

Left ventricular diastolic dysfunction: an early sign of diabetic cardiomyopathy?

S Cosson¹, JP Kevorkian²

SUMMARY

The existence of a diabetic cardiomyopathy has been proposed as evidence has accumulated for the presence of myocardial dysfunction in diabetic patients in the absence of ischemic, valvular or hypertensive heart disease. Diastolic dysfunction has been described as an early sign of this diabetic heart muscle disease preceding the systolic damage. Abnormalities in diastolic performance have been first demonstrated by cardiac catheterisation and subsequently by mainly using echocardiography. The pathogenesis of this left ventricular dysfunction is not clearly understood. Microangiopathy, increased extracellular collagen deposition, or abnormalities in calcium transport alone or in combination are considered to be associated with this dysfunction. The relationship between diastolic dysfunction and glycemic control is still a matter of debate. Some epidemiological and clinical arguments suggest that diastolic abnormalities may contribute to the high morbidity and mortality among diabetic patients. However, the prognostic importance of subclinical diastolic dysfunction and the possibilities for intervention are not fully known. Eventually, despite numerous studies, evidence of an intrinsic diastolic dysfunction in diabetes mellitus remains questionable. Indeed, quite contradictory results have been reported. They have been obtained in small, inhomogeneous populations, with sometimes confounding factors, using various echocardiographic indices with known limitations. Also, further studies using more refined techniques for the evaluation of diastolic function are needed, as a prerequisite, to unequivocally relate diabetes mellitus to a specific cardiomyopathy.

Key-words: Diabetes mellitus · Diastolic function · Echocardiography · Cardiomyopathy.

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RÉSUMÉ

Dysfonction diastolique ventriculaire gauche : un signe précoce de cardiomyopathie diabétique ?

En l'absence d'étiologie ischémique, valvulaire ou hypertensive, la dysfonction myocardique observée au cours du diabète est classiquement considérée comme une entité pathologique : la cardiomyopathie diabétique. La dysfonction diastolique ventriculaire gauche serait l'expression initiale de cette atteinte myocardique, propre au diabète et précéderait l'altération de la fonction systolique. Initialement décrites par cathétérisme cardiaque, les anomalies de la fonction diastolique sont évaluées essentiellement par échocardiographie. La physiopathologie exacte de cette atteinte myocardique reste encore mal définie. La microangiopathie, l'excès de dépôts de collagène dans la matrice extracellulaire, les anomalies de transport du calcium sont les facteurs étiologiques habituellement retenus, qui exercent leurs effets isolément ou en association. Le lien entre l'équilibre glycémique et la dysfonction diastolique reste encore controversé. Des données épidémiologiques et cliniques suggèrent que la dysfonction diastolique pourrait contribuer en partie à la morbi-mortalité élevée du diabétique. Cependant, la valeur pronostique de la dysfonction diastolique au stade préclinique et les possibilités thérapeutiques ne sont pas encore établies. Finalement, malgré de nombreuses études, les preuves d'une dysfonction diastolique intrinsèque chez le sujet diabétique restent discutables. En effet, des résultats contradictoires ont été retrouvés. Ils ont été obtenus dans des études de faible effectif, dans des populations hétérogènes, avec parfois des facteurs de confusion. Surtout, ces études utilisaient divers indices échocardiographiques aux limites bien connues. Ainsi, il apparaît nécessaire de réaliser de nouvelles études avec des méthodes plus performantes, actuellement disponibles, pour établir de manière incontestable, en clinique, l'existence d'une cardiomyopathie diabétique.

Mots-clés : Diabète · Fonction diastolique · Échocardiographie · Cardiomyopathie.

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Diabetes is associated with increased cardiovascular complications, the most common of which are ischemic cardiomyopathy and left ventricular (LV) dysfunction. Diabetes is also associated with heart failure, mainly through its association with hypertension and coronary artery disease [1]. However, the existence of a primary myocardial disease, “diabetic cardiomyopathy”, has been proposed as evidence has accumulated for the presence of myocardial dysfunction in diabetic patients in the absence of ischemic, valvular or hypertensive heart disease [2-8]. The existence of a diabetic cardiomyopathy was first proposed by Rubler *et al.* in 1972 on the basis of postmortem findings [2]. Subsequently, abnormalities in both systolic and diastolic performance in diabetic subjects have been demonstrated in animal [9] and human studies [10-14]. Diastolic dysfunction has been described as an early sign of this diabetic heart muscle disease preceding the systolic damage. The pathogenesis of this ventricular dysfunction remains unknown and has been somewhat controversial [15]. The purpose of this article was to review the clinical and experimental features of diabetic cardiomyopathy, with particular relevance to the diastolic function.

