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DOTTORATO DI RICERCA IN FISIOPATOLOGIA SPERIMENTALE - INDIRIZZO CARDIOVASCOLARE

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"LEFT VENTRICULAR MYOCARDIAL PERFORMANCE"

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INTRODUCTION

Recently, a conceptually new Doppler index that combines the assessment of systolic and diastolic left ventricular (LV) performance was proposed by Tei and co-workers (1, 2). This Myocardial Performance Index (MPI), which is defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by the ejection time, was reported to be simple, non-geometrical, non-invasive, reproducible and independent of the heart rate and blood pressure (1). The MPI has been shown to have significant clinical utility. It is prolonged in many cardiac diseases even in the absence of clinical signs. Studies have demonstrated that MPI correlates well with invasive measures of both systolic and diastolic function in adults (3) and provides prognostic information about morbidity and mortality in patients with ischemic heart disease (4), cardiac amyloidosis (5), dilated cardiomyopathy (6), primary pulmonary hypertension (7) and detects early LV functional improvement as a result of drug therapy (8). MPI is also abnormal in individuals without overt cardiac disease who have risk factors such as diabetes mellitus (9) and treated and untreated hypertension (10-12). Orem et al. demonstrated progressively more abnormal MPI with increasing degrees of albuminuria in a diabetic population (9). More recently, the MPI has shown promise in the assessment of right ventricular function in fetus (13, 14), children (15-87) and adults with various heart disease (19-21).

The main limits of the MPI are represented by its dependence from heart rate and loading conditions, as demonstrated in previous papers (22-24) that must to be considered during the interpretation of the data.

The aim of this thesis was to analyse the LV myocardial performance, applying the MPI in various physiological and pathological conditions to elucidate some aspects of LV myocardial dynamic.

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CHAPTER 1

IMPACT OF MYOCARDIAL GEOMETRY ON LEFT VENTRICULAR PERFORMANCE IN HEALTHY BLACK AND WHITE YOUNG ADULTS

Source: **P Pattoneri,** G Pelà, FB Sozzi, Alberico Borghetti. ***Echocardiography 2007. Adapted***

ABSTRACT

Racial differences in left ventricular structure are suggested by clinical and experimental studies. This study evaluates if racial differences in left ventricular performance exist comparing black to white young males, by Tissue Doppler Echocardiography and Myocardial Performance Index. We examined 40 healthy males, 20 blacks (mean age 27.6 ± 4.4 years) and 20 whites (mean age 26.5 ± 6.7 years). All subjects underwent conventional echocardiography, Tissue Doppler Echocardiography and Myocardial Performance Index assessment. No differences were found in left ventricular diameters, volumes, mass and hemodynamic measurements. Septal and posterior wall thicknesses were significantly increased in black subjects, as well as the relative wall thickness. Systolic and diastolic function estimated by conventional parameters were superimposable in the two groups. In black subjects a significant increase of septal S wave, peak velocity and time velocity integral were found. Myocardial Performance Index was significantly higher in black compared to white subjects (0.46 ± 0.05 vs 0.40 ± 0.06, $p < 0.002$). A significant correlation between Myocardial Performance Index and relative wall thickness ($r = 0.54$) was demonstrated. Besides, Myocardial Performance Index correlated with S_{pv} ($r = 0.55$) and S_{tvi} ($r = 0.38$) at the septal site. In conclusion our data show an higher Myocardial Performance Index in black subjects that seems to be geometry-dependent. Correlations between Myocardial Performance Index and Tissue Doppler Echocardiography systolic indexes were found. Our findings suggest that racial differences in left ventricular performance exist, especially, in the systolic function, even in absence of other conventional echocardiographic changes.

KEYWORDS: Myocardial Performance Index, racial differences, left ventricular geometry, Tissue Doppler Echocardiography.

