

Diastolic Dysfunction in Diabetic Patients Assessed With Doppler Echocardiography: Relationship With Coronary Atherosclerotic Burden and Microcirculatory Impairment

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Introduction and objectives. Diabetes mellitus (DM) is associated with the development of both impaired left ventricular diastolic function (LVDF) and pathological changes in the coronary macro- and microcirculation. The aim of this study was to investigate the relationship between these manifestations of diabetic heart disease.

Methods. The severity of atherosclerosis in the left anterior descending coronary artery (LAD) was quantified using intravascular ultrasound (IVUS) in 13 patients with DM and ischemic heart disease. The coronary flow velocity reserve (CFVR), instantaneous hyperemic diastolic velocity pressure slope index (IHDVPS) zero-flow pressure were derived from digital intracoronary pressure and flow velocity measurements. The relationships between indices of LVDF (ie, E/A and E/e' ratios) and intracoronary measurements were assessed.

Results. The left ventricular ejection fraction was 66% (7%), and the LVDF indices were: E/A=0.92 (0.38) and E/e'=9.90 (2.80). There was a direct proportional relationship ($r=0.62$; $P=.02$) between E/e' and coronary resistance ($1.93 [0.74]$ mm Hg/s) and an inverse proportional relationship ($r=-0.64$; $P=.02$) between E/e' and IHDVPS ($1.56 [0.50]$ cm/s/mm Hg). However, no significant relationship was found between either LVDF index and CFVR ($2.43 [0.56]$) or coronary zero-flow pressure ($40.41 [10.66]$ mm Hg). The volume of atheroma in the proximal 20 mm of the LAD ($179.34 [57.48]$ μ L, with an average plaque area of $8.39 [2.20]$ mm²) was not related to either LVDF index.

Conclusions. In patients with DM and coronary atherosclerosis, there appeared to be a relationship between LVDF impairment (assessed by the E/e' ratio) and structural changes in the microcirculation.

Key words: Coronary microcirculation. Diastolic function. Diabetes mellitus. Atherosclerosis.

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Disfunción diastólica del paciente diabético estimada con ecocardiografía Doppler: relación con la ateromatosis y la disfunción microcirculatoria coronarias

Introducción y objetivos. La diabetes mellitus (DM) se asocia al desarrollo tanto de alteraciones de la función diastólica ventricular izquierda (FDVI) como al de patología macrovascular y microvascular coronaria. El objetivo del estudio fue estudiar la posible relación entre ambas manifestaciones de la cardiopatía diabética.

Métodos. En 13 pacientes con DM y cardiopatía isquémica se cuantificó la carga aterosclerótica (CA) mediante ecografía intracoronaria (IVUS) en la rama DA. A partir del registro digital de presión y velocidad de flujo intracoronarias, se calculó la reserva de velocidad de flujo coronario (RVFC), la conductancia coronaria, la presión de flujo cero (Pf0) y la resistencia coronaria. Se estudió la relación entre parámetros de FDVI (relaciones E/A y E/e') y las mediciones intracoronarias.

Resultados. Se documentó una FEVI del $66\% \pm 7\%$, y una FDVI con E/A = $0,92 \pm 0,38$ y E/e' = $9,9 \pm 2,8$. Se documentó una relación directamente proporcional ($r = 0,62$; $p = 0,02$) entre E/e' y la resistencia coronaria ($1,93 \pm 0,74$ mmHg/cm/s) y una relación inversamente proporcional ($r = -0,64$; $p = 0,02$) entre E/e' y la conductancia coronaria ($1,56 \pm 0,5$ cm/s/mmHg). No se encontró relación significativa entre los parámetros de FDVI y la RVFC ($2,43 \pm 0,56$) o la Pf0 ($40,41 \pm 10,66$ mmHg). El volumen de ateroma en los 20 mm proximales de la DA ($179,34 \pm 57,48$ μ L; área media de placa, $8,39 \pm 2,2$ mm²) no se relacionó con la FDVI.

Conclusiones. En los pacientes con DM y aterosclerosis coronaria parece darse una relación entre la disfunción de la FDVI (estimada con el índice E/e') y la afección estructural de la microcirculación.

Palabras clave: Microcirculación coronaria. Función diastólica. Diabetes mellitus. Aterosclerosis.