Definitions

Diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force [16]. By extension, diastolic dysfunction occurs when these processes are prolonged, slowed, or incomplete. Moreover, if diastolic function is truly normal, it must remain normal both at rest and during the stress of a variable heart rate, stroke volume, end-diastolic volume, and blood pressure.

Diastole is traditionally divided into four phases, i.e. isovolumic relaxation, early diastolic filling, diastasis and atrial contraction. In all phases, many factors determine LV filling with a varying relative importance (*Tab I*). These factors overlap in time and are influenced by each other, by LV

Table I
Factors affecting LV filling.

Myocardial relaxation
Atrial contraction
Viscoelastic properties
Diastolic restoring forces
Pericardial restraint
Ventricular interaction
Coronary artery turgor
Loading conditions
Atrial and ventricular nonuniformity
Cardiac conduction system

systolic function, heart rate, and by the cardiac conduction system [17]. Their final combined effect is on the transmitral pressure gradient, which actually determines LV filling.

In the clinical definition most often used, diastole is delineated by the time interval between closure of the aortic valve and closure of the mitral valve. It has been advocated, that only diastasis and atrial contraction represent true diastole physiologically.

Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. The causes of diastolic dysfunction may be subdivided into a decrease in passive myocardial diastolic compliance, and an impairment in active LV relaxation. Abnormalities in diastolic function may occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome.

Methods of diagnosing diastolic dysfunction

Cardiac catheterisation with simultaneous pressure and volume measurements is the “gold standard” for assessing LV diastolic function. The rate of LV relaxation, rate and timing of diastolic filling as well as myocardial and chamber stiffness can be determined [18]. However, this diagnostic method is invasive and cannot be performed in all patients with suspected diastolic dysfunction.

During the last two decades, Doppler echocardiography has emerged as an important and easy to perform non-invasive diagnostic tool providing reliable data on diastolic performance.

The transmitral flow across the mitral valve demonstrates a biphasic pattern, in which an early peak flow occurs during rapid early diastolic filling (peak E) and a late peak occurs during atrial contraction (peak A).

Based on Doppler transmitral flow, a grading system for diastolic dysfunction has been proposed. Indeed, it has been demonstrated that the transmitral flow shows a progression over time with diseases involving the myocardium. Three characteristic abnormal LV diastolic filling patterns mainly based on the E/A ratio have been proposed [19] (*Fig 1*).

The first abnormal filling pattern, called “delayed relaxation”, results in a reversed E/A ratio ($E/A < 1$) when relaxation impairs. It identifies patients with early stages of heart disease. The second pattern, representing abnormalities of both relaxation and compliance, has been termed pseudo-normalization, because of an apparently normal E/A ratio ($E/A > 1$). This results from an increase in left atrial pressure compensating for slow relaxation.

The third abnormal filling pattern, termed “restrictive filling”, found in patients with severe decrease in LV com-

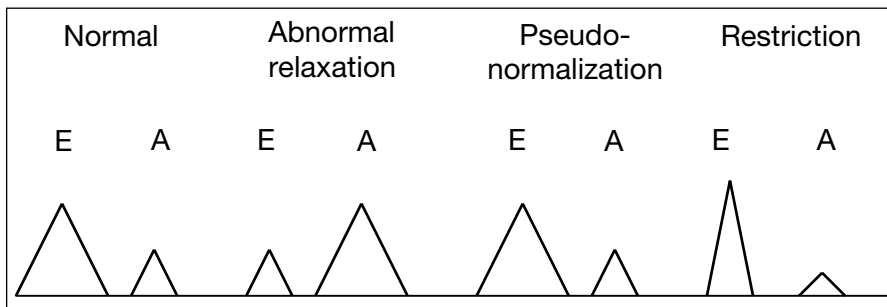


Figure 1
Schematic drawing of mitral inflow patterns during different stages of diastolic dysfunction.

pliance, causes an increased E/A ratio (often above 2). It identifies advanced, usually symptomatic disease with poor prognosis.

