

Subclinical Left Ventricular Dysfunction in Asymptomatic Type 1 Diabetic Children

Introduction

Diabetic cardiomyopathie (DCM) is a distinct new entity firstly described by Rubler et al. [1] in 1972. Pathophysiological mechanisms are not well known. In the presence of hyperglycemia, non-enzymatic glycosylation of several proteins, reactive oxygen species formation, and fibrosis lead to impairment of cardiac contractile functions. DCM is defined as the presence of abnormal myocardial performance or abnormal structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease. The relationship between type 1 diabetes (T1D) and cardiac function in children is not well established. Demonstration of an early systolic dysfunction help us to diagnose children's DCM, and is important for the timely interventions. In most of the previous studies, systolic function was restricted to measurement of left ventricular ejection fraction (LVEF) using standard two-dimensional (2D) echocardiography [2,3]. However, the LV contractility is a complex mechanism resulting from a three-dimensional structure. Myocardial fibers are orientated in different directions and responsible for three principal types of deformation: longitudinal; radial and circumferential deformation [4]. Myocardial strain assessment based on 2D speckle tracking analysis is a novel echocardiographic approach for a sensitive and angle-independent evaluation of myocardial deformation and an able tool to evaluate the three components of myocardial deformation. It has been shown to be the most sensitive echocardiographic tool for the detection of sub-clinical impairment of myocardial function observed in many conditions such as aortic stenosis, hypertrophic cardiomyopathy and hypertension. The objective of this study was to characterize global systolic function abnormalities using 2D Strain in T1D children and to assess the relationship between these myocardial data and glycemic control.

Keywords: Diabetic cardiomyopathie; Speckle tracking analysis; Systolic function; Type 1 Diabetes

Methods

Twenty healthy children and 24 T1D children were included. T1D children were aged 5 to 18 years and followed-up at the pediatric hospital of Tunis. T1D was diagnosed according to World Health Organization criteria. Exclusion criteria were the presence of cardiopathy, impaired renal function, significant concomitant disease, medication known to modify cardiac function, high blood pressure and smoking. T1D children were compared to healthy control children matched for age, gender and body mass index and having normal echocardiography. Patients provided their informed consent through legal representatives. The protocol of the study was approved by the hospital's ethical committee. All patients were subjected to history taking for demographic data, diabetes duration and insulin therapy. Clinical examination stressing on anthropometric measures, heart rate, systolic blood pressure (SBP) diastolic

Research Article

Volume 6 Issue 6 - 2016

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Received: May 29, 2016 | **Published:** October 31, 2016

blood pressure (DBP) and cardiac auscultation. A standard 12-lead electrocardiogram was recorded followed by measurement of blood pressure. Laboratory investigations included mean hemoglobin (HbA1c). Echocardiography with simultaneous ECG (standard lead II), including standard echocardiographic views, tissue Doppler imaging (TDI) and 2D strain analysis, was performed using Vivid 9, GE Ultrasound equipped with 3-5 MHz transducers. The recordings and measurements were obtained in accordance with the recommendations of the American Society of Echocardiography. Time motion (TM) mode of LV dimensions were obtained in parasternal long-axis view: Left ventricular end-diastolic diameter (LV-EDD), interventricular septal end-diastolic diameter (IVS-EDD) and left ventricular posterior wall end-diastolic diameter (LVPW-EDD). LV conventional Doppler parameters of diastolic function; peak early (E) and peak late (A) diastolic flow velocities, E-wave deceleration time and E/A ratio were measured on the basis of transmitral flow velocities. LVEF was assessed using the biplane Simpson's method in apical four and two chamber views. TDI was performed in four apical view. The following TDI variables were evaluated peak systolic (S), peak early diastolic (E'), peak late diastolic (A). All measurements were analyzed by one observer who was blinded to all patients' data.

Using a dedicated software package (EchoPac PC; GE Healthcare), 2D strain was measured. All images were recorded at a high image rate at > 50 Hz and stored for post-processing analysis. The LV was divided into 17 segments and each segment individually analyzed. Two-dimensional global longitudinal strain (GLS) was assessed in apical views: Four, three and two chamber views by tracing the endocardial contour on an end-diastolic frame, the software will automatically track the contour on subsequent frames. The operator ensured contouring and optimal tracking of the movements of each wall segment by the software. When myocardial tracking was considered optimal by the operator, the software analyzed the global and segmental strains and represented them as colored curves. The average of GLS was calculated for the 17 segments. Analysis was also performed according to LV segments (six basal, six mid-LV, and five apical).