ABBREVIATIONS

CFVR: coronary flow velocity reserve
 DM: diabetes mellitus
 IHDVPS: instantaneous hyperemic diastolic velocity-pressure slope (coronary conductance)
 LVDF: left ventricular diastolic function
 MRI: microcirculatory resistance index
 ZFP: zero-flow pressure

INTRODUCTION

Diabetes mellitus (DM) speeds up the process of coronary atherosclerosis and functional and structural cardiac impairments^{1,2} such as coronary microcirculatory dysfunction^{3,4} and the onset of left ventricular impairment, exhibiting diastolic dysfunction² at the early stages. Correlation between the left ventricular diastolic dysfunction (LVDF) and coronary diseases in diabetic patients has not been studied thoroughly,⁵ partly because of the direct toxic effect of hyperglycemia on myocytes,^{6,7} the microcirculatory disease,⁸ and the especially aggressive and diffuse nature of atherosclerosis in these patients.⁹ This study analyses the relation between the LVDF in diabetic patients, as documented with Doppler echocardiography,¹⁰⁻¹² and the atherosclerotic and microcirculatory involvement, as documented with intracoronary imaging and physiological techniques, to overcome the existing limitations of angiographic assessment or noninvasive determination of coronary flow reserve.

METHODS

Study population: diabetic patients who underwent coronary angiography as part of a scheduled follow-up after percutaneous revascularization or an interventional procedure. In both cases, coronary microcirculation was studied at the non-target, stenosis-free left anterior descending artery (LAD). All patients in this study gave prior written consent to these tests, did not exhibit angiographically significant coronary stenosis (>30% of the diameter) in the LAD artery, and presented no contraindication to the administration of adenosine.

Cardiac Catheterization

Coronary angiography was performed from the femoral artery using 6 Fr catheters, following

a 200 µg intracoronary nitroglycerine bolus to vasodilate the epicardial vessels. Intracoronary instrumentation was inserted after administration of 5000 IU of sodium heparin.

Assessment and Evaluation of the Intracoronary Physiological Parameters

Coronary flow velocity was measured approximately 20 mm away from the ostium of the LAD artery using a 0.014" Doppler guide (Flowire, Cardiometrics, Rancho Cordova, USA) and the corresponding interface (FloMap). Coronary hyperemia was induced by the infusion of 140 µg/kg/min of adenosine in the femoral artery for 2 min. Given that the LAD artery was free of stenosis, pressure measurements taken by the guide catheter were considered to be equivalent to the intracoronary pressure.

To assess the indices of microcirculatory function from the coronary pressure flow-velocity relation, digital recordings of ECG, aortic pressure and flow velocity were taken using external equipment set up especially for this study, consisting of a 12-bit analog-to-digital converter (DI) 200 PGL, DataQ Instruments, Akron, Ohio, USA controlled by dedicated software (WinDaq 200, DataQ Instruments, Akron, Ohio), and a PC. Frequency acquisition was 125 Hz/channel. Analog ports of the equipment were also used to obtain instantaneous intracoronary flow velocity signals, pressure, and ECG. These measurements were edited and processed according to the following protocol:

1. Data selection during maximum hyperemia. Using WinDaq and Advanced Cudas software (DataQ Instr., Akron, Ohio) for the ECG graphic preview, and pressure and flow velocity recordings, the period of maximum hyperemia was identified as the one having the highest intracoronary velocity following intravenous adenosine infusion. Data from the interval of interest was stored in a PC for later analysis.

2. Data selection from meso-telediastolic phase. Using StatView® statistical analysis and data management software (Abacus Concepts, Inc.), all intervals of data from pressure and flow velocity in the region of interest for each physiological index were identified. Identification of the mid-diastolic phase used for calculation of the slope of the pressure-flow velocity relationship was performed according to the methodology described by Di Mario et al.¹³

3. Assessment of the slope of the instantaneous hyperemic diastolic flow velocity - pressure slope (IHDVPS). By performing linear regression analysis, the coronary pressure-flow velocity slope