Thus, a continuum in Doppler patterns of diastolic function exists, including normal diastolic function, impaired relaxation, pseudonormal filling and restriction (*Fig 1*). These patterns can evolve from one to another in a single individual, with changes in disease evolution, treatment and loading conditions. However, in an individual, a certain pattern of LV diastolic filling will always result from multiple intrinsic factors that include the rate of LV relaxation and elastic recoil (suction), LV compliance, left atrial pressure as well as varying patients conditions, such as load, age and heart rate. Thus, non-invasive Doppler measurements never provide direct assessment of relaxation or diastolic compliance and should always be interpreted with caution. Other Doppler derived indices have been proposed, of which deceleration time (the time interval of peak E wave velocity to zero), and isovolumic relaxation time (time from the end of systolic ventricular outflow to mitral valve opening) are applied most often. Further echocardiographic examinations may be useful in the analysis of diastolic function when it remains indeterminate: the analysis of pulmonary venous flow [20], the relatively new techniques of Doppler tissue imaging and color M-mode assessment of flow propagation velocity which appear to be relatively preload independent [21].

Radionuclide angiography may be used to study the rapid filling phase of diastole, the duration of isovolumic relaxation phase, the relative contribution of rapid filling to total diastolic filling [22]. Magnetic resonance imaging also offers promising opportunities for measuring diastolic function [23]. However, these two latter techniques are not performed in routine clinical practice.

Diastolic dysfunction in diabetes

Numerous studies have shown that impairment of the LV diastolic function may be detected in patients with diabetes. Diastolic LV abnormalities have been initially disclosed by cardiac catheterisation [10, 24]. Regan *et al.* [10] demonstrated in normotensive, diabetic patients without coronary artery disease and without clinical evidence of

heart failure, increased left-ventricular end-diastolic pressure, a decreased left-ventricular end-diastolic volume with a normal ejection fraction. Non-invasive studies subsequently demonstrated abnormalities of diastolic function in the diabetic population by using several methods: abnormal time intervals by phonocardiograms [25, 26], abnormal LV filling by standard and digitized echocardiography [27-30], radionuclide studies [31] and subsequently Doppler echocardiography [32, 33].

Of note, impairment of the LV diastolic function was observed in patients free of diabetic complications, hypertension and symptomatic coronary artery disease.

Indeed, abnormalities in diastolic performance are non specific and are frequently observed in many diseases (hypertension, coronary artery disease, hypertrophic cardiomyopathy), while systolic function remains intact.

Thus, diastolic abnormalities present in diabetic patients without diabetic complications or cardiovascular disease has been suggested as an earliest functional effect of a specific diabetic cardiomyopathy [34, 35]. Various abnormalities in diastolic function, e.g. prolonged isovolumic relaxation period, delayed mitral valve opening and impairment in rapid diastolic filling, increased atrial contribution of LV filling, reduced E/A mitral ratio have been characteristics findings.

In the large majority of studies, abnormalities of LV diastolic function have been demonstrated in diabetic patients with intact systolic function.

This has been illustrated by the study of Raev *et al.* [35]. A high prevalence of diastolic dysfunction with preserved systolic function was observed in asymptomatic, young, type 1 diabetic patients. Diastolic dysfunction began 8 years after the onset of diabetes while systolic dysfunction was found much later, occurring after 18 years of diabetes duration.

Studies on cardiac dysfunction in diabetes deal largely with type 1 diabetic patients, although reports on diastolic dysfunction in type 2 diabetic patients are also available.

Some of these studies have disclosed abnormalities in diastolic function even in young type 1 patients with normal systolic function [32, 36-38]. All of these studies have demonstrated a shift in the filling pattern from the early passive filling phase to the late atrially augmented filling phase. In the study of Paillolle *et al.* [36], 16 type 1 diabetics (36 ± 8 years old) free of microangiopathy, hypertension or coronary ar-

tery disease and with a diabetes duration of at least 10 years, were compared to 16 healthy control subjects. A significant reduction in mitral E wave, E/A ratio and an increase of isovolumic relaxation time was observed in the diabetic group. Lastly, 69% of diabetic patients had abnormalities of diastolic parameters. Similar findings were also obtained in a younger population [38], and even in adolescents [37].

Some technical limitations from Doppler echocardiographic studies of diastolic function in diabetics patients have to be considered.

Impaired diastolic function was inferred in some studies on transmitral flow velocity patterns of an increased atrial contribution of LV filling or reduced E/A mitral ratio. However, increased values for peak velocity of late filling and a reduced ratio of early to late peak velocity are observed in case of higher heart rate. For example, in the studies of Zarich *et al.* [32] and Airaksinen *et al.* [39] with type 1 diabetics, patients had a significantly higher heart rate than control subjects, which was discussed as a possible factor contributing to the results. In the studies of Grossmann *et al.* [40] and Romanens *et al.* [41], a significantly decreased E/A mitral ratio in type 1 diabetic patients compared to control subjects was observed, but after a correction of velocities for differences in heart rate, significant differences were no longer present.

Surprisingly, until recently, the existence of the pseudonormal LV filling pattern, a more advanced stage of LV diastolic dysfunction, was not evaluated in all the previous Doppler studies.

