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Early impairment in left ventricular longitudinal systolic function is associated with an increased risk of incident atrial fibrillation in patients with type 2 diabetes

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ABSTRACT

Aims: It is known that type 2 diabetic patients are at high risk of atrial fibrillation (AF). However, the early echocardiographic determinants of AF vulnerability in this patient population remain poorly known.
Methods: We followed-up for 2 years a sample of 180 consecutive outpatients with type 2 diabetes, who were free from AF and ischemic heart disease at baseline. All patients underwent a baseline echocardiographic-Doppler evaluation with tissue Doppler and 2-D strain analysis. Standard electrocardiograms were performed twice per year, and a diagnosis of incident AF was confirmed in affected patients by a single cardiologist.
Results: Over the 2-year follow-up period, 14 (7.8%) patients developed incident AF. In univariate analyses, echocardiographic predictors of new-onset AF were greater indexed cardiac mass, larger indexed left atrial volume (LAVI), lower global longitudinal strain (LS_{SYS}), lower global diastolic strain rate during early phase of diastole (SR_E), lower global diastolic strain rate during late phase of diastole (SR_L), and higher E/SR_E ratio. Multivariate logistic regression analysis showed that lower LS_{SYS} remained the only significant predictor of new-onset AF (adjusted-odds ratio 1.63, 95%CI 1.17–2.27; $p < 0.005$) after adjustment for age, sex, diabetes duration, indexed cardiac mass and LAVI. Results were unchanged even after adjustment for body mass index, hypertension and glycemic control.
Conclusions: This is the first prospective study to show that early LS_{SYS} impairment independently predicts the risk of new-onset AF in type 2 diabetic patients with preserved ejection fraction and without ischemic heart disease. Future larger prospective studies are needed to confirm these findings.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major global health problem with an estimated worldwide prevalence of 2.8% in 2000, projected to increase to approximately 4.5% in 2030 (Wild, Roglic, Green, Sicree, & King, 2004). Patients with T2DM have at least twice the risk of developing cardiovascular complications and death compared with subjects without diabetes (Huxley, Barzi, & Woodward, 2006).

Similarly, there is now convincing evidence of progressive increases in prevalence, incidence, and morbidity and mortality related to atrial fibrillation (AF) between 1990 and 2010 worldwide, with significant public health implications (Benjamin et al., 1998; Chungh et al., 2014; Miyasaka et al., 2006).

AF is very common in patients with T2DM with estimates of prevalence which range from 5 to 8% in primary care setting (Du et al., 2009; Ostgren, Merlo, Råstam, & Lindblad, 2004) to 15% in hospitalized patients (Movahed, Hashemzadeh, & Jamal, 2005). It has been estimated that the presence of T2DM, irrespective of coexisting comorbidities, confers an approximately 1.5-fold increased risk of new-onset AF (Anonymous, 2014; Huxley, Filion, Konety, & Alonso, 2011).

The increased risk of new-onset AF observed in patients with T2DM is likely due to coexisting comorbidities, such as obesity, hypertension and ischemic heart disease (IHD) (Anonymous, 2014). However, convincing evidence also suggests that T2DM per se may affect cardiac function and structure, irrespective of these comorbidities, consistent with the existence of a distinct diabetic cardiomyopathy (Bonapace et al., 2015; Fang et al., 2003; Kadappu et al., 2012; Kannel, Hjortland, & Castelli, 1974).

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Speckle-tracking echocardiography is a diagnostic tool that provides useful information about the presence of early left ventricular (LV) systolic dysfunction, which is unmasked by global longitudinal strain (LS_{SYS}) alterations that may be predictive of cardiovascular events and death in people with diabetes before the appearance of overt diabetic cardiomyopathy (Fang et al., 2003; Nakai, Takeuchi, Nishikage, Lang, & Otsuji, 2009; Ng et al., 2009). In community-based studies, impaired LS_{SYS} predicted major cardiovascular events and improved cardiovascular risk stratication in subjects with normal LV ejection fraction (Russo et al., 2014; Stanton, Leano, & Marwick, 2009). Recently, the Northern Manhattan Study showed that impaired LS_{SYS} independently predicted also the risk of new-onset AF in the elderly population and improved AF risk stratification in addition to established risk factors and echocardiographic parameters, like left atrial volume (Russo et al., 2015).

