Assessment of left atrial function by tissue Doppler as a predictor of early diabetic cardiomyopathy

Thesis

Submitted for partial fulfillment of Master Degree

In Cardiology

By

Malak Nageeb Asaad
M.B.B.CH

Under Supervision of

Prof. Azza Abd-Allah El-Fiky
Professor of Cardiology
Faculty of Medicine
Ain Shams university

Doctor. Sherif Mansour Soliman
Lecturer of Cardiology
Faculty of Medicine
Ain Shams university

2011

INTRODUCTION

The left atrium serves as both a reservoir and a conduit for passage of blood from the pulmonary veins to the left ventricle and as a contractile chamber that augments left ventricular filling. Vortical flow has been observed in the atrium during systole and diastolic diastasis ***(Fyrenius et al., 2001)***. Previous studies indicate that the atria contribute up to 30% of left ventricular filling and cardiac output and are particularly important in the setting of impaired left ventricular function ***(Matsuda et al., 1983).***

Non-invasive estimation of left atrial contraction has normally been done assessing transmitral blood flow using conventional pulsed Doppler echocardiography. Traditionally, blood flow velocity during atrial contraction, the peak mitral inflow A wave velocity, its velocity time integral and atrial emptying fraction have been used as surrogate markers of atrial function. New tools, such as automatic boundary detection, have made it possible to validate various indexes of both systolic and diastolic left atrial function ***(Waggoner et al., 1993).***

A primary diabetic cardiomyopathy represents a high risk factor of heart failure in the absence of ischemic, valvular and hypertensive heart disease in the diabetic population ***(Zarich et al., 1989) & (Raev DC, 1994).*** Diabetic cardiomyopathy is characterized by an early left ventricular (LV) diastolic dysfunction and a late LV systolic dysfunction. At conventional echocardiography, LV diastolic dysfunction has been documented also in subjects with impaired glucose tolerance ***(Celentano et al., 1995),*** and a short duration of type 2 diabetes mellitus. Unquestionably, an early detection of LV damage is a major goal for the prevention of cardiac disease in the diabetic population ***(Di Bonito et al., 1996).***

Pulsed wave tissue Doppler imaging (PW-TDI) is a relatively new echocardiography tool for analyzing high amplitude and low frequency Doppler signals from the cardiac muscle. An excellent signal-to-noise ratio and the possibility of analyzing the data quantitatively are some of the new and attractive advantages of PW-DTI ***(Gorcsan J, 1999).***

This technique has been used to evaluate velocities and time intervals of the contraction and relaxation of both ventricles in different clinical situations ***(Moreno R et al.,1999&2001)*** However, there are very few studies that have

provided quantitative data on atrial function using PW-DTI ***(Iglesias I.,2002).***

AIM OF THE WORK

-To analyze the profile of left atrial wall velocity by pulsed wave tissue Doppler parameters in diabetic patients, and its relationship with the transmitral velocities and the left atrial pump function parameters obtained by conventional echocardiography for early detection of diabetic cardiomyopathy.

DIABETES MELLITUS

Definition of Diabetes Mellitus:

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia and disturbance of carbohydrates, lipids and proteins-metabolism with disturbance of water and electrolytes homeostasis, resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eye, kidney, heart and blood vessels ***(The Expert Committee on the Diagnosis of DM, 2003)***.

Prevalence of Diabetes Mellitus:

Diabetes mellitus remains one of the most challenging diseases for workers in the medical field ***(Yuan et al., 1999)***. Its prevalence in adults worldwide was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025. It is higher in developing countries than in developed countries ***(The Expect Committee on the Diagnosis of DM, 2003)***.Type II diabetes mellitus is the predominant form of diabetes worldwide accounting for 90% of cases globally ***(John et al., 2003)***.The

incidence of DM is similar in men and women throughout most age ranges but is slightly greater in men > 60 ***(Alvin, 2001)***.

Diagnosis of Diabetes Mellitus:

When classic symptoms of polyuria and polydispsia are associated with hyperglycemia and glucosuria, the glucose tolerance test is not needed to support the diagnosis.

The old criteria of ***The National Diabetes Data Group (NDDG), (1979)*** of diabetes mellitus were based on a level of fasting plasma glucose (FBG) of ≥ 7.8 mmol/L (≥140 mg/dL) and 1 or a 2 hours post oral glucose tolerance test, plasma glucose level of ≥ 11.1 mmol/L (≥ 200 mg/dL) on more than one occasion ***(Dinneen et al., 1998)***.