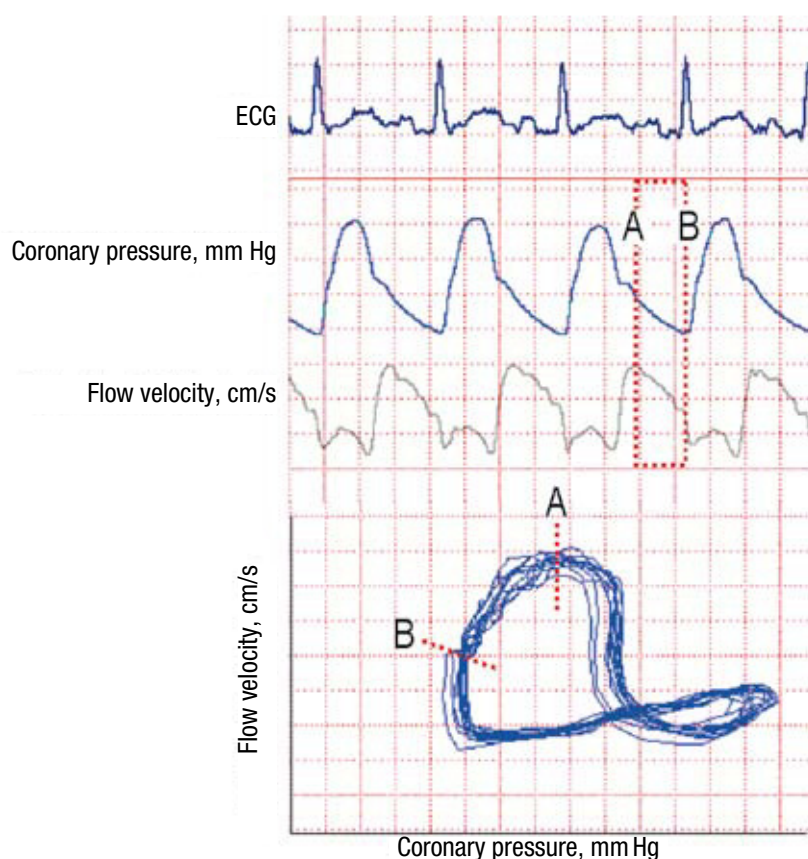


Figure 1. Digital recordings of ECG signals, pressure, and coronary flow velocity showing the existing relation between the last 2 variables (pressure cycles / flow velocity). Points A and B show the meso-diastolic phase at its early stage and the end of the telediastolic phase respectively. Data from this segment was used for the assessment of the slope of the hyperemic diastolic pressure-flow velocity relation - ShDPFVR and the ZFP index.

during the aforementioned interval was established (using the term b in the general expression $y=a+bx$ of the regression equation, expressed in cm/s/mm Hg, and the correlation coefficient r and the square of the correlation coefficient or explanatory value (r^2) expressing both the degree of linearity in the relation between pressure measurements and flow velocity measurements in the meso-telediastolic phase (Figures 1 and 2).

4. Assessment of zero-flow pressure. Zero-flow pressure (ZFP) was calculated from the linear regression used to assess IHDVPS. The ZFP is the value of coronary pressure for which flow value = 0 (intersection of the regression line with the pressure axis)¹³ (Figures 1 and 2).

5. Assessment of coronary flow velocity reserve (CFVR). Evaluation was done from the hyperemic average peak flow velocity / basal average peak flow velocity ratio. 6. Assessment of the index of microcirculatory resistance index (MRI). Evaluation was done from the average pressure / average peak flow velocity quotient measured during hyperemia in three consecutive cardiac cycles.^{14,15}

Quantification of the Atheromatous Plaque

Forty MHz mechanical rotation intracoronary ultrasound catheters (IVUS) (Atlantis, Boston Scientific Corporation, Sunnyvale, California) and 0.5 mm/s pullback were used. Images were digitized and analysed quantitatively (EchoScan, Tomtec, Unterchleissheim, Germany) every 0.3 mm within the proximal 20 mm of the LAD artery. The overall vessel area and volume, the atheroma plaque, and the percentage of stenosis of the resultant area were assessed separately.