Given the growing epidemiological relevance of T2DM and AF worldwide, the identification of early echocardiographic predictors of AF in T2DM is of paramount importance to further improve the prevention and treatment strategies aimed at reducing the risk of morbidity and mortality attributed to AF in this particularly high-risk patient population.

Currently, no data are available regarding a link between early LS_{SYS} impairment and risk of new-onset AF in patients with T2DM. Thus, the aim of this hypothesis-generating study was to examine whether early LS_{SYS} impairement may predict subsequent development of AF in T2DM patients with preserved LV ejection fraction and without ischemic heart disease.

2. Materials and methods

2.1. Patients

In this exploratory analysis, we followed for 2 years a sample of 180 outpatients with T2DM, who were consecutively selected among those regularly attending our diabetes clinic during a period of 18 months. For this study, we had excluded patients with 1) a history of ischemic heart disease (IHD), chronic heart failure or LV systolic dysfunction (defined as LV ejection fraction <50%); 2) a history of moderate-to-severe valvular heart diseases, paroxysmal/persistent atrial fibrillation or flutter; 3) a pacemaker or implantable cardioverter defibrillator; 4) a history of alcohol abuse, cirrhosis, cancer and overt nephropathy; and 5) a poor and unstable glycemic control. Patients who were taking antiarrhythmic agents were also excluded from the study.

As consequence of this selection, 189 outpatients with T2DM were initially screened. All these patients underwent exercise stress myocardial perfusion scintigraphy (as detailed below) in order to exclude the presence of asymptomatic myocardial perfusion defects (which were detected in 9 patients); thus, a sample of 180 patients with T2DM was followed-up for subsequent 2 years and included in the present analysis. All the 180 patients were periodically seen at the diabetes clinic (every 6–8 months) for medical examinations of glycemic control, and chronic diabetic complications; standard 12-lead electrocardiograms (ECG) were also performed twice per year. The ascertainment at the end of the 2-year follow-up period was 100% for the whole sample.

The local ethics committee approved the study protocol. All participants gave their 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 anti-hypertensive drugs. Information on smoking, alcohol consumption and medication use was obtained from all patients via interviews during medical examinations.

Venous blood samples were drawn in the morning after an overnight fast. Serum lipids, creatinine and other biochemical blood measurements were determined using standard laboratory procedures. LDL-cholesterol was calculated using the Friedewald's equation. Hemoglobin A1c (HbA1c) was measured using an automated high-performance liquid chromatography analyzer; the upper limit of normal for our laboratory was 5.6%. Estimated glomerular filtration rate (eGFR) was calculated by the four-variable Modification of Diet in Renal Disease study equation (Stevens, Coresh, Greene, & Levey, 2006).

In all patients, the presence of microvascular diabetic complications was also recorded. At baseline, nephropathy was defined as the presence of eGFR <60 mL/min/1.73 m^2 or abnormal albuminuria (i.e., an albumin-to-creatinine ratio ≥ 30 mg/g creatinine on a morning spot urine sample) (Stevens et al., 2006). A single ophthalmologist diagnosed diabetic retinopathy using fundoscopy after pupillary dilation. The presence of lower-extremity sensory neuropathy was recorded by the medical history and examination and by the use of biothesiometer Vibrotest.

2.3. Echocardiography

A trans-thoracic 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 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 (EF) at rest were measured at the apical 4-chamber and 2-chamber views by modified Simpson rule (Lang et al., 2015). LA minimum volume (LAV_{min}) was determined at the end of LV diastole at the first frame after mitral valve closure and LA maximum volume (LAV_{max}) was measured at the end of LV systole right before mitral valve opening from the apical 4-chamber and 2-chamber views using the modified Simpson rule (Lang et al., 2015). LAV index minimum ($LAVI_{min}$) and maximum ($LAVI_{max}$) were calculated as LA volumes 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). Pulsed-wave tissue Doppler echocardiography of the septal and lateral mitral annulus was used to measure the systolic (s') and early peak (e') diastolic tissue velocities, and the mean values of septal and lateral annulus measurements were used for analysis. The ratio of trans-mitral E-wave velocity to e' was calculated as previously proposed (Nagueh, Middleton, Kopelen, Zoghbi, & Quiñones, 1997; Sohn et al., 1997).

