

Left Ventricle Diastolic Dysfunction in Diabetes: an Update

atualização

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ABSTRACT

Diabetes mellitus, a disease that has been reaching epidemic proportions, is an important risk factor to the development of cardiovascular complication. Diabetes causes changes within the cardiac structure and function, even in the absence of atherosclerotic disease. The left ventricular diastolic dysfunction (VE) represents the earliest pre-clinical manifestation of diabetic cardiomyopathy, preceding the systolic dysfunction and being able to evolve to symptomatic heart failure. The doppler echocardiography has emerged as an important noninvasive diagnostic tool, providing reliable data in the stages of diastolic function, as well as for systolic function. With the advent of recent echocardiographic techniques, such as tissue Doppler and color M-mode, the accuracy in identifying the moderate diastolic dysfunction, the pseudonormal pattern, has significantly improved. Due to cardiometabolic repercussions of DM, a detailed evaluation of cardiovascular function in diabetic patients is important, and some alterations may be seen even in patients with gestational diabetes. (**Arq Bras Endocrinol Metab 2007;51/2:168-175**)

Keywords: Diabetes; Echocardiography; Diastole; Doppler; Cardiomyopathy

RESUMO

Disfunção Diastólica do Ventrículo Esquerdo no Diabetes: Uma Atualização.

O Diabetes Mellitus (DM), doença que vem atingindo proporções epidêmicas, é um importante fator de risco para o desenvolvimento de complicação cardiovascular. O DM leva a alterações cardíacas estruturais e funcionais, mesmo na ausência de doença aterosclerótica. A disfunção diastólica do ventrículo esquerdo (VE) representa a manifestação pré-clínica mais precoce da cardiomiopatia diabética, precedendo a disfunção sistólica e podendo progredir para insuficiência cardíaca sintomática. O Doppler ecocardiograma tem se mostrado uma importante ferramenta diagnóstica não-invasiva, fornecendo dados confiáveis dos estágios da função diastólica do VE, assim como da função sistólica. Com o advento de recentes técnicas de ecocardiografia, como o Doppler tecidual e o color M-mode, a acurácia em identificar a disfunção diastólica moderada, padrão pseudonormal, aumentou significativamente. Frente às repercussões cardiometabólicas do DM, é importante uma avaliação detalhada da função cardiovascular dos pacientes diabéticos, sendo que algumas alterações podem ser vistas até mesmo em pacientes com o diabetes gestacional. (**Arq Bras Endocrinol Metab 2007;51/2:168-175**)

Descritores: Diabetes; Ecocardiograma; Diástole; Doppler; Cardiomiopatia

DIABETES MELLITUS is one of the most common diseases in the world and is acquiring epidemic proportions. Its prevalence is growing in developed and developing countries. More than 5% of adults have this disease, with prevalence arising from 1% in the youth to 13% in those older than 60 years. Recently the American Diabetes Association (ADA) and the World Health Organization (WHO) sharpened the criteria for diagnosing DM, contributing to the increase in the number of diagnosis in earlier ages. Because of the increasing frequency of diabetes in the past 30 years, the importance of cardiovascular disease attributable to diabetes will continue to increase, even if the incidence in the non-diabetic population continues to diminish (1).

In 1997 and 2003, an International Expert Committee recommended changes to the diagnostic criteria for diabetes (2,3). So, precise statistical data regarding the prevalence of new categories of impaired glucose metabolism, such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) might have changed in different populations with the application of the most recent diagnostic criteria for diabetes and pre-diabetes. The American Diabetes Association data show that 20,8 million people have diabetes and other 54 million people have pre-diabetes, IFG or IGT (4). In two Brazilian population samples, they found a prevalence around 7,5% of IFG at that time (5,6).

The epidemic of diabetes represents a major burden to health care systems around the world. Both type 1 and type 2 diabetes are increasing in children and adolescents. However, more alarming is the increase in type 2 diabetes in the youth related to obesity and physical inactivity as was shown in clinical series and some population data from the USA and Canada (7,8).

Cardiovascular complications are known to be the main cause of death and morbidity in diabetic patients, as over 75% of all diabetic patients die from cardiovascular events (9). There is an increased rate of ischemic heart disease and cardiomyopathy, which may lead to congestive heart failure in the absence of coronary atherosclerosis. Heart failure is a common and serious co-morbidity of diabetes. The Framingham study (10) demonstrated an increased risk in heart failure in patients with diabetes and that it has a greater impact on the incidence of congestive heart failure, especially in women. It has been shown a 2-fold higher incidence of heart failure in men with diabetes and a 5-fold increase in women. Additional trials — Studies of Left Ventricular Dysfunction (SOLVD), the Heart Outcomes Pre-

vention Evaluation study (HOPE), the Cardiovascular Health Study (CHS) and nationwide case-control study — also identified diabetes as a major risk factor for the development of heart failure (11-13). Recently a study of health maintenance organization in nearly 10,000 type 2 diabetic patients, 12% had heart failure at entry and about 3.3% of type 2 diabetic subjects developed heart failure each year (14).