Echocardiographic Evaluation of the Systolic and Diastolic Ventricular Function

Before intracoronary examination, a complete echocardiographic analysis was carried out using 2 systems (Hewlett-Packard 5500 and ENVISOR Philips). An estimate of left ventricular diameters, and wall thickening and ejection fraction was calculated following guidelines from the American Society of Echocardiography.¹⁶ The LVDF was

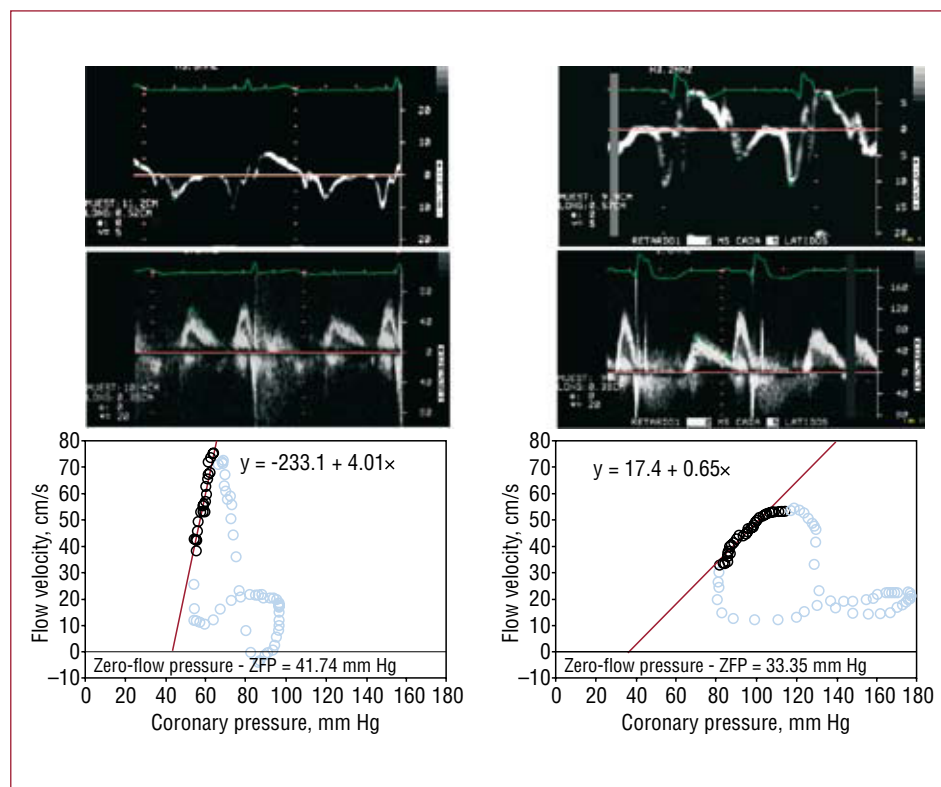


Figure 2. Graphic recordings from the conventional and tissue Doppler study and graphic representations of the pressure / intracoronary flow velocity relation in 2 patients (left and right). Pressure and flow measurements in the meso-telediastolic phase are highlighted in black and the regression line spotted in the linear regression analysis is highlighted in red. Beta coefficient in the regression equation represents the slope of the hyperemic diastolic pressure-flow velocity relation (ShDPFVR; a mild slope represents a minor IHDVPS) greater microcirculatory disease.

The line-point interception with the axis of pressure values is equivalent to ZFP. Left: charts from one of the studied patients exhibiting the following values: $E/e' = 6.8$; $E/A = 0.67$; ShDPFVR = 2.2 cm/s/mm Hg; ZFP = 41.74 mm Hg. Right: recordings from a patient with a much greater LVDF deterioration and a severe microcirculatory condition exhibiting the following values: $E/e' = 15.46$; $E/A = 0.5$; ShDPFVR = 0.65 cm/s/mm Hg; ZFP = 33.35 mm Hg.

assessed in all patients by combining conventional Doppler techniques and tissue Doppler imaging.

Early transmitral flow velocity (E) and late transmitral flow velocity (A) were measured at a speed of 100 mm/s using pulsed Doppler ultrasound and spotting the sample volume at the tips of the mitral valve cusps in diastole. E-wave deceleration time (EDT), isovolumetric relaxation time (IVRT) and E/A ratio were also assessed. The average of 3 consecutive measurements was obtained. The apical 4-chamber view was used to calculate the velocity of the mitral ring motion (e') and the sample volume of the pulsed Doppler ultrasound (2 mm) was identified in the septal portion of the mitral ring. The early diastolic peak velocity (e) was calculated to get an estimate of the E/e' ratio.