Myocardial deformation measurements were also performed off-line in 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 including all six LV myocardial segments from 4-chamber, 2-chamber, and long-axis apical views (Reisner et al., 2004). The average values of peak systolic longitudinal strain and peak systolic strain rate from the 3-apical views were calculated as global longitudinal strain (LS_{SYS}) and global strain rate (SR_{SYS}), respectively. Similarly, the global strain rate during the early (SR_E) and late (SR_L) phase of diastole was also calculated. The ratio of trans-mitral E-wave velocity to SR_E as an index of LV filling pressure was calculated as previously proposed (Wang, Khoury, Thohan, Torre Amione, & Nagueh, 2007). Standard echocardiographic views were obtained using frequency, depth, and sector width adjusted for frame-rate optimization (between 60 and 100 fps). In a previous study (Bonapace et al., 2011), we have shown that when tissue Doppler imaging signals

were re-measured by the same observer the mean absolute differences (±SD) in tissue velocities within the same observer were 0.10 ± 0.02 cm/s for s' velocity and 0.19 ± 0.17 cm/s for e' velocity, respectively ($p = 0.73$ for all differences). No significant differences were also found in the intra-observer and inter-observer variabilities for LS_{SYS} (0.79 ± 0.60% and 1.07 ± 0.80%), SR_{SYS} (0.08 ± 0.04 s^{-1} and 0.11 ± 0.07 s^{-1}), and SR_E (0.08 ± 0.06 s^{-1} and 0.12 ± 0.08 s^{-1}) (p-values not significant for all differences).

Effective arterial elastance was estimated as end-systolic pressure divided by stroke volume (Kelly et al., 1992) and systemic vascular resistance index by mean arterial pressure ÷ cardiac index × 80.

2.4. Myocardial perfusion scintigraphy

At baseline, stress and rest studies were done in all patients in a two-day (2 × 370 MBq) protocol using Technetium-99 m 2-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI), according to local standardized routine. During a bicycle exercise test, ^{99m}Tc-MIBI was injected at peak symptom-limited exercise testing. Bicycle exercise was performed following the Bruce protocol; ECG and blood pressure were recorded at rest and every 2 min during exercise and recovery. 370 MBq of ^{99m}Tc-MIBI was injected at rest and at peak exercise. Images were acquired 60 min after the injection of radiopharmaceutical drug on the two phases (at baseline and after bicycle ergometry test). The single photon emission computed tomography (SPECT) acquisition protocol usually started with the resting part, followed by SPECT at stress the day after. SPECT was performed using a double-head gamma-camera (Millennium MG, GE) equipped with two scintillation detectors, angled 90°, with high resolution and low energy parallel-hole collimators. The protocol included 32 projections, 40-s projections, and 12 frames per cycle used in association with a 15% window centered on the 140-keV photo peak of ^{99m}Tc-MIBI.

2.5. Diagnosis of incident atrial fibrillation

At baseline, all patients were free from AF as documented by a standard 12-lead ECG. A 24-h Holter monitor examination was not routinely performed either at baseline or during the follow-up period. During the follow-up, patients were diagnosed with AF if AF or atrial flutter was present on a standard ECG that was obtained either from a routine clinic examination in our diabetes clinic (i.e., a standard ECG was performed twice per year in all patients) or from reviewing hospital and physician charts from all patients. The diagnosis of AF was confirmed in affected patients by an experienced cardiologist, who was blinded to clinical details of participants.

2.6. Statistical analysis

Data are expressed as means ± SD or frequencies. Differences in baseline clinical/biochemical characteristics and echocardiographic parameters among patients stratified by their status of incident AF at follow-up were tested with the unpaired Student's t-test for normally distributed variables, the Mann–Whitney test for non-normally distributed variables, and the chi-squared test for categorical variables (Tables 1 and 2). Binary logistic regression analysis was used to examine the association between clinical/biochemical and echocardiographic parameters and the risk of incident AF, which was included as the dependent variable. For prediction of incident AF, four forced-entry logistic regression models were performed (Table 3). Covariates included in these multivariate regression models were chosen as potential confounding factors based either on their significance in univariate analyses or on their biological plausibility (e.g., age, sex and duration of diabetes). We performed a logistic regression analysis instead of a time-dependent Cox regression analysis since in presence of a small number of events a time-to-event type of analysis, such as Cox regression, is more susceptible to bias than binary logistic regression analysis when adjusted for predictor variables since there is the potential for a marked difference in time to event in the exposed versus the unexposed group. Indeed, we tested by graphical technics and likelihood ratio statistics that in our study the proportional-hazards assumption of Cox regression analysis was not satisfied. In addition, since the precise time to event (AF) may not be known in some people with asymptomatic AF (e.g., in patients with slow AF), we undertook logistic regression analysis. P-values <0.05 were considered statistically significant.