Hypertension and coronary artery disease, known co-morbidities of diabetes, are established causes of heart failure. The most prominent risk factor for heart failure in diabetic patients is prior history of coronary artery disease. Furthermore, heart failure is more frequent in diabetic than in non-diabetic patients with myocardial ischemic injury (11). Diabetes has been considered of such importance to the development of heart failure that it has been incorporated as an independent risk factor to it in the American College of Cardiology/American Heart Association (15).

Accumulating data from experimental, pathological, epidemiological and clinical studies have shown that diabetes causes changes within the cardiac structure and function, in the absence of coronary atherosclerosis, hypertension or any other known cardiac disease. However, the coexistence of myocardial ischemia, hypertension, and a specific diabetic cardiomyopathy seems to be independent but contributes to the biochemical, anatomic, and functional alterations in cardiac cells and tissues that impair cardiac function. Factors that can cause microvascular abnormalities, endothelial dysfunction, derangement of myocardial metabolism and autonomic neuropathy, such as hyperglycemia, hypertriglyceridemia and hypertension are postulated as etiological factors (13,16-18).

The most important mechanisms of diabetic cardiomyopathy are metabolic disturbances (increased free fatty acids, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis (increases in angiotensin II, IGF-I, and inflammatory cytokines), small vessel disease (microangiopathy, impaired coronary flow reserve, and endothelial dysfunction), cardiac autonomic neuropathy (denervation and alterations in myocardial catecholamine levels), and insulin resistance (hyperinsulinemia and reduced insulin sensitivity) (19).

The existence of a diabetic cardiomyopathy was first proposed by Rubler et al. (20) in 1972 on the basis of postmortem findings. Subsequently, abnormalities in both systolic and diastolic performance in diabetic subjects have been demonstrated. Several lines of evidence indicate that left ventricular diastolic dys-

function represents the earliest preclinical manifestation of diabetic cardiomyopathy, preceding the systolic dysfunction, and that it can progress to symptomatic heart failure (21,22).

DIASTOLIC HEART FAILURE

Diastole is the portion of the cardiac cycle that begins with aortic closure and ends with mitral closure. In diastolic dysfunction, the abnormality in LV relaxation and/or compliance alters the onset, rate, and extent of LV pressure decline and filling during diastole. These changes create an abnormal relation between left ventricular pressure and volume so that higher filling pressures are needed to maintain normal LV end-diastolic volume and cardiac output. This may result in higher filling pressures at rest; however, it more frequently produces elevated filling pressures during exercise, resulting in exertional dyspnea and fatigue. For the noninvasive assessment of diastolic function, we may rely on Doppler studies of mitral and pulmonary veins inflow patterns. Diastole can be divided into four stages, for descriptive purposes (23).

1st stage: Isovolumic relaxation time – the time taken from aortic valve closure to mitral valve opening. This phase is attributed mainly to myocardial relaxation and has been shown to be an energy-requiring process. During this interval, the intraventricular pressure falls at a rapid rate, while ventricular volume remains constant.

2nd stage: Rapid filling phase (E wave of mitral inflow and D wave in pulmonary vein flow) – when left ventricular pressure falls below atrial pressure, the mitral valve opens and the rapid filling begins resulting in a rapid increase in ventricular volume. It represents an interaction of an active relaxation (suction) and passive viscoelastic properties of the myocardium (compliance).

3rd stage: Passive filling (diastasis) – in this phase, left atrial and ventricular pressures are almost equal, so filling is the result of pulmonary venous flow. It is related to left ventricular compliance.

4th stage: Atrial contraction (A wave of mitral inflow and atrial reversal wave in pulmonary vein flow) – this is an active process and contributes with approximately 15% of left ventricular filling in normal subjects. The subsequent rise in left ventricular pressure leads to mitral valve closure. This phase is most affected by left ventricular stiffness (figure 1).

