

UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA
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ABSTRACT

**THE ROLE OF CONVENTIONAL AND MODERN
ECOCARDIOGRAPHIC METHODS IN THE ASSESSMENT OF
SUBCLINICAL MYOCARDIAL DYSFUNCTION IN YOUNG PEOPLE
WITH DIABETES TYPE 1**

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1. INTRODUCTION

The incidence of diabetes continues to grow and has quickly become one of the most widespread and costly chronic diseases worldwide.(1,2)

According to the International Diabetes Federation in 2017, there are estimated 451 million cases worldwide (1) and by the year 2045 it is expected that the number of cases will reach 693 million cases diagnosed with DM. (1,3)

Diabetes is one of the major cardiovascular risk factors and causes cardiovascular structural and functional changes, even in the absence of atherosclerotic disease. All of these cardiovascular changes have been brought together under the name of diabetic cardiomyopathy, a term introduced in 1972 by Rubler et al. (4)

Left ventricular diastolic dysfunction (VD) is the earliest manifestation of diabetic cardiomyopathy, which precedes systolic dysfunction and is able to evolve to symptomatic heart failure. Often these patients fall into the incipient stages of a cardiac failure with a preserved ejection fraction.

Early detection of subclinical heart disease in diabetic pathology by various imaging methods is of major importance because lifestyle changes and prompt medical interventions can prevent or delay the progression to heart failure.

2. DIABETES AND CARDIOVASCULAR DISEASE

The main cardiovascular manifestations of diabetes are: advanced atherosclerosis like coronary artery disease, ischemic stroke, peripheral arterial disease and cardiac failure manifested in the form of systolic and diastolic dysfunction combined as a distinct entity named diabetic cardiomyopathy.

3. DIABETIC CARDIOMIOPATHY

Diabetic cardiomyopathy is a diabetic mellitus specific myocardial dysfunction that occurs independently of atherosclerotic coronary artery disease and/or arterial hypertension and is characterized by diffuse interstitial fibrosis and hypertrophy of cardiac myocytes, which ultimately results in left ventricular dysfunction predominantly diastolic. (5-7)

In 1972, diabetes cardiomyopathy first appeared when Rubler described at the necropsy of four young people with Type 1 DM and heart failure a type of cardiac disease

with microscopic changes in diffuse interstitial fibrosis in the subendothelial layer of intramural arterioles without evidence of coronary ischemia, hypertension, valvular or congenital heart disease. (5,6,8,9).

3.1 Vascular cardiac changes

Myocardial ischaemia in diabetic patients in the absence of significant lesions in epicardial coronary arteries is explained by the impairment of small intracardiac coronary arteries (coronary microangiopathy), a feature of diabetic cardiomyopathy (5,10).

Coronary microcirculation has significant changes such as basal membrane thickening, focal narrowing of small vessel diameter, signs of angiogenesis, and reduction in capillary circulation. Reduction of capillary density is achieved by a process of fibrosis that develops around the vessel but also to the proliferation of endothelial cells, the accumulation of fibrous tissue in the vessel wall leading to its occlusion. Frequent episodes of vasoconstriction occur in microcirculation due to endothelial dysfunction and increased sensitivity to catecholamines. The coronary flow reserve is reduced in diabetics even in the absence of significant coronary stenosis (5,9,11)

3.2 Structural cardiac changes

Over time, studies have shown that myocardial fibrosis and hypertrophy are the main changes responsible for pathological processes in diabetic cardiomyopathy. The presence of diabetes mellitus and left ventricular hypertrophy that occurs early in the development of diabetic cardiomyopathy has been shown to be associated with insulin resistance.

3.3 Functional cardiac changes

Diastolic dysfunction is the first manifestation in diabetic cardiomyopathy, while systolic dysfunction subsequently develops in disease progression. (5,9,11,12) Fibrosis and ventricular hypertrophy are the main causes of diabetic cardiomyopathy.