The American Diabetes Association (ADA), (1997) expert committee adopted revised criteria for the diagnosis of diabetes mellitus. These guidelines included lowering of the diagnostic threshold for fasting plasma glucose (FPG) from 7.8 to 7.0mmol (140 to 126 mg/dL) ***(Perry et al., 2001)***.

The American Diabetes Association (ADA), (2010) expert committee revised the criteria for the diagnosis of diabetes mellitus and it includes the following:

(1) Criteria for Diagnosis of Diabetes Mellitus:

1. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

OR

2. Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

3. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

OR

4. Haemoglobin A1c ≥ 6.5%. The test should be performed in a laboratory using a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay.

(2) Categories of increased risk for diabetes:

Non-diabetic individuals who are at high risk to develop diabetes mellitus are classified as: (1) Non-diabetic individuals with a FPG 100 - 125mg/dL (5.6 - 6.9 mmol/L) are considered to have impaired fasting glucose (IFG) and (2) whose with 2-hour values in OGTT 140 - 199 mg/dL (7.8 - 11 mmol/L) are defined as having impaired glucose tolerance (IGT), both IFG and IGT are risk factors for future diabetes .Also, persons with haemoglobin A1C of 5.7 – 6.4 % have increased risk of diabetes ***(American Diabetes Association, 2010).***

Type II Diabetes Mellitus:

It is a term used for individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. At least initially, and often through their life-time, these individuals also don't need insulin treatment to survive ***(American Diabetes Association, 2003)***. Most of the patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance, the adiposities secret a number of products (leptin, tumor necrosis factor α, free fatty acids) that modulate the insulin secretion and insulin action ***(Alvin, 2001)***.

Complications of Diabetes:

(1) Acute Complications:

1. Diabetic ketoacidosis.
2. Lactic acidosis.
3. Hypersomolar diabetic coma.
4. Hypoglycemia.

(2) Chronic Complications:

These include:

1- Micro-vascular complications:
   a. Nephropathy.
   b. Retinopathy.
   c. Neuropathy.

2- Macro-vascular complication:
   a. Coronary artery disease.
   b. Heart failure.
   c. Hypertension.
   d. Cardiomyopathy.
   e. Peripheral vascular disease.
   f. Cerebro-vascular disease.

(Philip and Glenn, 2001).

Cardiovascular Disease in Diabetes:

Cardiovascular diseases in diabetics include several varieties which include:

1. Atherosclerotic heart disease:
   a. Angina.
   b. Myocardial infarction.
2. Congestive heart failure.
3. Hypertension.
4. Cardiomyopathy.
5. Peripheral vascular disease.

(1) Atherosclerotic Coronary Artery Disease:

Diabetes mellitus increases the risk of coronary events tenfold in men and fourfold in women. Part of this increase is due to the frequency of associated cardiovascular risk factors such as hypertension, dyslipidemia and clotting abnormalities ***(American Diabetes Association, 2003)***.

Young diabetics are at particular risk and by the age of 50 years, 33% of those requiring insulin have died from coronary heart disease. Indeed 75% of all deaths in patients with diabetes are from this cause ***(Adam, 2001)***. Diabetes also worsens early and late outcomes in acute coronary syndromes. In a 6-nation study of unstable angina and non-Q wave MI,

diabetes independently increases the risk of death by 57%. Patients with diabetes also have an adverse long-term prognosis after MI, including increased rates of reinfarction, congestive heart failure and death ***(Malmberg et al., 2000)***.

It is well known that diabetes is associated with silent ischemia and subjects with type II diabetes can often have a normal resting ECG and still have suffered previous myocardial infarction. So, exercise testing and/or cardiac imaging techniques should be used to detect silent ischemia without symptoms or exercise ECG (ST - segment changes), because a significant number of patients with type II diabetes [21%] with the absence of clinical symptoms or ECG signs suggestive of CHD, had significant (>50%) angiographic lesions moreover ***(Paul et al., 2000)***.

(2) Congestive Heart Failure:

A leading cause of death for diabetic patients is heart failure. The Framingham Heart Study (FHS) first demonstrated an increased risk of congestive heart failure (CHF) in patient with diabetes over 20 years ago ***(Gregory et al., 2001)***.

Clinical and epidemiological data indicate a significant association between diabetes mellitus and congestive heart

failure (CHF) with normal ejection fraction (EF) ***(Anderson et al., 2003)***.

Several lines of evidence indicate that left ventricular (LV) diastolic dysfunction represents the earliest preclinical manifestation of diabetic cardiomyopathy that can progress to symptomatic heart failure.