Heart failure is defined as a pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a

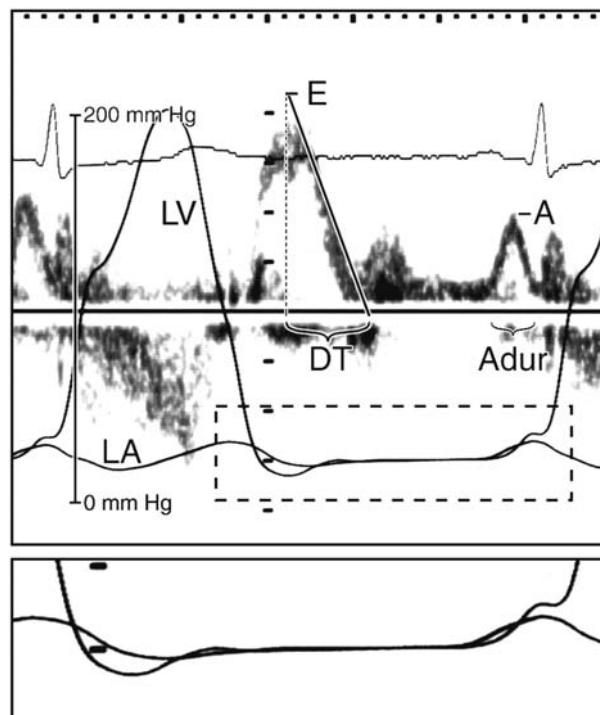


Figure 1. Mitral inflow pattern and left ventricular pressure curves.

LV= left ventricular; DT= deceleration time; LA= left atrium; E= E wave; A= A wave; Adur= duration of A wave.

rate commensurate with metabolic requirements or to do so only from an elevated filling pressure. It is usually, but not always, caused by a defect in myocardial contraction. However, in some patients with heart failure a similar clinical syndrome is present but there is no detectable abnormality in myocardial contraction function (24). Thus, heart failure, a clinical syndrome, may occur in the presence of either a normal or abnormal left ventricular ejection fraction (EF). It is widely accepted that the pathophysiology of heart failure in patients with decreased ejection fraction involves a predominant (though not isolated) decrease in systolic function justifying the term “systolic heart failure”. In contrast, the underlying pathophysiology of patients with heart failure with normal left ventricle systolic function — normal ejection fraction — involves a predominant (not isolated) abnormality in diastolic function, the “diastolic heart failure”. Further stratification of congestive heart failure (CHF) subjects into those with systolic dysfunction and those with predominantly diastolic dysfunction has been suggested as important for clinical decisions, once the therapeutic and prognostic differences between these 2 subsets of patients and, in most disease states, diastolic dysfunction precedes the onset of systolic dysfunction (25).

Cardiac heart failure is a major public health problem in developed countries, and a high proportion of patients admitted due to CHF have normal left ventricular systolic function. Diastolic heart failure is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved systolic function and abnormal diastolic function. In this situation the left ventricle is unable to accept an adequate volume of blood during diastole, at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume. These abnormalities are caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness (26).

This growing recognition that CHF may be caused by a common predominant abnormality, not in systolic, but in diastolic function, and that it causes significant morbidity and mortality, called for further definition of the diagnostic criteria. In the United States of America it is estimated that diastolic heart failure accounts for more than 25% of the total cost of CHF (27). The prevalence of asymptomatic diastolic dysfunction was estimated in 27% in the general population, reaching higher prevalence with aging. Of the patients hospitalized for heart failure, 35% to 40% present with diastolic heart failure and, in the community setting, this number increases from 45% to 55% (28).

Unfortunately, the differentiation between systolic and diastolic heart failure cannot be made at bedside, based on history, physical examination, ECG, or chest radiograph alone. A careful history will detect symptoms of CHF, although about 20% of patients with left ventricular systolic dysfunction do not report symptoms (table 1). Therefore, the diagnosis of heart failure, especially in diabetic patients who have many associated co-morbidities, may require further testing in order to make an appropriate diagnosis. Although electrocardiogram and chest X-ray may be helpful in

demonstrating hypertrophy or left ventricular enlargement, echocardiography is important to visualize the heart for any structural/functional changes, and is the recommended test if CHF is suspected (29).

Much effort was made to propose satisfactory diagnostic criteria for diastolic heart failure. A simple method suggested by Gandhi et al. (30) addressed the requirement for the presence of an EF \geq 50% within 72 hours of the heart failure event. Under most circumstances, measurement of EF within 72 hours is sufficient to meet diagnostic criteria for diastolic heart failure. According to Zile et al. (31), the diagnosis of diastolic heart failure can be made without the measurement of diastolic function if these two criteria are present together: 1) symptoms and signs of heart failure and, and 2) EF $>$ 50%. Therefore, the objective measurement of diastolic function serves to confirm rather than establish the diagnosis.