Functional abnormalities are the consequence of structural myocardial remodeling (LV hypertrophy) and are expressed by a normal or nearly normal end-diastolic volume accompanied by an increase in the LV volume/ mass ratio and the thickness of the wall / radius of the LV cavity. (5)

4. MYOCARDIAL DEFORMATION

The longitudinal fibers contract earlier than the circular ones, so at the beginning of the systole, so that the LV undergoes a geometrical deformation, becoming more spherical, so that later the circular fibers come into action and recover their shape of the cylinder.

The heart realizes a global movement of translation, rotation and inclination. For a certain interrogated myocardial point, the motion vector moves in three-dimensional 3-axis displacement space:

- Radial axis - perpendicular to the epicardium, oriented from the ventricular cavity to the outside;
- The longitudinal axis - perpendicular to the radial axis, tangential to the epicardium and oriented from the base of the ventricle to the apex;
- The circumferential axis - perpendicular to the longitudinal and radial axes, and anti-clockwise;

5. ECHOCARDIOGRAPHIC EVALUATION OF SUBCLINICAL MYOCARDIAL DISEASE

Over time, a number of imaging assessment methods have been studied, but none has gained recognition as a unique diagnostic method with well-established standard criteria.

Echocardiography is the most widely used, non-invasive technique, that evaluates anatomy and heart function using ultrasounds. Currently, this imaging approach is the "gold standard" method in the diagnosis of structural cardiac changes. It can also be useful for assessing disease progression and evaluating treatments. (16.17)

Conventional techniques - two-dimensional echocardiography (2D), the M-mode module and Pulse Doppler (PW) imaging, Tissue Doppler imaging, have been shown to have limitations and offer results that are not very conclusive. Newer techniques such as Speckle Tracking, Strain and Strain Rate are more sensitive and provide information on myocardial deformation

Using all these methods is possible to detect early diagnosis of myocardial dysfunction of LV and to identify patients at high risk for developing heart failure.

Table 1. Comparative analysis between tissue Doppler imaging and Speckle Tracking imaging

	Tissue Doppler	Speckle Tracking
Advantages	High frame rate Good time resolution Availability on most modern ultrasounds Analysis can be done online or offline	Frame rate reduced Independent angle Better reproducibility Little affected by artefacts Semi-automatic processing Evaluates deformation in two dimensions Measures both longitudinal and global strain
Disadvantages	Depending on the angle Predisposed to acoustic artifacts Evaluates deformation in one size Measures only regional strain	Requires excellent 2D image quality Smaller spatial resolution Small availability on new ultrasound systems

II. PERSONAL CONTRIBUTION

6. STUDY MOTIVATION

Early detection of subclinical heart disease in diabetic pathology by various imaging methods is of major importance because lifestyle changes and prompt medical interventions can prevent or delay the progression to heart failure, which is currently a major problem of health insurance. ance

The reason that led to this study was the desire to evaluate left and right ventricular dysfunction among patients with type I diabetes by conventional echocardiographic methods and modern methods such as "speckle tracking". "Speckle tracking" is a complex echocardiographic technique, non-invasive, relatively new one, wich analyzes and quantifies myocardial deformity. This technique is extremely important because it identifies changes in

myocardial dynamics prior to the occurrence of clinical symptomatology.

7. OBJECTIVES OF THE STUDY

To accomplish the primary purpose of our study, we have formulated the following Specific objectives:

- Analysis of myocardial function by conventional and modern methods in young subjects diagnosed with type 1 diabetes mellitus
- Comparing the results with those obtained from a control group, with healthy subjects
- In addition, the study of the feasibility and clinical reliability of longitudinal deformation analysis of the right ventricle by speckle tracking echocardiography.

8. WORK MATERIALS AND METHODS

8.1. STUDY TYPE

We have conducted a prospective, descriptive and comparative study with analysis the LV and RV function in diabetic patients by both conventional and modern imaging methods such as speckle tracking 2D echocardiography. The study was conducted in Cardiology Department of Emergency County Hospital in Craiova, Romania between June 2017 and June 2018.

8.2. STUDY POPULATION

A total of 60 patients diagnosed with type 1 diabetes and followed in the Diabetes Clinic of the Emergency County Hospital of Craiova and a control group of 90 normal subjects were evaluated for transthoracic echocardiography.

