabetic retinopathy was associated with both increased LAVI and increased LV mass, independently of age, sex, glycemic control, hypertension and previous ischemic heart disease (IHD).

To our knowledge, there is a paucity of published data regarding the relationship of the most important microvascular complications (retinopathy, nephropathy and peripheral neuropathy) with LAVI in patients with type 2 diabetes without overt IHD.

Thus, the aim of this study was to assess whether LAVI as measured by echocardiography was associated with the presence of microvascular complications in a large sample of type 2 diabetic patients free from IHD, and whether this association was independent of relevant hemodynamic and non-hemodynamic factors.

2. Materials and methods

2.1. Patients

We initially recruited 180 white consecutive outpatients with type 2 diabetes, who regularly attended our diabetes clinic during a period of 18 months. For the current study, we excluded patients with: (1) a prior history of IHD (myocardial infarction, angina, coronary revascularization), chronic HF, LV systolic dysfunction (i.e., LV ejection fraction <45%), moderate-to-severe heart valve diseases, paroxysmal or persistent atrial fibrillation and atrial flutter; (2) a prior history of cirrhosis, malignancy and overt nephropathy; and (3) a poor and unstable glycemic control. All these patients underwent an exercise stress myocardial perfusion scintigraphy to exclude the presence of inducible myocardial hypoperfusion/ischemia. After excluding those who had any myocardial perfusion defects on imaging ($n = 23$), we included 157 type 2 diabetic patients in the final analysis.

The local Ethics Committee approved the study protocol. All participants gave their written informed consent for participation in this research.

2.2. Clinical and laboratory data

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. A physician measured blood pressure with a mercury sphygmomanometer after patients had been seated quietly for at least 5 min. Patients were considered to have hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any anti-hypertensive drugs. Pulse pressure was determined as the difference between the systolic and diastolic blood pressure. Information on smoking status and use of medications was obtained from all patients via interviews during medical examinations.

Venous blood samples were drawn in the morning after an overnight fast. Serum creatinine (measured using a Jaffé rate-blanked and compensated assay) and other biochemical blood measurements were determined using standard laboratory procedures (DAX 96; Bayer Diagnostics, Milan, Italy). Low-density lipoprotein-cholesterol was calculated using the Friedewald's equation. Hemoglobin A1c (HbA1c) was measured by an automated high-performance liquid chromatography analyzer (HA-8140; Menarini Diagnostics, Florence, Italy); the upper limit of normal for the laboratory was 5.6%. The glomerular filtration rate (eGFR) was estimated by the four-variable Modification of Diet in Renal Disease study equation (Stevens, Coresh, Greene, & Levey, 2006). Albuminuria was measured by an immunonephelometric method on a morning spot urine sample and expressed as the albumin-to-creatinine ratio.

In all participants, the presence of microvascular diabetic complications was recorded. A single ophthalmologist diagnosed diabetic retinopathy using fundoscopy after pupillary dilation according to a clinical disease severity scale (no retinopathy, non-proliferative, proliferative or laser-treated retinopathy); the presence of proliferative retinopathy was confirmed by fundus fluorescein angiography (Targher et al., 2008). The presence of diabetic lower-extremity sensory neuropathy was recorded by the medical history and examination and by the use of biothesiometer Vibrotest to non-invasively measure the threshold of appreciation of vibration in three points on both feet. Nephropathy was defined as the presence of eGFR < 60 ml/min/1.73 m^2 and/or abnormal albuminuria (i.e., an albumin-to-creatinine ratio ≥30 mg/g creatinine) (Stevens et al., 2006). Presence of internal or common carotid artery stenoses was also ascertained by echo-Doppler scanning in all participants.

2.3. Echocardiography

A 12-lead standard resting electrocardiogram and a transthoracic echocardiographic Doppler evaluation with spectral tissue Doppler analysis (Vivid 7, GE Vingmed, Horten, Norway) were performed in all patients by a single experienced cardiologist, who was blinded to the participants' details. Conventional echocardiography was used to measure LV diameters, wall thickness, and mass according to standard criteria. LV end-diastolic and end-systolic volumes and ejection fraction (LV-EF) at rest were measured at the apical 4-chamber and 2-chamber views (by modified Simpson rule) (Lang et al., 2006). LA maximal volume was measured at the end of LV systole from the apical 4-chamber and 2-chamber views (maximum LA size) using the modified Simpson rule (Lang et al., 2006; Nagueh et al., 2009). LAVI was calculated as LA volume divided with the body surface area. Pulsed-wave Doppler was used to measure trans-mitral peak early diastolic velocity (E), peak late diastolic velocity (A) and E-wave deceleration time (Dte). Isovolumetric relaxation time (IVRT) was also calculated (Lang et al., 2006; Nagueh et al., 2009). Each value was obtained from the average of three measurements. Systemic arterial compliance (SAC) was estimated by the stroke volume-to-pulse-pressure ratio and systemic vascular resistance (SVR) index by mean arterial pressure ÷ cardiac index × 80 (Lang et al., 2006; Nagueh et al., 2009). Pulsed-wave tissue Doppler echocardiography of the septal and lateral mitral annulus was used to measure the early peak (e') and late (a') annular diastolic and systolic (s') tissue velocities, and the mean values of septal and lateral annulus measurements were used for analysis (Nagueh, Middleton, Kopelen, Zoghbi, & Quiñones, 1997; Ommen et al., 2000; Sohn et al., 1997).

Myocardial deformation measurements were also performed off-line in a subgroup of patients with adequate apical windows with the use of a standard EchoPac PC workstation application (GE Healthcare, Wisconsin, USA) for two-dimensional speckle-tracking myocardial strain analysis. Global longitudinal strain and strain rate curves were obtained in 127 patients, including all six LV myocardial segments from 4-chamber, 2-chamber, and long-axis apical views

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