Cardiac catheterization with simultaneous pressure and volume measurements is the "gold standard" for assessing left ventricular function. However, it is invasive and cannot be performed in the majority of patients with suspected diastolic dysfunction (32). Valuable knowledge has been acquired with the advent of Doppler echocardiography. Because diastole is a complex sequence of interrelated events, and the factors contributing to diastole are highly sensitive to changes in loading conditions, heart rate, and contractility, no currently available method can completely assess diastolic function. During the last two decades, Doppler echocardiography has emerged as an important and easy method to perform noninvasive diagnosis, providing reliable data on diastolic performance.

Based on Doppler transmitral flow, a grading system for diastolic dysfunction has been proposed. It has been demonstrated that mitral inflow shows a disease progression over time within the myocardium.

Table 1. Prevalence (%) of signs and symptoms in systolic and diastolic heart failure.

Symptoms and Signs	Diastolic Heart Failure (EF $>$ 50%)	Systolic Heart Failure (EF $<$ 50%)
Dyspnea on exertion	85%	96%
Paroxysmal nocturnal dyspnea	55%	50%
Rales	72%	70%
S3	45%	55%
S4	45%	56%
Edema	30%	40%
Cardiomegaly	90%	96%
Pulmonary Hypertension	75%	80%

EF= ejection fraction.

Three patterns mainly based on the E/A ratio have been proposed. The first abnormal filling pattern is the delayed relaxation that results in a reversed E/A ratio ($E/A < 1$), being the earliest stage of heart disease. The second pattern represents abnormalities in both relaxation and compliance and is known as pseudo-normalization because of an apparently normal E/A ratio ($E/A > 1$). This pattern implies an increase in left atrial pressure and represents a moderate compromise in diastolic function. The third abnormal filling pattern is termed restrictive filling found in patients with severe compromise of left ventricular compliance and elevated ventricular filling pressures, reflecting an advanced stage of disease (33) (figure 2).

These patterns can evolve from one to another in a single patient, with changes in disease evolution, treatment, loading conditions, and heart rate. Therefore, non-invasive assessment of relaxation or diastolic compliance should be interpreted with caution. Further echocardiographic examination must be used when diastolic function is indeterminate: the analysis of pulmonary venous flow pattern, analysis of mitral flow during the Valsalva maneuver, and new techniques of Doppler tissue imaging and color M-mode assessment of flow propagation velocity that are relatively load independent (34-36).

There is evidence that brain natriuretic peptide (BNP) levels are increased in patients with systolic and diastolic heart failure, although in diastolic heart failure it is not as established as for systolic heart failure. Such biochemical abnormalities could provide further evidence of an underlying disease process, and it may play a role in diagnosis of diastolic heart failure (37,38).

Radionuclide angiography and magnetic resonance imaging offer opportunities for studying diastolic function; however, they are not performed in routine clinical practice.

No large randomized clinical trial results are yet available to guide management of patients with diastolic heart failure. There are some ongoing clinical tri-

als to evaluate this issue. The American College of Cardiology/American Heart Association/European Society of Cardiology guidelines reflect this paucity of data (15,39). However, they recommend: control of symptoms by reducing ventricular filling pressures without reducing cardiac output; addition of diuretics and nitrates for symptomatic patients; control of arterial hypertension; probable benefit of adding calcium channel blockers, angiotensin-converting enzymes inhibitors and angiotensin II receptor blockers beyond the treatment of hypertension; and control of tachycardia. It's reasonable to infer that improved glucose control may improve diastolic heart failure in diabetic patients, although the effect of different diabetic treatments may not reverse the diastolic dysfunction. However, in a large cohort of diabetic patients, it was shown that a better glycemic control reduces the risk of heart failure (40-43).

DIABETES AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Many conditions besides aging are associated with and are likely to contribute to diastolic dysfunction and diastolic heart failure such as hypertension, coronary artery disease, atrial fibrillation, and diabetes. Diabetes has such an important influence on the development of CHF that it has been incorporated as a risk factor in the American College of Cardiology/American Heart Association guidelines (15).