8.3. PARAMETERS DERIVED FROM ECOCARDIOGRAPHY EVALUATED IN STUDY

CONVENTIONAL parameters derived from 2D echocardiography, M mode, color Doppler, PW and CW

v Parameters used to evaluate LV morphology

- Left Ventricle telediastolic diameter
- Left Ventricle telesystolic diameter
- Left ventricle volumes (systolic and diastolic)
- left ventricular wall thickness
- Interventricular septum thickness
- LV mass (g)

∪ Parameters used to evaluate LV systolic function

- Left ventricular ejection fraction
- Stroke volume indexed at body surface and heart rate

∪ Parameters used to evaluate LV diastolic function

- early diastolic velocity (E),
- delayed diastolic velocity (A)
- E / A report
- S systolic wave,
- early diastolic velocity (wave e')
- delayed diastolic velocity (wave a')
- E / e' ratio

∪ Parameters used to evaluate right ventricle function and systolic pressure in the pulmonary artery

- The right ventricle areas indexed to the body surface
- Systolic excursion of tricuspid ring to apex during systole (TAPSE, mm)
- S-wave on the right ventricle TDI - the velocity of the tricuspid ring displacement to the apex during systole.
- Systolic pulmonary pressure (PAPs) (mmHg).

∪ Parameters used to evaluate the LA and RAD function

- Left atrium volumes • Right atrium volumes

MODERN parameters derived from the speckle tracking method

◆ Echocardiographic evaluation of LV systolic deformation

- Left ventricle global longitudinal strain (GLS)
 - o Endocardic (GLSendo)
 - o Miocardic (GLSmio)
 - o Epicardic (GLSepi)

- Mechanical left ventricular dispersion
- Circumferential Strain (SC)
- Left ventricular torsion

◆ Echocardiographic evaluation of RV deformation

- Longitudinal global right ventricular strain (GLS_RV)
- The longitudinal strain on the right wall of the right ventricle
- The longitudinal strain at the level of the basal, medial and apical segments of RV

8.4. STATISTICAL ANALYSIS OF RESEARCH DATA

Clinical and echocardiographic characteristics have been introduced in several database tables in the Microsoft Excel module of Microsoft Office XP Professional (Microsoft Corp., Redmond, WA, USA), compatible with all the statistical analysis programs we used to process the information. Secondary data interpretation, calculation of fundamental statistical parameters, average and standard deviation, data comparison was performed using the SPSS program using either unpaired t test or one-way ANOVA and Student t-test. The charts (graphs) illustrating the evolution trends of the various evaluated parameters, as well as the statistical comparisons between them, were executed using the „SPSS” module of the Microsoft Office XP program package.

9. RESULTS AND DISCUSSIONS

For this purpose, we compared the study group consisting of young subjects with type 1 DM with a healthy control, composed of subjects without a history of cardiovascular disease and without a DM diagnosis.

By comparison, between the study groups, mean weight and body mass index of patients in the DM group were statistically superior to the mean values calculated in the control group.

Although, typically, patients with type 1 diabetes were considered to have lower BMI, current research has shown the opposite. (23) Adham Mottalib et al. has reported an increase in the prevalence of overweight and obesity among DZ1 patients in recent years, currently about 50% of patients with DZ1 being overweight or obese.(18)

Also, the statistical analysis revealed increased values of systolic and diastolic blood pressure in diabetic subjects compared to the control group. An increase in the prevalence of hypertension among subjects with DM 1 was demonstrated by Roonback et al (24) in 2004, being described as a consequence of arterial stiffness and a strong predictor of cardiovascular disease. In addition, although arterial stiffness is consistent with aging in subjects with and without diabetes, these changes tend to occur much earlier, with 15-20 years, in subjects with type 1 diabetes compared to normal, which suggests an accelerated vascular aging.

Conventional LV echocardiographic parameters, such as telediastolic and telesystolic diameters, did not show significant variations between groups. This result was, however, expected due to the young age of the patients included in the study groups. This result could not be compared to previous reports.

