Self-reported dyspnea is associated with impaired global longitudinal strain in ambulatory type 1 diabetes patients with normal ejection fraction and without known heart disease – *The Thousand & 1 Study*

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ARTICLE INFO

ABSTRACT

Aims: Identification of early signs and symptoms of heart disease is important in type 1 diabetes (T1DM). Global longitudinal strain (GLS) by speckle-tracking echocardiography can detect subtle impairments in myocardial function. We investigated the association between myocardial function and degree of dyspnea in patients with normal left ventricular ejection fraction (LVEF) and without known heart disease.
Methods: Ambulatory patients from Steno Diabetes Center. Conventional echocardiography and GLS was performed. Patients reported degree of dyspnea according to the NYHA classification. Patients with LVEF ≤ 45% were excluded. Data were analyzed in uni-and multivariable models.
Results: A total of 1075 T1DM patients were included. Mean age 49.5 years, 52% men, mean diabetes duration 25.8 years; 835 (77.7%) reported no dyspnea, 156 (14.5%) NYHA I, 68 (6.3%) NYHA II, and 16 (1.5%) NYHA III–IV. LVEF did not differ between groups of dyspnea in neither univariable nor multivariable models ($p > 0.1$). E/e' was associated with degree of dyspnea in both univariable ($p < 0.001$) and multivariable models ($p = 0.048$). GLS was associated with degree of dyspnea in a dose–response relationship in both univariable ($p < 0.001$) and multivariable models ($p < 0.001$).
Conclusions: Degree of dyspnea is independently associated with impaired myocardial function by GLS in T1DM patients with normal LVEF and without known heart disease.

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1. Introduction

Heart disease is the most common cause of mortality in diabetes. In type 1 diabetes (T1DM) the risk is increased between 6–12 times compared to the background population (Soedamah-Muthu et al., 2006).

Dyspnea is a cardinal sign of heart disease, and is one of the most common symptoms in the outpatient setting. Unlike in the acute setting, dyspnea in the ambulatory patient is often a subjective and unspecific complaint and is often not present at time of the ambulatory visit and therefore difficult to observe. Furthermore, symptoms in T1DM patients may even be more difficult to interpret compared to individuals without diabetes due to concomitant factors such as hypoglycemia or hyperglycemia, neuropathy and others. Altogether, self-reported dyspnea is a symptom which can make clinical inferences difficult for the clinician being presented with the symptom. If heart disease is suspected, an echocardiography may be warranted, and can reveal or rule out gross systolic impairment. However, it may be, that systolic dysfunction is not detectable by conventional echocardiography but could be observed using more sensitive echocardiographic measures, such as speckle-tracking echocardiography. This was suggested in a Norwegian study of 37 patients with symptoms of heart failure and preserved ejection fraction where global longitudinal

strain (GLS) was shown to be associated with performance in an exercise test (Hasselberg et al., 2015).

Type 1 diabetes is a chronic disease with no cure, and patients are usually followed regularly life-long in out-patient clinics. Identification of patients at risk of heart disease is of great importance in the prevention of complications to T1DM. Dyspnea is a common symptom and is routinely assessed as part of the medical interview.

In the present study, we investigated if self-reported dyspnea was related to myocardial dysfunction using conventional and speckle-tracking echocardiography in ambulatory T1DM patients without known heart disease and with normal ejection fraction.

2. Methods

2.1. Steno Diabetes Center and Department of Cardiology, Copenhagen University Hospital Gentofte

The Steno Diabetes Center is an integrated part of the Danish public health care system and 90% of the patients are referred from the Copenhagen Capital Region. The total number of patients followed at Steno Diabetes Center is around 6000 whereof 3500 patients have T1DM and the remaining patients have T2DM. T1DM patients are followed lifelong with outpatient visits approximately every 3rd month.

The Department of Cardiology, Copenhagen University Hospital Gentofte is an invasive center with a core echo lab performing more than 6400 echocardiographic examinations annually.

2.2. Study population

The Thousand & 1 Study is a cross-sectional cohort study of T1DM patients without known heart disease.

Invitation, screening, and inclusion of patients started April 1st 2010 and inclusion was completed April 1st 2012. Patients were eligible if they were 18 years or older; attending the outpatient clinic at Steno Diabetes Center; diagnosed with T1DM; without known heart disease; and willing to participate. Known heart disease was defined as heart failure; coronary artery disease, including previous myocardial infarction, stable angina, previous percutaneous coronary intervention, or coronary artery bypass surgery; atrial fibrillation or atrial flutter; left bundle branch block; congenital heart disease; pacemaker or ICD implantation, all of which were exclusion criteria. No financial compensation was offered to patients for their participation. The study population and study visit has previously been described in detail (Jensen et al., 2014; Jensen et al., 2015). As previously shown, the included study population was representative of T1DM patients without known heart disease followed at Steno Diabetes Center without any major selection bias.