INTRODUCTION

A number of observational studies using echocardiography has suggested that African subjects have a greater degree of concentric remodelling of the left ventricle compared to white subjects, expressed as relative wall thickness, with similar level of resting blood pressure (1-3). The racial difference in left ventricular (LV) geometry has been documented in both hypertensive (1-3) and normotensive subjects (3-4) and it is independent of age, gender and body mass index (BMI). However, little informations on LV mass and geometry in black and white healthy young subjects are known. Although previous investigators have reported that these early concentric remodelling may be partially mediated by hemodynamic influences such as a greater peripheral vascular resistances and a smaller nocturnal decline of blood pressure (5), the etiology of these ethnic differences in LV structure is uncertain. Moreover, conventional echocardiographic measures of the LV systolic and diastolic performance and hemodynamic indexes may have some limitations for the assessment of the LV contractile properties and do not reflect all aspects of the myocardial function in healthy young subjects.

The Myocardial Performance Index (MPI, also denoted as Tei Index) is a recently proposed indicator of combined ventricular systolic and diastolic function and it is considered a non-geometrical non-invasive marker of global LV function (6). It is defined as the ratio between the sum of isovolumic relaxation time and isovolumic contraction time and the ejection time (7). The MPI correlates to invasive measures of both systolic and diastolic function (8). In addition, it is a powerful independent predictor of cardiovascular mortality (9) in patients with heart failure (10), cardiac amyloidosis (11), dilated cardiomyopathy (12), myocardial infarction (13) and drugs cardiotoxicity (14). Nevertheless, only few systematic data are reported in physiological condition. Therefore the present study aims to investigate whether MPI is able to detect racial differences and to evaluate its relationship with LV geometry and with systolic and diastolic parameters evaluated by Tissue Doppler Echocardiography (TDE) in black and white healthy young adults. It is well known that TDE offers a more sensitive index of diastolic and systolic function compared to the

mitral inflow pattern and conventional echocardiographic systolic indexes. This study would further contribute to our understanding of the physiology of MPI, as this seems to be a very complex variable affected by several different components in the cardiovascular system.

METHODS

Subjects

We enrolled 40 healthy young volunteers men (20 blacks, mean age 27.6 ± 4.4, range 36 - 18 years, and 20 whites, mean age 26.6 ± 6.7, range 37 - 16 years). All the subjects were judged healthy on the basis of clinical examination, 12-lead standard electrocardiogram and echocardiogram. The subjects were defined normotensive if the blood pressure was <140/90 mmHg in at least four measurements by sphygmomanometer at different days. All of them were sedentary and no one was under therapy. BMI was calculated as Kg/m^2. No subjects had a previous history of heart disease or clinical symptoms of heart failure. Clinical characteristics of the study population are presented in Table 1.

Standard echocardiography

M-mode, two-dimensional and Doppler echocardiography were performed by an experienced physician (P. P.) using a commercially available equipment **(**Aspen instrument, Mountain View, California) with a multi-Hertz sector probe (2-4 MHz).

Images were acquired from the standard projections with the subject lying on the left lateral side. Systolic and diastolic thickness of the interventricular septum (IVS) and the posterior wall (PW) and systolic and diastolic LV dimensions (LVDs and LVDd) were measured according to the Penn-convention in the parasternal view (15-16).

The relative wall thickness (RWT) was computed at end-diastole as the ratio of IVS + PW and LVDd. Left ventricular mass (LVM) was calculated using the Penn-convention and indexed to Body Surface Area (LVM/BSA) (15-16).

LV end-diastolic and end-systolic volume as well as the ejection fraction (EF) were calculated according to the biplane Simpson rule. Fractional shortening (FS) was assessed by the percent ratio: (LVDd-LVDs)/LVDd. Left ventricular end-systolic meridional wall stress was estimated according to the formula of Devereaux and coll. (16).

The blood flow across the mitral valve was also determined by standard techniques. In the diastolic flow profile the peak velocity and the time velocity integral of the E and A wave were analysed. Deceleration time was measured as the time interval between the peak E-wave velocity and the intercept of the deceleration flow with the baseline.