Relative wall thickness and left ventricular mass showed significantly higher values in the DM1 group compared to the control group, suggesting the occurrence of LV remodeling in subjects with DM1. This remodeling could be partly explained by significantly higher blood pressure values in this patients. Sato et al also demonstrated an increased ventricular hypertrophy in patients with type I diabetes.(25) Increase in LV mass was considered an independent risk factor for sudden death, myocardial ischemia, ventricular arrhythmias and heart failure. (27).

Telediastolic and telesystolic volumes of LV were mild but significantly lower in study subjects compared to the control group. Another parameter to be mentioned is the stroke volume which has also been reduced and is closely related to the left ventricle telediastolic volume reduction. Studies showed that young people with type 1 diabetes had low left ventricular performance at rest and during exercise. Specifically, it exhibits a reduction in beating volume both in rest and physical exercise. Heart rate could be another parameter that could influence the reduction of the beating volume and implicitly of the VS telediastolic volume. In our study, this change can not be attributed to heart rate variations since both groups had similar mean resting values.

The systolic function of the left ventricle was characterized by the evaluation of the ejection fraction and the velocity of the systolic wave S 'evaluated by Tissue Doppler (TDI). As expected, there were no significant differences in the VS ejection fraction between the two groups, consistent with those in the literature.

In this study, the evaluation of TDI-derived systolic myocardial (S ') velocity revealed the presence of systolic dysfunction among patients with DM1. The results of our study are consistent with studies in adult diabetic patients who showed a decrease in the longitudinal strain of LV, both with TDI method and the two-dimensional speckle tracking. (28,29) These results suggest that the early impairment of left ventricle longitudinal function might be considered.

The data obtained from the evaluation of the transmittal diastolic profile and of the results from the TDI analysis suggested the presence of diastolic dysfunction of VS in diabetic subjects compared to the control group. Most of the results obtained were maintained in the reference norms according to the recommendations of the current guidelines, however, small

differences, but statistically significant were highlighted among the subjects in the study. Thus, in the present study, patients with diabetes had significant abnormalities of left ventricular filling pressures in conventional echocardiography and TDI (E/E' ratio), including a decrease in the LV early filling velocity (decrease of E wave) and a greater dependence on atrial contraction for ventricular filling (increase of wave A), with a consecutive decrease in E / A ratio. These results suggest early changes in myocardial relaxation, indicating a abnormalities of the diastolic function of VS.

Evaluation of left atrium volumes and function is of high interest since changes in AS size and function have been associated with cardiovascular events such as atrial fibrillation, stroke, diastolic and systolic VS dysfunction in the general and diabetic population. Large echocardiographic studies in the literature included patients with prediabetal and diabetes without a clear distinction between the two types of diabetes. Furthermore, Kadappu et al. reported a dilatation of the left atrium in DZ independent of associated hypertension and diastolic dysfunction, raising the issue of a form of atrial cardiomyopathy. (34)

In this study, we found that, although patients with type 1 diabetes had diastolic dysfunction with increased filling pressures, the AS volume and the AS reservoir did not show statistically significant differences. An explanation could be the relatively young age of the patients and the mild diastolic impairment observed in the DM1 vs control group. Also, due to the complex, irregular geometry of the LA, which often grows asymmetrically resulting in a variable form, the 2D echocardiographic parameters are varies between different limits.. Thus, superior techniques such as 2D speckle tracking or 3D speckle tracking are to be considered in the future to broaden the current study, starting from the results of small-scale studies in literature that highlighted the early remodeling of AS. (35)

Data on systolic RV function in patients with DM1 are rare. In the current paper I could not demonstrate RV systolic dysfunction either by measuring TAPSE or S 'TDI RV. This may be due to the different arrangement of RV myocardial fibers versus LV.

In our study, we demonstrated that type 1 DM is associated with subclinical systolic dysfunction of VS, which can be identified as a reduction of the longitudinal strain, with the preservation of the circumferential strain. Thus we analyzed the LV longitudinal strain parameters from the level of each myocardial layer (GLS endo, GLS mio and GLS epi) and the global, basal, medium and apical circumferential strain parameters by speckle tracking.

As expected, all subjects presented an endocardial-epicardial gradient, with the highest longitudinal myocardial deformation being found at endocardial level, and the smallest epicardial layer. These data are consistent with those in literature (13,21).