Indeed, identification of a pseudonormal filling can be easily overlooked if preload reducing maneuvers (Valsalva maneuver, Glyceryl Trinitrate) or if new echo Doppler indices are not used. In very recent studies, a pseudonormal diastolic function was reported in 17 to 28% of asymptomatic, normotensive type 2 diabetics [42, 43]. The Valsalva maneuver during echocardiography was used in these studies as a method of differentiating between normal and pseudonormal LV filling patterns. Similar findings were also obtained with Glyceryl Trinitrate [44]. These studies led to the conclusion that LV diastolic dysfunction could be much more common than previously reported in this population. These interesting preliminary results should however be confirmed in larger studies, including control populations, and by using new echocardiographic techniques.

Relation with diabetic complications

The influence of diabetic complications on LV diastolic dysfunction has been investigated in several studies. In the first studies, abnormalities have been observed especially in the population of diabetics with severe microvascular complications (marked proteinuria and proliferative retinopathy) [28, 14].

A gradual increase in abnormalities of diastolic function according to the frequency and severity of diabetic microvascular complications was also demonstrated [25-27, 35, 45, 46].

From these findings it is suggested that diabetic microangiopathy is a background factor for diabetic heart muscle disease. However, these conclusions should be taken with caution as most of these studies were performed with unsatisfactory echocardiographic methods (M-mode echocardiography). Moreover, the relationship between cardiac dysfunction and the presence of microangiopathic complications has not been documented consistently in other studies in which diastolic function was assessed by Doppler echocardiography [32, 47-49]. To further investigate the relation between diabetic complications and diastolic dysfunction, the role of each complication was specifically studied in a few reports.

Diabetic Retinopathy

Studies performed in diabetic patients free of coronary artery disease, have demonstrated that patients with mild to severe retinopathy exhibited LV diastolic dysfunction (lower E/A values) compared to age-matched controls [33, 50] or patients without retinopathy [46, 51]. In the most recent report [52], a higher prevalence of retinopathy (49%) was encountered in patients with abnormal mitral filling pattern (E/A ratio < 1) compared to patients with a normal diastolic function (20%) (Tab II).

This relation with retinopathy was however not constantly found. For example, in the study of Airaksinen [39] patients with retinopathy did not differ from the remainder of diabetic subjects with respect to the early-to-atrial flow velocity ratio. In the same way, in the study of Uusitupa *et al.* [53] diabetic subjects with abnormal diastolic peak filling rate did not differ significantly from those with normal filling with respect to the prevalence of retinopathy.

Nephropathy

Some studies looked at well-selected cohorts of diabetic patients and took special emphasis on the presence of nephropathy (Tab III).

Sampson *et al.* [54] found a gradual decrease in E/A ratio in type 1 diabetic patients according to the presence of microalbuminuria and proteinuria. A significantly higher proportion of abnormal diastolic function (E/A < 1) was observed in the group of diabetics with proteinuria. However, the possible influence of arterial blood pressure on the appearance of diastolic dysfunction in the early stages of diabetic nephropathy was postulated as a significantly higher blood pressure was observed in the subgroup of diabetics with proteinuria. Perez *et al.* [46] also observed similar findings in their population which included a percentage of hypertensive patients. In type 1 diabetic patients with microalbuminuria, Watschinger *et al.* [55] and Guglielmi *et al.* [56]

Table II

LV diastolic function (E/A mitral flow ratio) evaluated in different studies of diabetic patients with diabetic retinopathy.

References	Type of diabetes	N	Age	H	CAD	Controls	Retinopathy
Takenaka <i>et al.</i> 1988 [33]	2	60	60	0	0	1 ± 0.2	0.7 ± 0.4 *
Perez <i>et al.</i> 1992 [46]	1	54	35	1	0	1.4 ± 0.3	1.1 ± 0.4 *
Ragonese <i>et al.</i> 1992 [51]	1	82	17.7	0	0	1.71 ± 0.2	1.35 ± 0.2 *
Hiramatsu <i>et al.</i> 1992 [50]	2	246	40-79	0	0	0.85 ± 0.4	0.69 ± 0.4 *
Annonu <i>et al.</i> 2001 [52]	2	66	51	0	0		E/A ≥ 1 (20%) E/A < 1 (49%) *

N: number of subjects. H: hypertension. CAD: coronary artery disease. * p < 0.05 vs. controls.

demonstrated LV diastolic dysfunction, whereas controls and/or patients without microalbuminuria showed no diastolic impairment.