Two-dimensional echocardiographic stroke volume was calculated as the difference between end-diastolic and and-systolic volume multiplied by heart rate in order to derive the cardiac output. Total peripheral resistance (TPR) was derived {DBP + [0.33 x (SBP –DBP)])/CO} x 80. Stroke index, cardiac index and total peripheral resistance index were obtained by dividing stroke volume, cardiac output and total peripheral resistance with BSA, respectively. Endocardial border detection was enhanced by use of Coded second harmonic imaging (17).

Doppler data

Doppler time intervals were measured from mitral inflow and LV outflow Doppler tracings, as described by Tei et al (7). Other aspects of this technique were described previously (14). Briefly, MPI was obtained combining Doppler systolic and diastolic time intervals as demonstrated in Figure 1. The interval *"a"* from the cessation to the onset of mitral inflow was equal to the sum of isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT). The interval *"b"* was the duration of LV outflow velocity profile. Thus, the sum of ICT and IRT was obtained by the subtraction of b from a. The index of combined LV systolic and diastolic function (the sum of ICT and IRT divided by ET) was calculated as (a–b)/b. IRT was measured by subtracting the interval d, between the R wave and the cessation of left ventricle outflow, from the interval a. ICT was calculated by subtracting the IRT from a-b interval.

All the Doppler measurements were calculated at the end of the expiration phase from an average of three consecutive cardiac cycles. Thirty random subjects were analyzed to determine the inter and intra-observer variability in measurement of MPI. In our echocardiographic laboratory the mean inter-observer difference in the measurement of MPI was 3.1%, whereas the mean intra-observer variability was 3.4%.

Pulsed Tissue Doppler Echocardiography

The myocardial velocities of the LV were measured as previously described (18), sampling the mitral annulus excursion at lateral and at the postero-septum site in the four-chamber view. Measurements were usually done in triplicate on different heart cycles. Care was taken to keep the ultrasound beam perpendicular to the plane of the annulus in order to minimize the angle between the beam and the direction of the annular motion. The width of the sample volume was 3-5 mm. From each site TDE images were stored in digital format; measurements of peak velocities and calculation of the time-velocity integrals of each wave were performed off-line using the software package of the ultrasound machine. Usually, several cardiac cycles were acquired, and the best two consecutive cycles were analysed and averaged. In the text and figures below, peak velocities and time-velocity integrals are often abbreviated with the **pv** and **tvi** subscripts, respectively (e.g. $\mathbf{S'_{pv}}$, $\mathbf{E'_{tvi}}$). In our echocardiographic laboratory the intra-observer and inter-observer coefficient of variation were 7.3% and 6.5% for peak velocities, against 10.5% and 12.3% for integrals in the LV.

Statistics

Values are expressed as mean $\pm$ standard deviation (SD). Comparison between two means was made with Student's t test. The relationship between parameters were evaluated by means of Linear Regression data analysis. A p value < 0.05 was considered statistically significant. We used the statistical program Microsoft Excel Win Office XP for the purpose of statistical data analysis.

Table 1. Clinical data.

Parameters	*White subjects*	*Black subjects*
Age (years)	26.5 ± 6.7	27.6 ± 4.4
Body height (cm)	180.0 ± 0.07	179.4 ± 0.07
Body weigh (Kg)	74.5 ± 6.5	81.1^{*} ± 11.7
Body Mass Index (Kg/m^2)	23.1 ± 1.6	25.1^{*} ± 3.1
Body surface area (m^2)	1.92 ± 0.15	2.00 ± 0.16
Systolic blood pressure (mmHg)	121.2 ± 6.5	124.5 ± 11.8
Diastolic blood pressure (mmHg)	75.5 ± 7.2	83.0^{**} ± 6.2
Heart rate (bpm)	65.3 ± 10.3	76.1^{*} ± 14.0

Data are means ± SD; $^{*}p<0.04$, $^{**}p<0.002$.

Table 2. Conventional echocardiographic data and resting hemodynamic measurements.

