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Association between subclinical left ventricular systolic dysfunction and glycemic control in asymptomatic type 2 diabetic patients with preserved left ventricular function

Giacomo Zoppini [a,*], Corinna Bergamini [b], Stefano Bonapace [c], Andrea Rossi [b], Maddalena Trombetta [a], Alessandro Mantovani [a], Anna Toffalini [a], Laura Lanzoni [c], Lorenzo Bertolini [d], Luciano Zenari [d], Enzo Bonora [a], Giovanni Targher [a]

[a] Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Azienda Ospedaliera Universitaria Integrata, University of Verona, Verona, Italy
[b] Section of Cardiology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
[c] Division of Cardiology, "Sacro Cuore" Hospital, Negrar (VR), Italy
[d] Division of General Medicine and Diabetes Unit, "Sacro Cuore" Hospital, Negrar (VR), Italy

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ABSTRACT

Background: Type 2 diabetes is strongly associated with the occurrence of cardiovascular diseases, especially heart failure. Some studies have suggested that subclinical systolic dysfunction as assessed by tissue Doppler imaging (TDI) is already present in uncomplicated diabetic patients with normal left ventricular ejection fraction (LVEF). Considering the importance of this aspect, the aim of this cross-sectional study was to examine the relationship between glycated hemoglobin and mean s′ wave velocity (a reliable measure of early LV systolic dysfunction) in a cohort of type 2 diabetic outpatients with preserved LVEF and without ischemic heart disease.

Methods: Forty-four male patients with newly diagnosed and 172 male patients with established type 2 diabetes were recruited for this cross-sectional study. All patients were evaluated with a transthoracic echocardiographic Doppler. The statistical analysis was conducted by a linear multivariate regression analysis, including several potential confounders.

Results: The mean values of mean s′ wave velocity were lower in patients with a worse glycemic control and progressively decreased across the quartiles of glycated hemoglobin. The multivariate linear regression analysis showed that mean s′ wave velocity was inversely and independently associated with glycated hemoglobin (standardized beta coefficient −0.178; $p = 0.043$) after adjustment for age, duration of diabetes, body mass index, pulse pressure, estimated glomerular filtration rate, microvascular complication status, and indexed cardiac mass.

Conclusions: These results suggest that s′ wave velocity, as evaluated by TDI echocardiography, was an early marker of systolic dysfunction in type 2 diabetic patients with preserved LVEF and without prior ischemic heart disease. Moreover, early systolic dysfunction was independently associated with poor glycemic control in these patients. Future studies are needed to elucidate the pathogenic role of chronic hyperglycemia in the development of early LV systolic dysfunction.

1. Background

Type 2 diabetes is strictly interconnected with cardiovascular diseases, both ischemic heart disease and heart failure. Type 2 diabetes is an established risk factor of heart failure, which is also associated with poor prognosis.[1,2] Some studies reported the presence of early systolic dysfunction as assessed by tissue Doppler imaging in uncomplicated diabetes.[3–5] Conventionally, TDI parameters are obtained over both the septal and lateral mitral annulus and the average of the values is used.[6]

Systolic annular velocity (s′ wave) provides a measure of longitudinal systolic function, which is easy to measure[7] and shows a good relationship with exercise capacity.[8] Exercise s′ wave velocity was found to predict mortality risk, especially in patients with heart failure.[9] Previous studies reported early impairment of systolic function in type 2 diabetic patients compared to controls.[10,11] A significant and inverse association between glycated hemoglobin and TDI systolic parameters was also reported by a small study on

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* Corresponding author at: Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Azienda Ospedaliera Universitaria Integrata, Piazzale Stefani, 1, 37126 Verona, Italy. Fax: +39 045 8027314.
E-mail address: giacomo.zoppini@univr.it (G. Zoppini).

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asymptomatic type 2 diabetic patients,[12] while other studies did not observe such association.[13,14] So far, no large studies have focused their attention on a comprehensive evaluation of the relationship between s′ wave velocity and glycated hemoglobin in patients with diabetes. However, given the clinical relevance of this aspect, the main aim of this study was to evaluate the relationship between glycated hemoglobin and s′ wave velocity in a cohort of type 2 diabetic male outpatients with preserved left ventricular ejection fraction and without a previous history of ischemic heart disease.