Subendocardial fibers are longitudinally oriented, being most vulnerable to pathological and first-afflicted factors in cardiac pathologies. It has also been observed that disease progression is affected by myocardial and subepicardial average fibers that cause circumferential and radial dysfunction, resulting in a reduction in EF.

In the current study we evaluated the longitudinal and circumferential strain, not the radial strain. We chose not to analyze the radial strain because it has methodological limitations and it has proved to be a lesser method to the longitudinal and circumferential strain in identifying certain diseases. In addition, longitudinal and circumferential deformations have been validated with respect to the ejection fraction (EF) in previous studies (39).

The evaluation of left ventricular torsade in patients with type 1 diabetes vs. control in this study did not show statistically significant findings, this contrasting with the few literature results. Tadic et al. Showed that LV torsion was slightly increased in DZ subjects but with statistical significance at the limit. Left ventricular torsion, which contributes significantly to energy-efficient ejection during systole and is increased in asymptomatic subjects with type 1 diabetes as demonstrated by Milan K. et al. (22) None of these two studies included subjects with DM with age and clinical features similar to our study group.

Mechanical VS dispersion measured by speckle tracking echocardiography has been shown to be associated with ventricular arrhythmias in several cardiomyopathies. (5) This is an important observation because we need higher risk markers of the ejection fraction to identify patients at risk of developing life threatening cardiac arrhythmias.

Result of this parameter in the current study brought small but statistically significant results among subjects with type 1 diabetes. Patients with diabetes had significantly greater mechanical dispersion compared to the control group 33.6 ± 11.5 vs. 28.6 ± 6.6 . This finding may indicate that people entering these categories are more prone to ventricular arrhythmic events. The data we obtained could not compare to literature data as we did not find studies evaluating mechanical dispersion in patients with type 1 diabetes and young age.

Speckle tracking echocardiography has shown that it provides valuable information for assessing the right ventricle function, in addition to conventional echocardiography. However, this method was only validated for LV deformation analysis, with little data on the clinical reliability of LV deformation assessment. Also, up to the present study, there was no evidence of the superiority of the reproducibility of the longitudinal strain measurement method using a 6-segment model, including the interventricular septum versus the free wall tracing method (3 segment model).

In this study we demonstrated that the RV LS evaluation method by including the 6 segments in the analysis is the most reproducible, showing the lowest intraobservatory, interobservatory and retest test variability.

10. CONCLUSIONS:

The present study provided new insights into the cardiovascular assessment of young patients with DZ1, allowing the following conclusions

- Linear measurements of the interventricular septum and posterior wall diastolic diameter of left ventricular and VS mass showed higher values in young DM1 thus exhibiting a higher degree of hypertrophy vs. control batch
- This study shows a relatively low performance of LV in patients with type 1 traduced by a reduction in the stroke volume and the telediastolic and telesistolic LV volumes.
- Decreased relaxation properties of the LV myocardium can be detected by conventional echocardiographic parameters, TDI and speckle tracking, each with different sensitivity and specificity.
- The left ventricular Tissue Doppler method was superior to the ejection fraction for detecting VS systolic dysfunction.
- The present study has shown that the speckle tracking method becomes an important and sensitive tool for early detection of subclinical dysfunctions of VS, finding its applicability also in young patients with type 1 DZ.
- LV myocardial dysfunction measured by speckle tracking begins at the level of the sunbendocardic and myocardial layer, with the preservation of the epicardial layer in the early stages.
- Subclinical VS systolic dysfunction with normal EF occurs in the direction of the longitudinal axis
- Young diabetic patients have a risk for life-threatening cardiac arrhythmias compared with controls claiming by the mechanical dispersion wich is a better prognostic factor than the ejection fraction to identify patients at risk.
- Evaluation of LV and RV strain and free wall strain did not show statistically significant differences in DM1 vs control group.
- The longitudinal strain evaluation method of RV by including in the analysis the 6 RV segments (3 segment segments, 3 VD free segments) is the most reproducible, showing the

lowest variability intra, interobserver and retest compared to the inclusion method of 3 segments.

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