Statistical Analysis

Quantitative variables were described using means and standard deviations (SD), and qualitative variables were described using frequencies and percentages. Comparisons between subject data were performed with a paired Student t test, and comparisons with healthy volunteers with an independent-samples t test. The relationship between two quantitative variables was assessed using Pearson's correlation. A p value of <0.05 was considered significant. IBM-SPSS 20.0 for Windows was the statistical software used.

Results

Between January 2015 and July 2015, 24 children with T1D were consecutively recruited. The mean age was 11.13 years \pm 0.54. The T1D children and control group were comparable with respect to age, gender, heart rate, SBP and DBP. General Characteristics of our population. There were no significant differences between the two study groups in LVEF, LV diameters, diastolic function parameters and TDI parameters. GLS was significantly lower in the diabetes children comparing to control group ($-18.53\% \pm 0.5$ Vs $-25.52\% \pm 0.37$, $p < 0.001$).

In segmental analysis, GLS at the base, mid, and apical LV levels were also significantly lower in diabetic children compared with control subjects. Global and segmental strain values are shown in table III and Figure 2. In diabetic children, we observed an increase in longitudinal strain from base to apex ($-18.59\% \pm 0.73$ Vs $-22.23\% \pm 0.86$ respectively). Univariate analysis revealed that no correlation was noted between GLS and LVEF ($r=0.108$; $p=0.64$) and no correlation also with HbA1c ($r=0.152$; $p=0.477$). While GLS was significantly correlated with E/E' ratio ($r=0.568$, $p=0.004$) and with mitral E wave ($r=0.645$, $p=0.001$). The intra observer reproducibility was 5% for GLS.

Discussion

This study assesses the role of 2D strain, a new method to evaluate systolic function from bi dimensional acquisitions in diabetic children. The major findings can be summarized as: 1) the longitudinal strain can be measured with good reproducibility in normal children and in those with T1D; 2) GLS is significantly reduced in diabetic children; and 3) No correlation was found between GLS and HbA1c however there was a significant correlation with E/E' ratio. Our findings for longitudinal strain in normal children were in agreement with previously published studies [5,6]. Diabetes is known to be associated with the development of heart failure even without the presence of co-existing coronary artery disease [7,8]. This functional myocardial alteration is induced by various complex mechanisms in which chronic hyperglycemia plays a pathophysiological role [9,10]. Previous echocardiographic studies in diabetic children focused LV systolic function by evaluating EF, then, they concluded the absence of LV systolic dysfunction. However, cardiac contraction is a complex three plan myocardial deformation: longitudinal, circumferential and radial, and cannot be reduced to a simple variation of volume, as with assessment of LVEF. In addition, LV longitudinal deformation plays an important role in cardiac pump function; it is controlled by subendocardial longitudinal

myofibers, which are more susceptible to ischemia and fibrosis [11]. This explains why GLS is the first anomaly observed in many pathologies with preserved EF, such as HCM.

Our results agree with studies of Fang et al. [12], who reported decreases of GLS in the LV of 53 diabetic adults ($-21 \pm 4\%$ in T1D adults Vs $-26 \pm 4\%$ in control group ; $p < 0.001$). However, these reports are difficult to interpret because they included adult patients, in whom the influence of comorbidities especially coronary heart disease could not be excluded. Such comorbidities may be considered non-existent in our cohort of diabetic children. Our findings were also in agree with the pediatric study of F. Labombarda et al. [4] who evaluated GLS in 100 T1D children compared to 79 controls. Longitudinal deformation was significantly lower in T1D group ($-17.6 \pm 1.6\%$ Vs $-20.5 \pm 1.4\%$ respectively; $p < 0.001$). Then, in T1D children group, GLS was significantly reduced despite normal LVEF, suggesting the presence of a global subclinical systolic dysfunction in DCM. Hence, strain analysis appears to be a more sensitive index of global myocardial function than standard LV function assessment. The identification of early manifestations of diabetic heart disease would allow the institution of timely medical interventions to prevent the development of heart failure [13]. However, in our results, we could find no correlation between HbA1c and decreased GLS. These findings don't agree with studies demonstrating a relationship between glycemic control and cardiac function in diabetic children [14]. They found that a higher mean HbA1c was significantly associated with changes in LV structure and function in patients with T1D. We found that GLS is associated with early diastolic indices (E-wave velocity and E/E' ratio). Significant correlation between global GLS and E/E' ratio confirms the link between systole and diastole, which has been confirmed in previous studies [15,16].