2. Methods

2.1. Patients

The study sample was composed of 216 males affected by type 2 diabetes, 44 with new and 172 with established 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 myocardial infarction, angina, coronary revascularizations and chronic heart failure; (2) LV systolic dysfunction (i.e., LVEF <50%), aortic stenosis (i.e., defined as a trans-aortic peak instantaneous velocity ≥ 2.6 m/s), bicuspid aortic valve disease, mitral stenosis, moderate or severe aortic and mitral regurgitation, atrial fibrillation or atrial flutter; (3) a prior history of cirrhosis, malignancy or overt nephropathy; and (4) a poor and unstable glycemic control.

Oral hypoglycemic agents were taken by 63.4% of patients, none of them were treated with pioglitazone or SGLT2 inhibitors, while 31.5% were treated by insulin. Antihypertensive therapy was reported in 71.8% of patients.

The local ethics committee approved the study protocol. All participants gave their written informed consent for participation to this research.

2.2. Clinical and laboratory variables

Duration of diabetes was computed from the date of diagnosis of diabetes, available in the clinical records. Body mass index (BMI) was calculated by dividing weight in kilograms by height in squared meters. A physician measured blood pressure with a mercury sphygmomanometer after patients had been seated quietly for at least 5 minutes. Patients were considered to have hypertension if their blood pressure was ≥140/90 mm Hg or if they were taking any anti-hypertensive drugs. 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 glomerular filtration rate ($eGFR_{CKD\text{-}EPI}$) was estimated by the CKD Epidemiology Collaboration (CKD-EPI) equation.[15] Albuminuria was measured by an immuno-nephelometric method on a morning spot urine sample and expressed as the albumin-to-creatinine ratio. 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. 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). In all participants the presence of retinopathy or nephropathy was recorded as microvascular complication, whereas the absence of both complications was considered to identify those subjects without microvascular complications. Among patients with microvascular complications, 9% had creatinine clearance lower than 60 ml/min/1.73 m^2, 20.2% had albuminuria and 13.6% had retinopathy of any degrees.

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 two experienced cardiologists, who were 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 LVEF at rest were measured at the apical 4-chamber and 2-chamber views (by modified Simpson rule).[16] Left atrial volume index (LAVI) 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.[16] LAVI was calculated as LA volume divided by 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.[16] Each value was obtained from the average of three measurements. 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.[17,18]

In a previous study,[19] 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, 0.19 ± 0.17 cm/s for e′ velocity, and 0.23 ± 0.20 cm/s for a′ velocity, respectively (p = NS for all differences).

2.4. Statistical analysis

Data are summarized as means ± SD or percentages. Differences in clinical/biochemical characteristics and echocardiographic parameters between two groups of patients were compared by the unpaired t-test for normally distributed variables and the Mann–Whitney test for non-normally distributed variables. One-way ANOVA was used to compare sets of variables among three groups of patients or more. The χ^2 test was used for categorical variables to study differences in proportions or percentages between the groups. To estimate the independent predictors of mean s′ wave velocity a multivariate linear regression analysis was also performed. Age, glycated hemoglobin, duration of diabetes, pulse pressure, $eGFR_{CKDEPI}$, BMI, microvascular complication status and indexed cardiac mass were included as covariates. Covariates for this multivariate regression model were chosen as potential confounding factors based on their significance in univariable regression analyses or based on their biological plausibility. A p-value <0.05 was assumed to indicate a statistical significance.

3. Results

Main clinical and biochemical characteristics of patients stratified by the median values of glycated hemoglobin are summarized in Table 1. Patients with higher glycated hemoglobin had a longer duration of diabetes and higher serum triglyceride levels and were more likely to be hypertensive compared to those with lower glycated hemoglobin. All other variables were comparable between the two groups of patients.

Table 2 shows the echocardiographic characteristics of patients stratified by the median values of glycated hemoglobin. Compared to those with lower glycated hemoglobin, patients with higher glycated

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