Table 1
Baseline clinical and biochemical characteristics of patients with T2DM stratified by status of incident atrial fibrillation at follow-up.

	No AF at follow-up ($n = 166$)	New-onset AF at follow-up ($n = 14$)	p
Sex (male/female) (n)	124/42	11/3	0.74
Age (years)	68.8 ± 6.2	68.9 ± 5.1	0.97
Weight (kg)	82.1 ± 14.9	85.7 ± 12.1	0.37
BMI (kg/m^2)	28.6 ± 4.7	29.3 ± 3.9	0.60
Diabetes duration (years)	15.2 ± 10.1	12.4 ± 7.8	0.32
Systolic blood pressure (mmHg)	142.2 ± 16.7	142.8 ± 14.3	0.77
Diastolic blood pressure (mmHg)	77.3 ± 8.8	82.1 ± 4.7	<0.05
Pulse pressure (mmHg)	66.8 ± 14.1	60.7 ± 13.7	0.11
Fasting glucose (mmol/l)	8.2 ± 2.3	7.8 ± 1.2	0.62
Hemoglobin A1c (%)	7.2 ± 1.2	7.6 ± 1.0	0.34
Total cholesterol (mmol/l)	4.45 ± 0.9	4.70 ± 1.3	0.34
HDL cholesterol (mmol/l)	1.25 ± 0.3	1.24 ± 0.3	0.91
Triglycerides (mmol/l)	1.61 ± 0.7	1.65 ± 0.5	0.83
Estimated GFR_{MDRD} (ml/min/1.73 m^2)	80.1 ± 21.2	74.5 ± 24.8	0.35
Current smokers (%)	36.1	57.1	0.28
Hypertension (%)	83.7	85.7	0.84
Diabetic retinopathy (%)	16.8	14.2	0.79
Peripheral sensory neuropathy (%)	13.8	21.4	0.43
Nephropathy (%)			
Abnormal albuminuria with normal $eGFR_{MDRD}$	22.3	14.3	0.11
$eGFR_{MDRD}$ < 60 ml/min/1.73 m^2 ± albuminuria	11.5	28.6	
Oral hypoglycemic drug users (%)	78.3	57.1	0.09
Insulin users (%)	44.6	42.8	0.90
ACE-inhibitors/ARB users (%)	41.6	78.6	<0.01
Calcium-channel blocker users (%)	40.4	35.7	0.73
Diuretic users (%)	41.6	57.1	0.26
Beta-blocker users (%)	21.7	35.7	0.25
Statin users (%)	77.7	85.7	0.48

Sample size, $n = 180$. Data are expressed as means ± SD or percentages.
ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; $eGFR_{MDRD}$, estimated glomerular filtration rate (by the MDRD study equation).

3. Results

Among the 180 patients included in the study (mean age: 68.9 ± 6 years, mean duration of diabetes 15.3 ± 10 years), 14 (7.8%) patients developed incident AF during the 2-year follow-up period.

At baseline, no patients had mitral stenosis, bicuspid aortic valve disease or aortic stenosis. In addition, a few patients had mild aortic/mitral regurgitation, but none of them had moderate or severe aortic and mitral regurgitation. By study design, all patients had normal myocardial perfusion scintigraphy and preserved LVEF.

Table 1 shows the baseline clinical and biochemical characteristics of patients stratified by their status of incident AF at follow-up. At baseline, patients who developed AF at follow-up had higher diastolic blood pressure values and were more likely to be treated with anti-hypertensive drugs compared with those who did not. Notably, age, sex, diabetes duration, BMI, systolic blood pressure, pulse pressure, hypertension, lipids, smoking, HbA1c, diabetes treatment and microvascular complication status did not significantly differ between the two groups.