However, the association of diastolic dysfunction with diabetic nephropathy was not consistently found. Sato *et al.* [57] compared 17 normotensive type 1 diabetics with nephropathy (albuminuria > 300 mg/24 h) and 34 matched normoalbuminuric diabetics. The nephropathic group did not have a significant reduced diastolic function. In a more recent study conducted in normotensive type 2 diabetics, no

correlation could be found between gross proteinuria and diastolic function [52].

Autonomic neuropathy

Cardiac autonomic neuropathy has been suggested to be a potential contributor to impaired diastolic function in several studies. Indeed, a relation between cardiac autonomic neuropathy and diastolic dysfunction was observed in most of studies including diabetic patients with this complication.

Table III

LV diastolic function (E/A mitral flow ratio) evaluated in different studies of diabetic patients with diabetic nephropathy.

References	Type of diabetes	N	Age	H	CAD	Controls	Microalb	Proteinuria
Sampson <i>et al.</i> 1990 [54]	1	39	20-60	1	0	1.42 ± 0.1	1.08 ± 0.1	0.98 ± 0.06 *
Perez <i>et al.</i> 1992 [46]	1	54	35	1	0	1.3 ± 0.4		1 ± 0.3 *
Watschinger <i>et al.</i> 1993 [55]	1	39	38	0			1.48 ± 0.1	0.99 ± 0.04 *
Gluglielmi <i>et al.</i> 1995 [56]	1	34	20-45	0			1.58 ± 0.18	1.14 ± 0.12 *
Sato <i>et al.</i> 1998 [57]	1	17	40	0	0	1.42 ± 0.36		1.25 ± 0.31
Annonu <i>et al.</i> 2001 [52]	2	66	51	0	0			NS

N: number of subjects. H: hypertension. CAD: coronary artery disease. * p < 0.05 vs. controls. NS: non significant.

Kahn *et al.* [31] first reported in 28 patients with type 1 diabetes without evidence of ischemic heart disease, that 21% had abnormal diastolic filling and differed from diabetic patients with normal filling in their greater severity of cardiac autonomic neuropathy evidenced by radionuclide study. A few studies addressed specifically the relation between autonomic neuropathy and diastolic function evaluated by echocardiography (*Tab IV*).

Airaksinen *et al.* [39] demonstrated in type 1 diabetics that filling abnormalities were most prominent in patients with autonomic neuropathy. Indeed, among 21 diabetic patients, the six with autonomic neuropathy had a significantly lower early-to-atrial flow velocity.

Cardiac autonomic neuropathy is a frequent complication of diabetes, affecting the sympathetic or parasympathetic sections or both. The influence of cardiac autonomic neuropathy on diastolic dysfunction was demonstrated for both the sympathetic or parasympathetic sections.

Mustonen *et al.* [58] demonstrated the impact of sympathetic dysfunction on diastolic function. Indeed, they showed a correlation between a myocardial sympathetic innervation function score derived from scintigraphy and E/A ratio in Doppler echocardiography, providing evidence that an abnormal sympathetic innervation of the heart may contribute to LV filling disturbances. The role of sympathetic dysfunction, evaluated clinically, was also demonstrated recently [52]. Abnormal systolic blood pressure response to standing was significantly correlated with a reduced mitral E/A ratio.

Other studies have related parasympathetic neuropathy with LV diastolic dysfunction [53, 59, 60].

Uusitupa *et al.* [53] found a significantly lower mean heart rate variation during deep breathing in diabetic sub-

jects with abnormal diastolic peak filling rate than in those with normal filling. Monteagudo *et al.* [59] found a lower mitral E/A ratio at echocardiography (1.1 vs. 1.6, $p < 0.005$) in the group of patients with autonomic neuropathy compared to those without; furthermore, a significant correlation between E/A ratio and autonomic neuropathy ($r = -0.6$, $p = 0.005$) was also found.

Relation with glycemic control

Initial studies performed in diabetic animals have revealed impaired myocardial contraction and relaxation and biochemical changes reversed after adequate insulin therapy [62, 63], the degree of reversibility depending on the dose of insulin [64].

The relationship between diastolic dysfunction and glycemic control in diabetic patients is still a matter of debate.

In a first study of 36 children with type 1 diabetes [65], severity of diastolic dysfunction, evaluated by computer-assisted analysis of M-mode echocardiograms (time interval between minimal cavity dimension and mitral valve opening), was related to the long-term quality of metabolic control (mean value of HbA_{1c} over the last two years).

Fiorina *et al.* [66] demonstrated a reduction in the rate of diastolic dysfunction, evaluated using radionuclide ventriculography, in every uremic patient (68 type 1 diabetics) after a kidney-pancreas transplantation. This amelioration of LV diastolic function appeared to be positively associated with glycemic control.