Statistical Analysis

Continuous variables were expressed as arithmetic mean (standard deviation) and categories were expressed in percentages. The Kolmogorov-Smirnov test was used to confirm the normal distribution of continuous values. The relationship among continuous variables was estimated through a simple linear regression analysis and a calculation of the Pearson coefficient. A P value less than .05 was considered significant.

RESULTS

Study Population

Initially 17 diabetic patients were part of this study but 4 were ruled out due to the poor quality of the physiological parameters of the digital recordings. Data shown refer to the 13 remaining patients. Table 1 shows baseline patient characteristics. Ninety-two percent of patients had been diagnosed as DM2 8 (3) years ago; 4 (30%) were under insulin treatment. Renal clearance (Cockcroft Gault) was 105.3 (16.23) mL/min. The average glycated hemoglobin was 7.23% (1.12%).

TABLE 1. Demographic Data and Clinical Variables

Age, mean (SD), y	60 (10)
Male	10 (77%)
Active smoking	3 (23%)
Dyslipidemia	8 (61%)
Arterial hypertension under treatment	8 (61%)
Cardiac frequency, b/min	72 (5.14)
LVTDP, mmHg	15.95 (3.9)
Serum creatinine, g/dL	0.91 (0.29)
Creatinine clearance, mL/min	106.3 (26.23)

LVTDP indicates left ventricular telediastolic pressure.

TABLE 2. Echocardiographic Data from the Systolic and Diastolic Functions

LVEF, %	66.15 (7.67)
Indexed mass, g/m ²	113 (15)
Relative thickness	0.45 (0.83)
Regional myocardial contractility abnormalities, %	5 (38)
E-wave peak velocity, cm/s	67.62 (15.53)
A-wave peak velocity, cm/s	81.46 (28.41)
E/A ratio	0.92 (0.38)
Isovolumetric relaxation time, ms	122 (18)
E-wave deceleration time, ms	162 (15)
e wave peak septal tissue velocity, cm/s	7.12 (1.92)
E/e' ratio	9.9 (2.8)

LVEF indicates left ventricular ejection fraction (Simpson's method).

Assessment of the Left Ventricular Systolic and Diastolic Function

Table 2 shows data from the left ventricular function. Even though 38% of the analysed sample exhibited some mild impairments of the regional myocardial contractility all patients exhibited preserved general ventricular function. Semiquantitatively, 92% of all patients exhibited a certain degree of diastolic dysfunction, with the relaxation disorder or stage 1 diastolic dysfunction being the most frequent.

TABLE 3. Intracoronary Measurements

Physiological measurements (pressure and flow velocity)	
Baseline velocity, cm/s	24.65 (9.92)
Hyperemic velocity, cm/s	53.45 (13.9)
Average aortic pressure, mm Hg	96.01 (18.45)
Microcirculatory resistance index, mm Hg/cm/s	1.93 (0.74)
Coronary flow velocity reserve	2.32 (0.56)
IHDVPS, cm/s/mm Hg	1.56 (0.5)
Zero-flow pressure, mm Hg	40.41 (10.66)
Measurements using intracoronary ultrasound	
Vessel diameter, mm	5.05 (0.64)
Luminal diameter, mm	3.86 (0.59)
Vessel area, mm ²	20.35 (4.82)
Luminal area, mm ²	11.73 (4.02)
Plaque area, mm ²	8.39 (2.2)
Vessel volume, μ L	438.95 (161.2)
Luminal volume, μ L	259.61 (119.05)
Plaque volume, μ L	179.34 (57.48)

Average diameter and area values for the in 20 mm segment analysed with IVUS.

Assessment of the Indices of Coronary Microcirculation and Relation to the Left Ventricular Diastolic Function

Table 3 shows data from the indices of microcirculatory function. An excellent coefficient of determination was estimated ($r^2=0.84$ [0.1]),