Many studies have demonstrated that up to 60% of asymptomatic, normotensive patients with type II diabetes have diastolic dysfunction when assessed by conventional echocardiography including the response to the Valsalva maneuver ***(John et al., 2004)***.

(3) Hypertension:

Diabetes mellitus is a major risk factor for the development of hypertension ***(Vinicore, 1996)***.In both men and women, diabetes mellitus was associated with higher systolic and diastolic blood pressure with a higher-frequency of hypertension ***(Howard et al., 1998)***. The goal of treatment for hypertension in diabetes have been changed from 160/95 mmHg ***(WHO, 1983)***, to 140/90 ***(JNC-V and WHO, 1993)***, and then to 130/85 mmHg ***(Joint National Committee, 1997)***, and then to 130/80 mmHg ***(Joint National Committee, 2003)***.

(4) Diabetic Cardiomyopathy.

DIABETIC CARDIOMYOPATHY

Diabetic cardiomyopathy (DCM) was originally described in 1972 on the basis of observations made in four diabetic patients who presented with heart failure (HF) without evidence of hypertension, coronary artery disease (CAD), valvular or congenital heart disease ***(Rubler et al., 1972).***

This finding was later confirmed in separate diabetic patients who showed evidence of myocardial dysfunction in the absence of CAD ***(Regan et al., 1977) & (D'Elia et al., 1979)***.

Analysis of data from the Framingham Heart Study revealed echocardiographic evidence for increased heart rate, left ventricular (LV) wall thickness, LV end-diastolic dimension and mass in diabetic patients ***(Galderisi et al., 1991).***

Table (1) lists several epidemiologic studies that have suggested that there is a consistent association between diabetic cardiomyopathy and the presence of cardiac hypertrophy and myocardial stiffness, both independent of hypertension. Such associations have provided credible evidence to support the existence of diabetic cardiomyopathy as a unique clinical entity. ***(Ashish et al., 2008).***

Table 1: Main Echocardiographic, Population-Based Studies on Diabetic Cardiomyopathy.

Authors	Year	Findings	Population Sample
Galderisi e al, Framingham Heart Study	1991	Increase of LVM in women	111 DM, 381 IGT
Lee et al. Cardiovascular Health Study	1997	Increase of LVM in both genders	2697 DM or IGT,>65 yr
Devereux et al Strong Heart Study	2000	Increase of LVM, reduction of EFS and MFS	1810 DM
Palmieri et al. HyperGEN Study	2001	Increase of LVM and RWT, reduction of MFS	386 DM=HTN
Ilercil et al. Strong Heart Study	2001	Increase of LVM and RWT	457 IGT
Bella et al Strong Heart Study	2001	Progressive increase of LVM and reduction of EFS and MFS in DM and DM+HTN	642 DM 874 DM+HTN
Liu et al. Strong Heart Study	2001	Progressive reduction of E/A ratio and prolongation of DT in DM and DM_HTN	616 DM 671 DM+HTN
Rutter et al. Framingham Heart Study	2003	Progressive increase of LVM, RWT, and LA in IGT and DM	186 DM 343 IGT

DM=diabetes mellitus; EFS=endocardial fractional shortening; HTN=hypertension; IGT=impaired glucose tolerance; LA=left atrium; LVM=left ventricular mass; MFS=midwall fractional shortening; RWT=relative wall thickness.

PATHOPHYSIOLOGICAL MECHANISMS OF DIABETIC CARDIOMYOPATHY

A clear understanding of the precise pathophysiologic mechanisms of diabetic cardiomyopathy is still lacking. However, several pathophysiologic mechanisms have been proposed to explain the structural and functional changes associated with diabetic cardiomyopathy .These processes are not mutually exclusive and likely act synergistically to develop diabetic cardiomyopathy.

1. Free Fatty acid Metabolism Disturbances:

The heart is one of the most metabolically active organs in the body, needing to generate 5 kg of adenosine triphosphate (ATP)/day for contractile function and maintenance of cellular homeostasis and completely turning over its ATP supply every 13 second ***(Shah A et al., 2003)*** . To accomplish this goal, the heart metabolizes 3 fuels; free fatty acids (FFA), glucose, and (to a limited extent) lactate. The normal, unstressed adult heart predominantly uses FFA (approximately 70% of ATP production), owing to the high energy yield per molecule of substrate metabolized ***(An D et al., 2006)***. However, in the stressed state (e.g., ischemia, pressure load, injury), the heart