Other studies have however shown a lack of correlation between impaired diastolic function and HbA_{1c} levels. All were performed in type 1 diabetics [34, 14, 47, 67]. For instance, in the study of Punzengruber *et al.* [67], no interrela-

Table IV

LV diastolic function (E/A mitral flow ratio) evaluated in different studies of diabetic patients with diabetic neuropathy.

References	Type of diabetes	N	Age	H	CAD	Neuropathy-	Neuropathy+
Airaksinen <i>et al.</i> 1989 [39]	1	21	48	0	0	1.29 ± 0.25	0.99 ± 0.15 *
Perez <i>et al.</i> 1992 [46]	1	54	35	1	0	1.3 ± 0.3	1.1 ± 0.3 *
Irace <i>et al.</i> 1996 [61]	1	61	40	0	0	0.86 ± 0.15	1.0 ± 0.2
Willhenheimer <i>et al.</i> 1998 [60]	1	34	40	0	0	1.4 ± 0.7	1.1 ± 0.2 *
Monteagudo <i>et al.</i> 2000 [59]	1	19	31	0	0	1.6 ± 0.3	1.1 ± 0.3 *
Annonu <i>et al.</i> 2001 [52]	2	66	51	0	0		E/A ≥ 1 (4%) E/A < 1 (29%) *

N: number of subjects. H: hypertension. CAD: coronary artery disease. * $p < 0.05$ vs. neuropathy.

tion between glycemic control over a period of 12 months and LV diastolic function in a fairly well-controlled group of young type-1 diabetics could be observed.

Some studies have prospectively evaluated the effect of glycemic control on diastolic function by repeating echocardiography over a period of up to 15 months (*Tab V*). All these studies dealt with type 2 diabetes and reached different conclusions.

Hiramatsu *et al.* [50] found that a short term glycemic control resulted in a decrease in diastolic filling abnormalities. 48 out of 246 patients were randomly selected and treated with insulin for 6 months. Doppler echocardiographic examination was repeated 1 and 6 months after the initiation of the insulin treatment. Improvement in diastolic function was observed one month after insulin treatment and was comparable after six months. This positive outcome was observed only in patients without retinopathy (n=28), contrary to patients with retinopathy.

Vanninen *et al.* [68] also demonstrated in a population of newly diagnosed diabetics, an improvement of diastolic function concomitantly with declining blood glucose levels evaluated after a 15-month period. Of note, this was demonstrated with a complex echocardiographic indice but not with the conventional mitral E/A ratio.

Only one study, conducted in a limited population of 22 type 2 diabetics, evaluated the effect of an antidiabetic drug [69]. A member of the insulin-sensitizing thiazolidinedione (troglitazone) was administered for 6 months. After treatment, an improvement in diastolic function was observed in normotensive patients (n = 12), but not in hypertensive patients.

On the other hand, some studies showed that improvement in glycemic control was not associated with changes in diastolic function even with 12 months of follow-up [70, 71].

In the study of Gough *et al.* [70] LV diastolic function was assessed with pulsed wave Doppler mitral flow velocities in

20 normotensive patients with a new diagnosis of type 2 diabetes mellitus. The E/A ratio was significantly reduced in the diabetic group but despite improvements in glycemic control over 3 months (HbA_{1c} 9.9% to 7.4%), maintained at 6 months (HbA_{1c} 7.0%), there were no changes in the E/A ratio.

In the study of Beljic *et al.* [71] LV diastolic function was evaluated at the onset of disease and after 6 and 12 months of adequate glycemic control. A significantly reduced value of peak E/A ratio was found in the diabetic patients before treatment, but did not significantly change after 1 year of adequate glycemic control with therapy.

Finally, the largest (n = 136), prospective, randomized, radionuclide study led to the conclusion that improvement of glycemic control over a period of two years with intensive treatment did not affect the LV diastolic function [72].

Diastolic dysfunction and diabetes duration

Evidence of an alteration in LV diastolic function at an early stage of diabetes without correlation with specific complication is suggested in a few studies. Indeed, abnormalities in diastolic function have been found in patients with newly diagnosed diabetes or with a short duration of the disease.

Attali *et al.* [73] in an initial study observed LV diastolic dysfunction in asymptomatic, type 1 and type 2 patients (n=49) compared with controls. All patients were free of cardiovascular diseases and had diabetes mellitus for less than 5 years. However, the evaluation of diastolic function used an imperfect parameter assessed by M-mode echocardiography and phonomechanography.