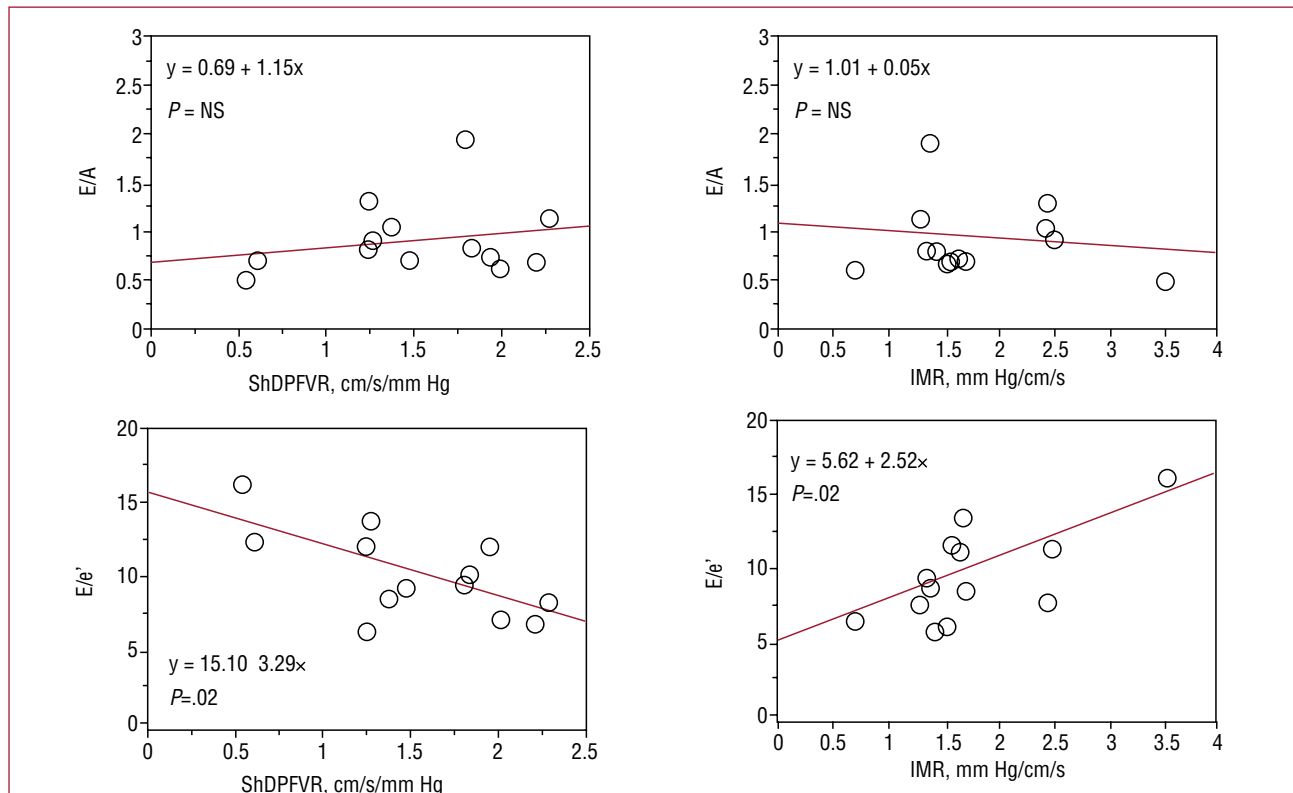


Figure 3. Linear regression analysis of the 2 Doppler indices of diastolic function (E/A and E/e' ratios) used and analysis of microcirculatory hemodynamics—pending the hyperemic diastolic pressure-flow velocity relation (ShDPFVR) and index of microcirculatory resistance (IMR)—in the study population.

TABLE 4. Relation Between Echocardiographic Parameters of the Diastolic Function and Intracoronary Measurements

	E/A Ratio		E/e' Ratio	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Coronary flow reserve	0.07	NS	0.44	NS
Zero-flow pressure-ZFP, mm Hg	0.27	NS	0.08	NS
Microcirculatory resistance index, mm Hg/cm/s	-0.10	NS	0.62	.02
IHDVPS, cm/s/mm Hg	0.21	NS	-0.64	.02
Average plaque area, mm ²	0.34	NS	0.30	NS
Average plaque volume, μ L	0.01	NS	0.07	NS

guaranteeing the linearity of the relation between the aortic pressure and the intracoronary flow velocity in the mid-end diastolic phase needed to calculate IHDVPS and ZFP.