One of the factors that are associated with the development of diabetic cardiomyopathy is hyperglycemia. Increasing evidence suggests that altered substrate supply and utilization by cardiac myocytes could be the primary injury in the pathogenesis of this specific heart muscle disease. However, even in type 2 diabetic patients without cardiac involvement, uncontrolled hyperglycemia is described to provoke diastolic left ventricular dysfunction (44,45). Alteration in left ventricular diastolic function seems to be related to



Figure 2. Schematic drawing of mitral inflow patterns during different stages of diastolic dysfunction. E= early inflow wave; A= atrial contraction, A wave.

concentrations of fasting plasma glucose and glycated hemoglobin even below the threshold of diabetes (46). Furthermore, each 1% increase in HbA_{1c} value has been associated with an 8% increase in the risk of heart failure (12,43), and glycosylated hemoglobin > 8 has also been associated with diastolic dysfunction (47), although the glycemic control may not reverse the diastolic dysfunction (48-50).

Other changes closely associated with abnormalities in diastolic function in diabetic patients are the impairment of gene expression to what has been called the fetal gene program, leading to myocardial impairment of calcium handling and altered regulation of genes for α and β -myosin heavy chains (29,51).

Of note, impairment of diastolic performance is non-specific and frequently observed in many diseases such as hypertension, hypertrophic cardiomyopathy and coronary artery disease, while systolic function remains intact. However, alterations in diastolic function have been observed in diabetic patients without any co-morbidities and before cardiovascular traditional complications. Investigations using cardiac catheterization showed alterations in left ventricular diastolic filling pressures in diabetic patients without any significant coronary artery disease or systolic dysfunction (52,53). Raev et al. (21) showed alterations in diastolic function in young type 1 diabetic patients without cardiovascular disease and suggested that these alterations could be the earliest signs of the diabetic cardiomyopathy. Their findings were quite plausible because diastolic abnormalities generally occur 8 years after the onset of type 1 diabetes, and systolic dysfunction establishment has been described even later in the disease evolution (48).

With the advent of recent echocardiographic techniques such as tissue Doppler imaging and color M-mode, the ability to accurately detect diastolic dysfunction has significantly improved. Boyer et al. detected altered left ventricular filling in 46% in asymptomatic normotensive type 2 diabetic patients when screened by conventional Doppler, whilst newer techniques showed diastolic dysfunction in 75% of patients (54). A more recent study in patients with type 2 diabetes free of any detectable cardiovascular disease found that 47% of the subjects had diastolic dysfunction, of which 30% had the first stage dysfunction — impaired relaxation, and 17% had second stage dysfunction — pseudonormal filling, a more advanced abnormality of left ventricular relaxation and compliance, which otherwise would be classified as having a normal diastolic physiology (55).

These new techniques, especially tissue Doppler image and color M-mode, have provided information

to overcome some technical limitations concerning traditional Doppler echocardiographic studies of diastolic function. Until recently, the existence of the pseudonormal left ventricular filling pattern, a second stage of diastolic dysfunction, was not evaluated in all the earlier studies. Therefore it is possible that many patients with diabetic diastolic dysfunction with a pseudonormal pattern would not have missed this diagnosis if these new techniques had been available by the time the studies were done. Furthermore, this may account for the discrepancies previously related to the prevalence of diastolic dysfunction, especially in a young diabetic population.

The problem of diabetes and metabolic syndrome appearing in young ages should prompt early interventions because by the time type 2 diabetes is diagnosed, more than 30–50% of patients will already have some evidence of vascular disease (56,57). We now know that diabetes may be doing silent and continuous harm to heart, even in those with no known manifested cardiac complications, as shown by some degree of diastolic dysfunction early shown. But we do not know however, how early these damages to cardiac function occur.

We considered whether a temporary condition of diabetes such as gestational diabetes mellitus (GDM) could have any impact in cardiac function. GDM may be considered as an early expression of insulin metabolic syndrome and a harbinger to type 2 diabetes (58), providing an excellent model for the study of precursors of diabetic cardiomyopathy in a young, apparently healthy population. We found that these patients had different left ventricular diastolic filling profile when compared to normal pregnant patients, and we also showed that some of these changes persisted post partum (49).

All of these backgrounds emphasize the need of a closer follow-up and early intervention for cardiovascular risk factors and metabolic glucose control in patients with the diagnosis of diabetes, GDM and metabolic syndrome. However, there is no available data on the literature supporting an early investigation in clinical practice with Doppler echocardiography and its new techniques in the approach of these patients at risk for cardiovascular complications.

In summary, this manuscript highlights the importance of heart failure in the diabetic population and points out the importance of understanding diastole and its dysfunctions as potential tools to disclose some early heart alterations in high-risk asymptomatic diabetic populations. Further studies should address the cost benefit of diagnosing such subtle diabetic

diastolic alterations, so as these techniques can be routinely recommended as screening tests for cardiovascular impairment in this population.

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