Di Bonito *et al.* [74] reached to the same conclusions in a case-control study using Doppler echocardiography (E/A ratio). They observed diastolic dysfunction in 16 normoten-

Table V
Effect of glycemic control on LV diastolic function evaluated by echocardiography.

References	Type of diabetes	N	Age	H	CAD	Follow-up	Improvement
Hiramatsu <i>et al.</i> 1992 [50]	2	48	40-79	0	0	1-6 months	Yes
Vanninen <i>et al.</i> 1992 [68]	2	43	40-64	1	1	3-15 months	Yes
Beljic <i>et al.</i> 1994 [71]	2	10	42	0	?	6-12 months	No
Gough <i>et al.</i> 1995 [70]	2	20	50	0	0	3-6 months	No
Hirayama <i>et al.</i> 2001 [69]	2	22	58	1	0	6 months	Yes

N: number of subjects. H: hypertension. CAD: coronary artery disease.

sive type 2 diabetic patients, free of microvascular complications with a disease duration of less than 4 years and even less than 1 year.

Vanninen *et al.* [68] demonstrated mild alterations in diastolic function in an heterogeneous non selected population including patients with hypertension an/or coronary artery disease with newly diagnosed type 2 diabetes. As previously mentioned, this was demonstrated with a complex echocardiographic indice but not with the conventional mitral flow ratio.

Similar findings have been reported with Doppler echocardiography (E/A ratio), in newly diagnosed type 2 diabetic patients free of microvascular complications, without evidence of hypertension and coronary artery disease [70, 71].

These observations of an impaired diastolic function in patients with newly diagnosed diabetes or with a short duration of the disease and with no microangiopathic complications suggest that this alteration may occur early in the history of type 2 diabetes and would not be related to microvascular complications.

Conversely, the lack of correlation between the occurrence of LV diastolic dysfunction and the duration of diabetes in some studies [14, 67] also suggests that diabetic microangiopathy is not the only factor contributing to this dysfunction.

Relation with severity of glycemic disturbance

Only scanty information on LV diastolic function in patients with minor abnormalities of glucose homeostasis is available.

Celentano *et al.* [75] studied 64 subjects with normal glucose tolerance (n = 25), with impaired glucose tolerance (n = 15) and with type 2 diabetes mellitus (n = 24) diagnosed by an oral glucose tolerance test according to the recommendations of the World Health Organization. They found early signs of diastolic dysfunction (assessed by E/A mitral flow ratio), not only in patients with diabetes but also in those with impaired glucose tolerance, independent of the confounding role of ischemia, body weight, and blood pressure.

Holzmann *et al.* [76] showed in a middle-aged population without previously diagnosed diabetes mellitus a continuous relation between concentrations of fasting plasma glucose, HbA_{1c} and LV diastolic function. They suggested that cardiac function is related to the concentration of glucose and HbA_{1c} already below the threshold of diabetes. Of note, their results were observed in a limited population (n = 35), using some non previously validated indices of a new ultrasound technique (Tissue Doppler imaging). Furthermore, the relations were not observed with conventional echocardiography.

Potential pathogenesis

Animal studies

Several investigations of myocardial function and structure in experimental animal studies with induced diabetes have partly clarified the pathogenesis of diabetic myocardial dysfunction. Most have focused on the mildly diabetic dog and the severely diabetic rat. A study conducted by Regan *et al.* [77] performed on diabetic dogs after one year of diabetes, showed an increased interstitial connective tissue without myocyte damage. Furthermore, diastolic dysfunction (decreased ventricular compliance) was demonstrated while there was no evidence for systolic dysfunction. In addition to abnormalities of systolic function (decrease in the speed of contraction, prolongation of contraction), a marked slowing of relaxation, have been demonstrated in several diabetic rat studies [9, 78]. Modest structural changes were found in the rat studies [79]. Several biochemical explanations for mechanical changes have been determined. For example, a decline in myosin ATPase activity associated with a change in the myosin isoenzyme distribution, resulting in a predominance of the slow (V3) isoform of myosin was observed [80]. With respect to the slowing of relaxation, there is evidence that Ca⁺⁺ transport by isolated sarcoplasmic reticulum from diabetic rats is markedly diminished [81]. Alterations in adrenergic and cholinergic receptors and in carbohydrate, lipid, and adenine nucleotide metabolism in the diabetic heart have also been demonstrated [82-85]. In summary, diabetes appears to primarily cause reversible changes in myocardial contractile proteins and intracellular Ca⁺⁺ handling, resulting in slowing of both contraction and relaxation. There are only modest structural changes, at least with short term diabetes. It still remains to demonstrate that these alterations described in the diabetic rat and dog may account for the preclinical ventricular dysfunction in humans.