Table 4 shows results from the linear regression between the indices of microcirculatory function and the LVDF. Correlation between the E/e' ratio and the MRI proved positive and statistically significant, while IHDVPS showed a significant and inversely proportional correlation with E/e ratio (Figure 3). On the contrary, this regression analysis showed no relation between these indices and the E/A ratio-estimated diastolic function. The CFVR and ZFP indices showed no statistically significant correlation with any of the LVDF indices.

Assessment of the Coronary Atheroma Burden and Relation to the Left Ventricular Diastolic Function

Table 3 shows data from coronary atheromatosis recorded using IVUS analysis. Even though angiography proved no evident stenosis had occurred, all patients exhibited atheromatosis with an average atheromatous plaque area and atheromatous plaque volume of 8.57 (1.55) mm² and 184.7 (48.95) μ L, respectively. In the regression analysis, no statistically significant relation between the indices of atheromatosis and the LVDF could be observed (Table 4; Figure 4).

DISCUSSION

This study performed in a diabetic population confirmed a correlation between LVDF impairment and microcirculatory impairment, and a possible absence of relation between LVDF and atherosclerotic burden. Since the complexity of this study dictated the inclusion of a small number of patients, our findings should be

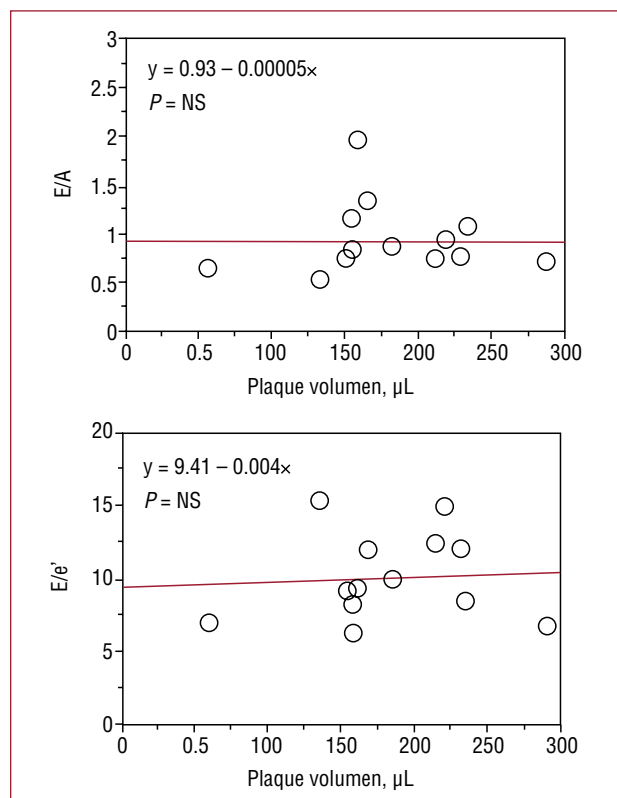


Figure 4. Linear regression analysis of the 2 Doppler indices of diastolic function (E/A and E/e' ratios) used and the atheroma volume in the proximal 20 mm of the LAD artery.

considered as hypothesis-generating, to be used in future studies.

In patients with DM we investigated the relation between LVDF and 2 different elements of coronary circulation: epicardial vessels and microcirculation. The consequences of DM in these 2 coronary vascular compartments are quite different. In epicardial vessels, formation of atheroma³ is predominant, leading to luminal obliteration, recurrent thrombosis, distal embolization, and clinically silent micro-infarctions.⁹

Microcirculatory disease resulting from the intrinsic toxic effect and the formation of free radicals associated to persistent hyperglycemia might cause the onset of endothelial dysfunction, arteriolar thickening, capillary rarefaction, or perivascular myocardial fibrosis.^{2-4,6,7} Being basically intramyocardial, coronary microcirculation can also be affected by extravascular compression secondary to increased interstitial or tissue pressure.¹⁷

The methodological approach to a separate study of these processes constitutes one of the original aspects of our work, and requires detailed discussion (below).