Study Limitation

The study size was relatively small. Thus, our results cannot be extrapolated to the general diabetic pediatric population

Conclusion

Subclinical LV systolic dysfunction may be identified by a reduction in longitudinal function, assessed 2D Strain, in diabetic children. Alteration of GLS may be considered the first marker of preclinical DCM. Further studies are now required to determine the prognostic value of these subclinical abnormalities of cardiac function in diabetic children.

References

1. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, et al. (1972) New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 30(6): 595-602.
2. Suys BE, Katier N, Rooman RPA, Matthys D, Op De Beeck L, et al. (2004) Female children and adolescents with type 1 diabetes have more pronounced early echocardiographic signs of diabetic cardiomyopathy. *Diabetes Care* 27(8): 1947-53.
3. Gunczler P, Lanes R, Lopez E, Esaa S, Villarroel O, et al. (2002) Cardiac mass and function, carotid artery intima-media thickness and lipoprotein (a) levels in children and adolescents with type 1 diabetes mellitus of short duration. *J Pediatr Endocrinol Metab* 15(2): 181-186.

4. Labombarda F, Leport M, Morello R, Ribault V, Kauffman D, et al. (2014) Longitudinal left ventricular strain impairment in type 1 diabetes children and adolescents: a 2D speckle strain imaging study. *Diabetes Metab* 40(4): 292-298.
5. Bussadori C, Moreo A, Di Donato M, De Chiara B, Negura D, et al. (2009) A new 2D-based method for myocardial velocity strain and strain rate quantification in a normal adult and paediatric population: assessment of reference values. *Cardiovasc Ultrasound* 7: 8.
6. Lorch SM, Ludomirsky A, Singh GK (2008) Maturational and growth-related changes in left ventricular longitudinal strain and strain rate measured by two-dimensional speckle tracking echocardiography in a healthy pediatric population. *J Am Soc Echocardiogr* 21(11): 1207-1215.
7. Bell DS (2007) Heart failure in the diabetic patient. *Cardiol Clin* 25(4): 523-538.
8. Fang ZY, Prins JB, Marwick TH (2004) Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev* 25(4): 543-567.
9. Poornima IG, Parikh P, Shannon RP (2006) Diabetic cardiomyopathy: the search for a unifying hypothesis. *Circ Res* 98(5): 596-605.
10. Rajesh M, Bátkai S, Kechrid M, Mukhopadhyay P, Lee WS, et al. (2012) Cannabinoid 1 receptor promotes cardiac dysfunction, oxidative stress, inflammation, and fibrosis in diabetic cardiomyopathy. *Diabetes* 61(3): 716-727.
11. Lumens J, Delhaas T, Arts T, Cowan BR, Young AA (2006) Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. *Am J Physiol Heart Circ Physiol* 291(4): H1573-H1579.
12. Fang ZY, Leano R, Marwick TH (2004) Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci (Lond)* 1979 106(1): 53-60.
13. Galderisi M (2006) Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol* 48(8): 1548-1551.
14. Kim EH, Kim YH (2010) Left ventricular function in children and adolescents with type 1 diabetes mellitus. *Korean Circ J* 40(3): 125-30.
15. Shishehbor MH, Hoogwerf BJ, Schoenhagen P, Marso SP, Sun JP, et al. (2003) Relation of hemoglobin A1c to left ventricular relaxation in patients with type 1 diabetes mellitus and without overt heart disease. *Am J Cardiol* 91(12): 1514-1517.
16. Malhotra A, Sanghi V (1997) Regulation of contractile proteins in diabetic heart. *Cardiovasc Res* 34(1): 34-40.