The study was performed in accordance with the 2nd Helsinki declaration and approved by the regional ethics committee (*H-3-2009-139*), and the Danish Data Protection Agency (*00934-Geh-2010-003*). All subjects gave written informed consent.

2.3. Study Visit

Prior to the echocardiographic examination, all patients received study information, signed the consent form, and filled out a questionnaire about lifestyle factors, including smoking, leisure time physical activity, cardiorespiratory symptoms, and type of medication used. All patients received exogenous insulin. Blood pressure and ECG at rest was recorded in the supine position.

2.4. Self-Reported Dyspnea

Patients reported degree of dyspnea according to the NYHA classification (Yancy et al., 2013), with "Nil" being no symptoms with

ordinary or with strenuous physical activity; class "I" being no dyspnea with ordinary physical activity; "II" being ordinary activity resulting in symptoms; "III-IV" being marked limitation of physical activity, with less than ordinary activity causing symptoms.

2.5. Echocardiography

Echocardiography was performed with a General Electric, Vivid 7 Dimension imaging system device (GE Vingmed Ultrasound AS, Horten, Norway) with a 3.5 MHz transducer in accordance with the recommendations from the European Association of Echocardiography/American Society of Echocardiography (Lang et al., 2006). Echocardiographic examinations were read and analyzed using General Electric EchoPAC software (BT11). Three consecutive heart cycles were recorded. Left ventricular ejection fraction was determined by Simpson's biplane method. Pulsed-wave Doppler was performed in the apical 4-chamber view with the sample volume placed between the mitral leaflet tips to obtain diastolic mitral early (E). Pulsed-wave early diastolic tissue Doppler velocities (e') were determined from the apical 4-chamber view at the lateral region of the mitral annulus (Nagueh et al., 2009), and E/e'_{lat} was calculated, which has been shown to be the best correlate of invasively measured diastolic function (Kasner et al., 2007). Global left ventricular longitudinal strain (GLS) was measured using 2D speckle-tracking where deformation of the left ventricle is determined by tracking speckles from frame-to-frame. The method has previously been described in detail (Jensen et al., 2015). GLS was determined as the average of the 3 apical views, thereby providing a global longitudinal strain measure for the entire left ventricle. Normal systolic function was defined as LVEF > 45% (Lee et al., 2009; Solomon et al., 2005).

2.6. Biochemistry

Information about biochemistry such as HbA_{1c}, p-creatinine, and albuminuria status was collected from electronic patient files at Steno Diabetes Center from the ambulatory visit closest to study inclusion, which was maximally $+/-4$ months from inclusion. This information was collected after the study visit and analysis of the echocardiography, ensuring that the investigators were blinded to the clinical data.

Urinary albumin excretion rate (UAER) was measured in 24-h sterile urine collections by enzyme immunoassay. Patients were categorized as normoalbuminuric if UAER, in two out of three consecutive measurements, was <30 mg/24 h, microalbuminuric if UAER was between 30 and 300 mg/24 h, and macroalbuminuric if UAER >300 mg/24 h. HbA1c was measured by high-performance liquid chromatography (normal range: 21–46 mmol/mol, [4.1–6.4%]; Variant; Bio-Rad Laboratories, Munich, Germany) and serum creatinine concentration by an enzymatic method (Hitachi 912; Roche Diagnostics, Mannheim, Germany). Estimated GFR was calculated by the MDRD method (Levey et al., 1999).

2.7. Statistical Analysis

All analyses were performed with STATA 12.1 (STATACorp LP, TX USA). Categorical variables were analyzed with the $\chi 2$–test and continuous variables with Student's t-test or ANOVA. Continuous variables were reported as means (SD). Patients with LVEF ≤45% were excluded. Multivariable regression models, testing the association between LVEF, GLS, E/e' and self-reported dyspnea, were performed by including covariables from the baseline tables in a backward stepwise selection model with a significance level of 0.1. Variables that reached this significance level in any of the models (LVEF, GLS, E/e') were included in the final multivariable model. Furthermore, in the analyses of GLS and E/e', LVEF was also included in the full multivariable model. Variables included in the full model included age, sex, diabetes