Relation Between the Left Ventricular Diastolic Function and Coronary Microcirculation

Previous studies on coronary microcirculation in DM patients have been carried out within the theoretical framework of CFVR,^{5,18,19} which can also be assessed using transthoracic echocardiography.^{5,20} In this regard, CFVR shows significant limitations. First, being a relative measurement, CFVR is dependent on a baseline reference coronary flow measurement, which can be influenced by many factors, including DM.^{21,22} The second limitation stems from the use of averaged flow velocity over the complete cardiac cycle, and not using selectively coronary diastolic flow, which is predominant in left ventricular perfusion.^{23,24} This can make CFVR more sensitive to interferences due to systolic phenomena.²⁴⁻²⁶ For this reason, we used indices of microcirculatory function derived from the coronary pressure-flow relation, widely used in experimental physiology.^{21,23,27} On the other hand, the methodological advantages of some of these indices of microcirculatory function present the problem of greater complexity and the absence of commercially available systems.

Although IHDVPS and MRI used in this study are assessed from pressure and coronary flow, the differences between these indices should be underlined. IHDVPS or coronary conductance^{13,28} is assessed using the linearity of the pressure-flow velocity relationship in the meso-telediastolic phase of the cardiac cycle, where resistance remains relatively stable. The absence of a linear relationship in early diastole caused by capacitance changes and systolic flow can be thus avoided to overcome the aforesaid limitations.²⁹

Although MRI is easier to obtain than IHDVPS, it provides a less specific average estimate of coronary resistance for the complete cardiac cycle.^{14,15} Another index used in our study is the zero-flow pressure, a parameter derived from experimental physiology³⁰⁻³² that has been applied in the clinical field.^{33,34}

ZFP can be defined as the value of intracoronary pressure higher than that of central venous pressure under which coronary flow becomes interrupted. This phenomenon has been attributed to a vascular waterfall³¹ or intramyocardial capacitance phenomena³² and for practical purposes it can be understood as the interstitial and intramyocardial pressure exerted against microcirculation in diastole. It would provide, therefore, specific information about microcirculatory impairment secondary to diastolic extravascular compression.

Echocardiographic Indices of Diastolic Function and Coronary Microcirculation

Doppler echocardiography has become the most widely used method for LVDF¹⁰⁻¹² assessment, especially useful in diabetic heart disease.¹⁰ The early and late transmitral diastolic flow (E/A) ratio was one of the first indices developed for LVDF assessment, but given its dependence on ventricular preload conditions, its use in clinical practice^{10,15,17} is somehow limited, particularly in cases of stage 2 diastolic dysfunction with pseudonormalization pattern.³⁵

Introduction of peak velocity of the mitral ring in protodiastole (e'), assessed using pulsed tissue Doppler ultrasound as a substitute for early transmitral flow A (E/e' quotient), has enabled a more independent assessment of LVDF from ventricular preload conditions.^{10,36} Our study reported a statistically significant relation between the E/e' ratio and IHDVPS and MRI values.

This backs up the theory that coronary microcirculation is affected at early stages of diastolic dysfunction in patients with DM. The fact that a statistically significant relation could be established only with the E/e' ratio, and not with the E/A ratio, might be due to the aforementioned greater sensibility and ventricular preload independence, making it advisable to consider using the E/e' ratio in future studies on LVDF and coronary microcirculation.

Relation Between the Pattern of Coronary Atheromatosis and the Echocardiographic Indices of the Diastolic Dysfunction

Angiographic studies on the relation between atherosclerotic disease and diastolic dysfunction can underestimate the degree of atheromatosis due to coronary compensatory remodeling associated to atherogenesis.³⁷ In this study we used intracoronary ultrasound as the optimal technique to assess the degree of atheromatosis in diabetic patients.³⁸ Our analysis found no significant correlation between the pattern of coronary atheromatosis assessed using IVUS and echocardiographic indices of the diastolic function.

Limitations of this study

The invasive nature and complexity of this study are the main reasons contributing to the small number of patients studied, a fact that also limits the performance of multivariable analysis. The studied patients exhibited a variable degree of diastolic dysfunction.

Assessment of atherosclerotic burden was limited to the proximal third of the anterior descending coronary artery; it remains possible that a more extensive assessment of coronary atheromatosis (for example, extended to small branches) might disclose a relationship with diastolic function. It has been pointed out that extrapolation of ZFP from a linear regression can be limited by the existence of a curvilinear relation in the low range of intracoronary pressure¹²; this limitation is difficult to overcome with current technology. However, this has not impeded the use of the index by other authors.^{32,33}

CONCLUSIONS

The results from this study back up the theory that LVDF impairment in DM is partly due to ongoing coronary microcirculatory disease.

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