Parameters	*White subjects*	*Black subjects*
LV end-diastolic diameter (mm)	48.3 ± 4.8	46.4 ± 3.6
LV end-systolic diameter (mm)	29.5 ± 4.2	28.1 ± 3.1
Septal wall thickness (mm)	8.5 ± 1.4	9.9^{*} ± 1.0
Posterior wall thickness (mm)	8.4 ± 1.3	9.5^{**} ± 1.2
Relative wall thickness	0.35 ± 0.05	$0.42^{\S}$ ± 0.04
LV mass index (g/m^2)	88.7 ± 20.6	93.5 ± 17.7
LV fractional shortening (%)	39.1 ± 7.0	38.8 ± 5.0
Ejection fraction (%)	61.4 ± 4.2	61.2 ± 3.6
LV end-diastolic volume (ml)	103.4 ± 22.1	94.5 ± 17.2
LV end-systolic volume (ml)	42.2 ± 10.9	38.4 ± 7.1
LV end-systolic meridional stress	53.2 ± 16.2	47.2 ± 11.0
Cardiac index ($ml*min/m^2$)	2048.8 ± 343.5	2108.8 ± 479.7
Stroke index (ml/m^2)	31.9 ± 6.4	27.9 ± 5.2
Total peripheral resistance index (dyne $*s*cm^{-5}/m^2$)	1.00 ± 0.20	0.97 ± 0.24

Data are means ± SD; $^{*}p< 0.002$, $^{**}p< 0.04$, $^{\S}p< 0.002$. LV = left ventricle

Table 3. Summary of Doppler time intervals and mitral flow patterns.

Parameters	***White subjects***	***Black subjects***
LV MPI	0.40 ± 0.06	0.46* ± 0.05
LV ICT (ms)	52.0 ± 10.4	62.1**± 19.1
LV IRT (ms)	59.3 ± 12.5	62.6 ± 22.4
LV ET (ms)	279.6 ± 22.4	271.8± 18.4
E-wave deceleration time (ms)	132.4 ± 16.8	127.5 ± 15.1
E_{pv} (cm/s)	81.0 ± 17.7	79.7 ± 15.6
E_{tvi} (cm)	11.5 ± 2.7	11.9 ± 3.1
A_{pv} (cm/s)	48.2 ± 9.9	52.0 ± 15.3
A_{tvi} (cm)	4.4 ± 1.2	5.5 ± 2.1
E_{pv}/A_{pv} (cm/s)	1.8 ± 0.6	1.6 ± 0.5
E_{tvi}/A_{tvi} (cm)	2.8 ± 1.1	2.4 ± 0.9

Data are expressed as a mean value ± SD, *p< 0.002, **p< 0.05. MPI, myocardial performance index; IRT, isovolumic relaxation time; ICT, isovolumic contraction time; ET, ejection time; E, early diastolic filling wave; A, atrial contraction wave; $_{pv}$, peak velocity; $_{tvi}$, time velocity integral.

RESULTS

Clinical Characteristics

Subjects demographics are shown in Table 1. Black and white subjects had similar age and BSA, but weight and BMI were increased in blacks. Office blood pressure was increased in black subjects with a significant difference of the diastolic value. In addition, heart rate was significantly higher in black subjects (Table 1). ECG tracings did not indicate any pathologic pattern in all subjects.

Standard Echocardiographic Parameters

Echocardiographic measures of the LV structures in black and white subjects are shown in Table 2. Significant differences were noted in LV geometry. Blacks tended to have a smaller chamber size and greater wall thicknesses. This resulted in a greater relative wall thickness that shows a tendency to a LV concentric remodelling (Table 2). Black subjects also had a non significant increase of indexed LV mass than whites (Table 2). No differences in cardiac index, stroke index, total peripheral resistance index and end-systolic meridional wall stress were found between the two groups (Table 2). The LV systolic function evaluated as EF and FS was unchanged (Table 2). The LV diastolic function assessed by transmitral inflow pattern, was superimposable in the two groups (Table 3).

Myocardial Performance Index

Figure 1 shows an example of an index measurement. In our study, MPI was easily obtained in all subjects. The ICT and the IRT were prolonged in black subjects especially for ICT ($p < 0.05$). Ejection time (ET) was superimposable in both groups. Thus, the index that combine these variables, was significantly increased in black subjects compared to whites (Table 3).