Table 2
Baseline echocardiographic characteristics of patients with T2DM stratified by their status of incident atrial fibrillation at follow-up.

	No AF at follow-up ($n = 166$)	New-onset AF at follow-up ($n = 14$)	p
LV end-diastolic volume (ml)	103.1 ± 23.4	115.5 ± 58.2	0.12
LV end-systolic volume (ml)	38.3 ± 15.1	48.8 ± 46.6	0.07
LV ejection fraction (%)	63.7 ± 7.9	62.9 ± 12.1	0.72
LV mass index (g/m^2)	114.0 ± 21.6	133.8 ± 46.7	<0.01
LAVI max (ml/ m^2)	32.6 ± 10.5	37.5 ± 21.6	0.13
LAVI min (ml/ m^2)	16.1 ± 8.2	22.3 ± 19.4	<0.05
E/A ratio	0.73 ± 0.15	0.81 ± 0.25	0.07
Dte (ms)	264.4 ± 65	258.5 ± 69	0.59
s' velocity (cm/s)	9.2 ± 1.8	8.5 ± 2.1	0.25
e' velocity (cm/s)	7.9 ± 1.9	7.1 ± 1.8	0.16
E/ e' ratio	8.8 ± 2.8	9.6 ± 3.4	0.32
IVRT (ms)	84.3 ± 15.1	94.6 ± 17.9	<0.05
SAC (mmHg/ml)	1.01 ± 0.28	1.09 ± 0.28	0.35
SVR index (dyne/s/cm^5)	2320.4 ± 745.5	2427.2 ± 770.1	0.63
LS_{SYS} (%)	−16.2 ± 2.6	−12.6 ± 4.0	<0.001
SR_{SYS} (s^{-1})	−1.02 ± 0.22	−0.93 ± 0.19	0.14
SR_E (s^{-1})	1.08 ± 0.26	0.89 ± 0.22	0.01
SR_L (s^{-1})	1.16 ± 0.32	0.83 ± 0.21	<0.001
E/SR_E ratio (m)	0.64 ± 0.21	0.79 ± 0.34	<0.05

Sample size, $n = 180$. Data are expressed as means ± SD.
AF, atrial fibrillation; LAVI left atrial volume index; IVRT, isovolumetric relaxation time; LS_{SYS}, global longitudinal strain; LV, left ventricular; SAC, systemic arterial compliance; SVR, systemic vascular resistance; SR_{SYS}, global strain rate; SR_E, global diastolic strain rate during early phase of diastole; SR_L, global diastolic strain rate during late phase of diastole.

Table 2 shows the baseline echocardiographic characteristics of participants stratified by their status of incident AF at follow-up. At baseline, patients who developed AF at follow-up had higher indexed LV mass and larger LAVI compared with those who did not. They also had longer IVRT. Among the global LV strain and strain rate measurements at baseline, patients who developed AF at follow-up had lower LS_{SYS}, lower SR_E, lower SR_L and higher E/SR_E ratio compared with those who did not. LV volumes, LVEF, E/A ratio, Dte, s' velocity, e' velocity, E/e' ratio, SVR index and SAC did not differ between the two groups of patients.

Table 3 shows the independent predictors of new-onset AF in four multivariate logistic regression models. Impaired LS_{SYS} was associated with an approximately 1.4-fold increased risk of incident AF after adjustment for age, sex, duration of diabetes and SR_L (model 1). Further adjustment for either LV mass index and LAVI (model 2) or E/SR_E ratio (model 3) did not weaken the strong association between impaired LS_{SYS} and AF risk. Results remained unchanged when we adjusted for age, sex, duration of diabetes, HbA1c, hypertension, BMI and SR_L (model 4). Almost identical results were also found in more parsimonious logistic regression models when we removed age, sex and duration of diabetes (that were included in the above-mentioned models on the basis of their biological plausibility but did not significantly differed at baseline between patients who developed AF at follow-up and those who did not, as shown in Table 1) from the list of covariates included in all these multivariate regression models.

4. Discussion

The main finding of this pilot, prospective study is that impaired LS_{SYS} was associated with an increased risk of new-onset AF over a 2-year follow-up period in T2DM patients with preserved LVEF and without IHD at baseline. Notably, this association was independent of multiple clinical and echocardiographic risk factors for AF. This finding suggests that early LS_{SYS} impairement is among the first myocardial alterations that predispose this particularly high-risk patient population to subsequent development of AF.