Human studies

Besides the experimental findings in animal studies, numerous studies in humans have explored the association of diabetes with histopathological abnormalities. Alterations in intramyocardial coronary arteries, similar to those seen in other organs of diabetic patients have been reported. Endothelial proliferation and subendothelial hyaline thickening with PAS-positive material in the vessel wall have been described in some but not all patients with or without overt congestive heart failure [86]. Capillary basement membrane thickening and capillary microaneurysms have also been observed in hearts of diabetics [87, 88].

In the study of Zoneraich *et al.* [89] conducted in young normotensive type 1 diabetics, a small vessel disease was reported in 72% of diabetic patients while it was present in only 12% of non diabetic subjects.

Interstitial accumulation of advanced-glycated end products (AGEs), which include collagen, elastin and other connective tissue proteins, as well as fibrosis in the myocardium have been reported in biopsy or post-mortem studies of human diabetic hearts [10, 90-93].

The mechanism of collagen accumulation in the diabetic myocardium seems to be due to impaired degradation rather than enhanced synthesis [94]. The interstitial abnormalities could explain an increase in end-diastolic stiffness as well as LV mass and contribute to the diastolic dysfunction [10]. In the less advanced forms of tissue abnormality, the interstitial changes seem to predominate for some time and are associated with preserved cell morphology that is consistent with normal systolic function. As a potential diagnostic tool, it has been suggested that collagen accumulation in the extracellular matrix of the heart is responsible for abnormal acoustic properties of the myocardium in diabetic patients [46].

The coexistence of diabetes and hypertension, has been considered as a major factor in the expression of the abnormalities in human diabetic myocardium. This concept initially suggested in diabetic rats studies [95] was illustrated in the human study of Van Hoven *et al.* [93]. They demonstrated, in hearts obtained at autopsy, that interstitial and replacement fibrosis and myocytolitic necrosis were substantially more prominent in heart of hypertensive diabetics than in patients with isolated diabetes or hypertension. From these data emerged the concept that this association, which is very frequent in this population, is very likely to have synergistic relationship as a cause of LV dysfunction.

The pathogenesis is however not completely elucidated, which explains why the relationship of type, duration and severity of the diabetes to the myocardial abnormalities still remain uncertain.

Clinical significance of LV diastolic dysfunction in diabetes

Congestive heart failure is a major public health problem in developed countries. Several epidemiological investigations have confirmed that up to half of patients in the community have heart failure due to diastolic dysfunction despite normal LV ejection fraction [96].

Some epidemiological and clinical arguments suggest that diastolic abnormalities may contribute to the high morbidity and mortality among diabetic patients.

Indeed, in the community setting, data from the Framingham Heart Study have shown an increased incidence of congestive heart failure in diabetic subjects irrespective of coronary heart disease and hypertension [3]. It was also observed in patients enrolled in clinical trials of myocardial infarction. Despite similar LV systolic function, patients with diabetes have more pronounced heart failure symptoms, use more diuretics, and have an adverse progno-

sis compared with those without diabetes. One putative explanation for this discrepancy is diastolic dysfunction of the left ventricle [97].

The prognostic implications of diastolic dysfunction have been recently underlined.

Diastolic dysfunction as rigorously defined by comprehensive Doppler techniques is common, often not accompanied by recognized cardiac heart failure, and associated with marked increases in all-cause mortality [98].

It has also been demonstrated that a reduced mitral E/A ratio is independently associated with increased all-cause mortality as well as cardiovascular mortality in a population-based sample of middle-aged and elderly adults [99].

It is important to point out that these prognostic data included diabetic patients for whom no specific analysis was performed. By the way, to date, the prognostic impact of isolated diastolic dysfunction in diabetics is unknown.

The impact of isolated diastolic dysfunction in diabetes only concerned exercise ability but did not address mortality evaluation. Indeed, some studies have demonstrated that in absence of LV systolic dysfunction, the impairment of LV relaxation can influence exercise tolerance [100, 101]. LV diastolic dysfunction was supposed to influence maximal treadmill performance and explain lower maximal performance observed in patients with type 2 diabetes.

Conclusion

Despite numerous studies, evidence of an intrinsic diastolic dysfunction in diabetes mellitus remains questionable. Conclusions were obtained in small, inhomogeneous populations, using various indices with known limitations leading to sometimes contradictory results. Further studies using more refined techniques for the evaluation of diastolic function are needed, as a prerequisite, to unequivocally relate diabetes mellitus to a specific cardiomyopathy.

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