Pulsed Tissue Doppler Echocardiography

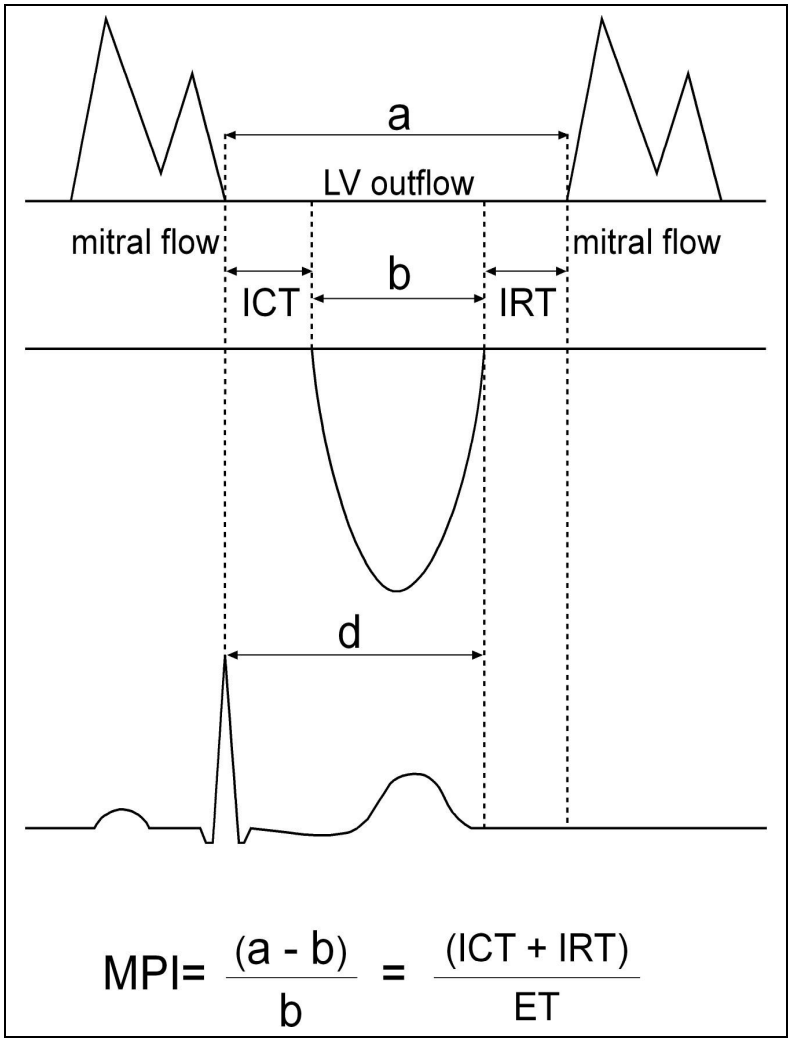
In the study of the diastolic function the E/A ratios of the postero-septum and the lateral wall were similar in both groups. Black subjects showed changes in systolic property expressed as a

significant increase of S_{pv} and S_{tvi}, estimated at the postero-septum. Non significant increase was observed at the lateral site of the mitral annulus (Figure 3).

Correlations

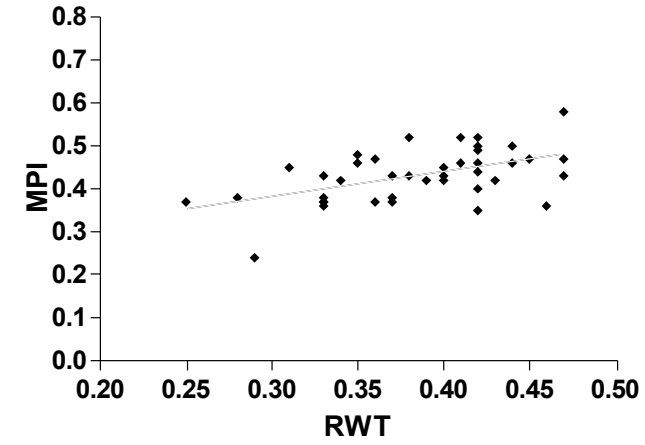
A significant correlation between MPI and RWT ($r= 0.54$, $p< 0.001$) was demonstrated (Figure 2, top panel), but not with LVM and LVM/BSA. A significant correlation was also found between MPI and S_{pv} ($r= 0.52$, $p< 0.001$) and S_{tvi} ($r = 0.38$, $p < 0.01$) derived from the mitral annulus at the postero-septal site (Figure 2, bottom panel). No correlations were found between MPI and conventional echocardiographic systolic (EF and FS), diastolic (E and A waves, E/A ratio and DT) and hemodynamic indexes. No correlations were found between MPI and LV diastolic function evaluated by TDE. In addition, a significant correlation was found between MPI and DBP in black subjects ($r= 0.37$, $p< 0.01$).