Impaired LS_{SYS} is an emerging, powerful predictor of cardiovascular morbidity and mortality in patients without clinical LV systolic disfunction (Russo et al., 2014; Stanton et al., 2009), in patients with chronic systolic heart failure (Motoki et al., 2012) and in those with persistent/permanent AF (Su et al., 2013). Moreover, impaired LS_{SYS} is associated with hypertension, obesity, subclinical atherosclerosis, increased large elastic artery stiffness and mitral regurgitation (Di Salvo et al., 2006; Kamperidis, Marsan, Delgado, & Bax, 2016; Russo et al., 2011, 2013), which are all established risk factors for AF (Anonymous, 2014).

Recently, Russo et al. firstly reported that impaired LS_{SYS} was also significantly associated with an increased risk of new-onset AF among elderly participants from the population-based Northern Manhattan Study. Interestingly, in this study the prognostic value of LS_{SYS} for incident AF was incremental over established risk factors and LAVI (Russo et al., 2015).

To our knowledge, this is the first prospective study to show that impaired LS_{SYS} was a powerful predictor of new-onset AF also in people with T2DM, i.e., a group of individuals in which AF (Anonymous, 2014; Du et al., 2009; Huxley et al., 2011; Movahed et al., 2005; Ostgren et al., 2004) and early LS_{SYS} impairement (Nakai et al., 2009; Ng et al., 2009) are two highly prevalent pathologic conditions. An early LS_{SYS} impairement in T2DM patients without obstructive IHD may be, at least in part, due to coexisting coronary microvascular dysfunctions or myocardial perfusion defects (Marciano et al., 2012) as well as to increased myocardial fibrosis, which is a known marker of diabetic cardiomyopathy (Kang et al., 2008) that may lead to early LS_{SYS} impairement occurring even before the appearance of LV diastolic dysfunction. In fact, early LS_{SYS} impairement may exist despite normal LV diastolic function in patients with T2DM, indicating that diastolic dysfunction should not

Table 3
Multivariate logistic regression analyses: independent predictors of incident atrial fibrillation in T2DM patients.

Multivariate logistic regression models								
	Model 1	p	Model 2	p	Model 3	p	Model 4	p
Age (years)	1.00 (0.89–1.12)	0.99	1.00 (0.89–1.12)	0.99	1.00 (0.89–1.13)	0.99	1.00 (0.88–1.13)	0.99
Sex (male)	0.18 (0.02–1.77)	0.22	0.35 (0.04–3.19)	0.41	0.18 (0.01–1.78)	0.14	0.20 (0.02–1.94)	0.16
Diabetes duration (years)	1.01 (0.94–1.08)	0.89	0.99 (0.93–1.08)	0.97	1.00 (0.93–1.08)	0.86	1.00 (0.93–1.08)	0.93
LS_{SYS} (%)	1.43 (1.06–1.91)	<0.01	1.63 (1.17–2.27)	<0.005	1.47 (1.07–2.02)	<0.01	1.41 (1.03–1.90)	<0.05
SR_L (s^{-1})	0.18 (0.01–1.38)	0.08	Not included	–	0.05 (0.01–1.27)	0.07	0.06 (0.01–1.26)	0.07
LAVI min (ml/m^2)	Not included	–	0.96 (0.88–1.05)	0.38	Not included	–	Not included	–
LV mass index (g/m^2)	Not included	–	1.02 (0.99–1.06)	0.22	Not included	–	Not included	–
E/SR_E ratio (m)	Not included	–	Not included	–	0.33 (0.01–8.19)	0.50	Not included	–
HbA1c (%)	Not included	–	Not included	–	Not included	–	1.27 (0.72–2.24)	0.41
Hypertension (yes vs. no)	Not included	–	Not included	–	Not included	–	1.17 (0.11–12.6)	0.90
BMI (kg/m^2)	Not included	–	Not included	–	Not included	–	1.01 (0.83–1.20)	0.99

Sample size, $n = 180$. Data are expressed as odds ratios ±95% confidence intervals (in parenthesis) as assessed by multivariate logistic regression analysis.
Incident AF was the dependent variable in all multivariate logistic regression models.

be considered the first marker of a preclinical form of diabetic cardiomyopathy (Ernande et al., 2011).