Figure 1.

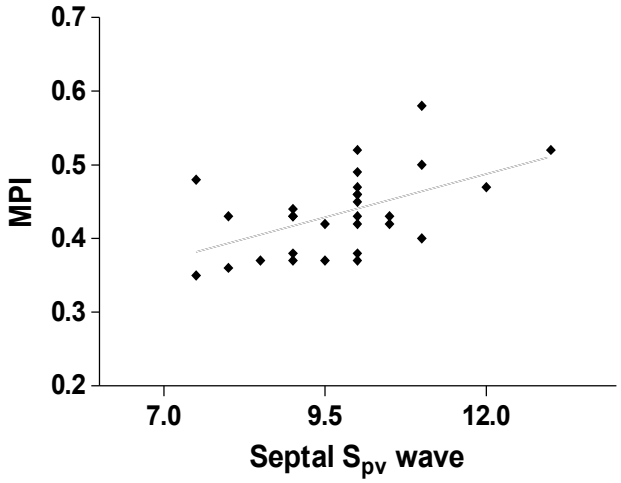


Diagrams illustrating measurement of the Doppler index by simple calculations and measurement of the individual isovolumic times. The myocardial performance index (ICT+IRT/ET) is derived as (*a-b/b*), according to Tei *et al.* (7).

Figure 2.