Interestingly, both in our study and in that of Russo et al. (2015) LVEF did not provide any additional prognostic information for risk of incident AF. This is likely due to the fact that at the early stage of diabetic cardiomyopathy the radial contractility may compensate for reduced longitudinal contractility (Fang, Leano, & Marwick, 2004). This compensatory mechanism may also explain the predictive role of LV fractional shortening (a measure of radial systolic function) on risk of new-onset AF observed in a previous study (Vaziri, Larson, Benjamin, & Levy, 1994).

It is known that in hypertensive patients with no other major predisposing conditions, the risk of new-onset AF increases progressively with increasing cardiac mass (Verdecchia et al., 2003). Also in our study, we observed that increased cardiac mass at baseline was associated with a higher risk of new-onset AF. In our study, obviously, it is not easy to discriminate whether the increased cardiac mass is mainly related to coexisting hypertension or diabetes per se. However, the lack of any significant differences in the frequency of hypertension and in total vascular load (both in terms of arterial stiffness and in terms of systemic vascular resistance as shown in Table 1) we observed between the two groups of patients suggests that the observed increase in LV mass may be, at least in part, dependent on diabetes per se.

Also minimum LAVI was a significant, positive predictor of new-onset AF in our diabetic population. This finding confirms previous results in older patients without heart valve disease, in which minimum LAVI was found to be superior to maximal LAVI in predicting the risk of new-onset AF, irrespective of LVEF and diastolic dysfunction (Fatema et al., 2009). It is important to underline that a close interplay does exist between LA volume and ventricular systolic performance throughout the cardiac cycle (Barbier, Solomon, Schiller, & Glantz, 1999). Indeed, LA volume is influenced not only by the atrial characteristics but also by the LV end-systolic volume and the descent of LV base during the systole (Hoit, 2014). A significant association between impaired LS_{SYS} and LA volume and function was in fact described (Russo et al., 2012). However, it is also important to underline that in our study impaired LS_{SYS} was the only significant predictor of new-onset AF after adjusting for LV mass and diastolic function parameters, such as LAVI and E/SR_E ratio, thus further supporting an important role of early LS_{SYS} impairement in predicting the risk of new-onset AF in T2DM. It is reasonable to assume that impaired LS_{SYS} is the most early marker of disease related to coexisting coronary microvascular dysfunction and subclinical atherosclerosis that involve both the left ventricle and the left atrium, and that predisposes to the development of fibrotic changes that favor myocardial electrical instability and subsequent development of AF. In fact, the existence of an atrial diabetic cardiomyopathy paralleling an LV diabetic cardiomyopathy, irrespective of coexisting loading conditions, was also recently suggested (Bonapace et al., 2015; Kadappu et al., 2012).

Our study has some important limitations that should be mentioned. Firstly, there were a relatively small number of clinical events during the 2-year follow-up period (i.e., a total of 14 (7.8%) cases of incident AF) and, therefore, the results of our multivariate regression analyses should be interpreted with some caution. Secondly, we could not assess the impact of temporal changes in LS_{SYS} on subsequent development of AF. Finally, since a 24-h Holter monitor examination was not routinely performed, the case ascertainment of AF might have been incomplete in this study, especially if patients had some episodes of asymptomatic paroxysmal AF. Although a standard ECG was performed twice a year in all patients and no patients were treated with antiarrhythmic drugs at baseline, cases of asymptomatic paroxysmal AF may have been missed, so reducing the power to detect some significant associations.

Despite these limitations, our study has important strengths that include its prospective design, the complete nature of the dataset, the close follow-up, the ECG measurements twice per year, and the review of hospital and physician charts from all patients over the follow-up that reduce the potential for missed or misclassified study outcome(s). In addition, none of our patients had myocardial perfusion defects on myocardial scintigraphy; we believe that the inclusion of such patients would have confounded the interpretation of the results of this study.

In conclusion, our pilot prospective study is the first to show a strong association between early LS_{SYS} impairment and increased risk of incident AF in T2DM patients with preserved LVEF and without IHD. Notably, this association was independent of multiple clinical and echocardiographic risk factors for AF. However, the findings of this hypothesis-generating study need to be prospectively validated in larger cohorts of patients with T2DM.

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