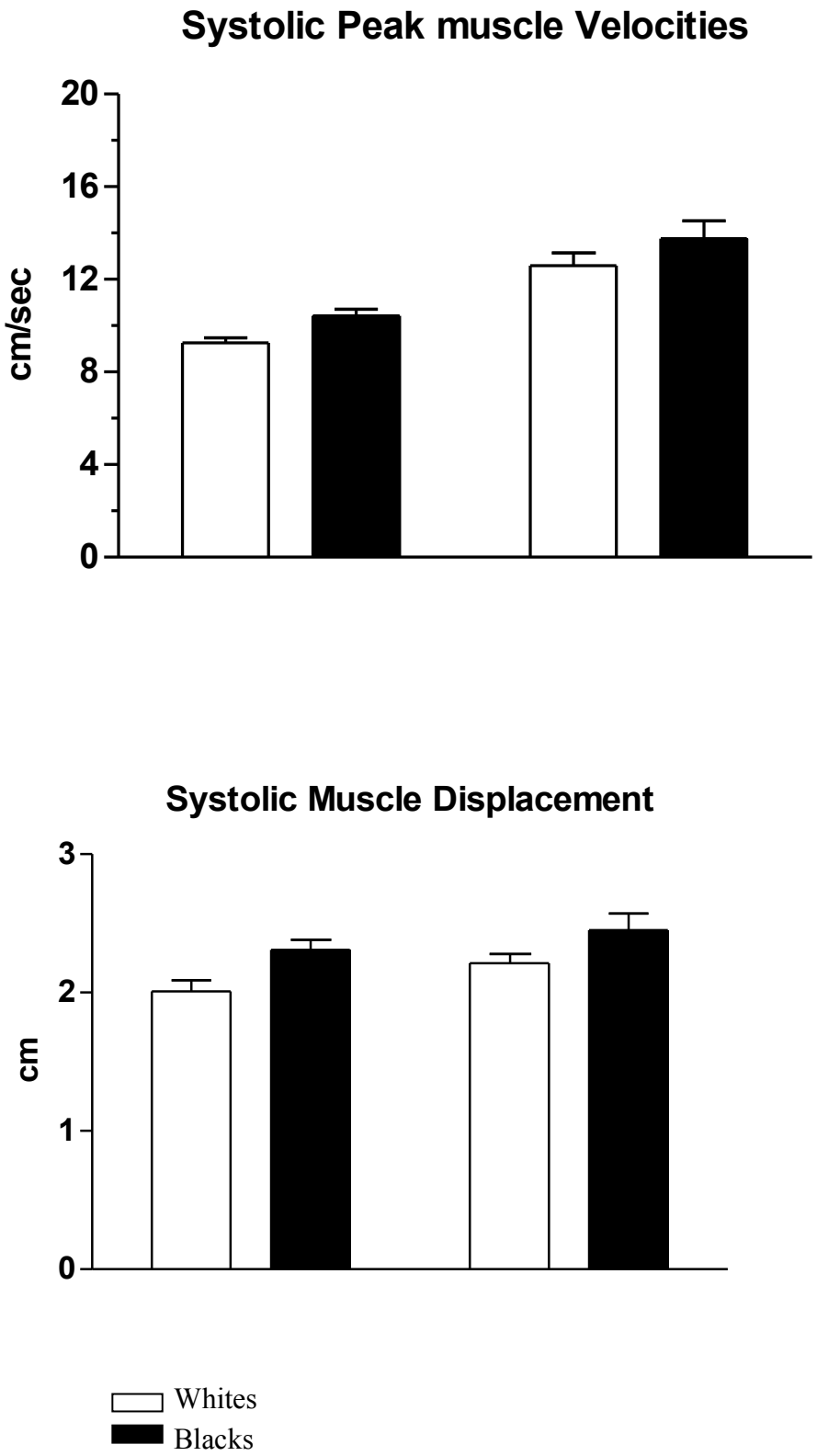
r = 0.54
p < 0.001



r = 0.52
p < 0.001

The relationship between MPI and RWT (top panel), and between MPI and systolic velocity of postero-septal mitral annulus (S_{pv}) (bottom panel).

Figure 3.



Comparison of black and white subjects with regard to ventricular systolic velocities and displacement (* $p < 0.02$, ** $p < 0.03$).

DISCUSSION

This is the first study that analyzes the LV myocardial performance differences between healthy black and white young males. The major finding of the present study is that LV geometry represents an important determinant of the myocardial performance. In fact, our data demonstrates a correlation between MPI and RWT but not with LVM/BSA, with a significant increase of MPI in healthy black subjects, who are well-known to have a higher tendency to LV concentric remodelling expressed as greater RWT, compared to age-matched white subjects.

Recently, TDE has been used as a tool for new cardiac functional measures. Again, the LV has been the main focus of studies in which the velocities of muscle contraction and relaxation were used as indices of normal or diminished performance in different conditions (19-22).

In this study TDE analysis was used to evaluate the relationship with MPI and to clarify the differences in the systolic and diastolic properties resulted in a higher MPI. These observations address the question on the etiology of the racial differences in LV geometry and performance, which still remain uncertain.

Previous findings suggest that differences in cardiac structure may be a consequence of vascular properties that result in higher peripheral resistances in blacks (4). Harshfield and co-workers (23) found a greater nocturnal decrease in BP in white adolescent boys than in age-matched black subjects, a phenomenon that may protect against the development of LV hypertrophy (24).

Comparing black and white subjects we had not found differences in hemodynamic indexes; on the contrary we demonstrated different systolic mechanic TDE especially at the septal annulus ($p < 0.05$, Figure 3). Because of the small group size, we demonstrated that S_{pv} and S_{tvi} significantly correlated with MPI only at the septal annulus. We can speculate that between black and white healthy young men an heterogeneous pattern of ventricular wall contraction was found and this might be related to a different complex distribution and arrangement of the longitudinal myocardial fibers in blacks. Moreover, these results suggest that MPI and TDE data detect better racial

differences in LV function compared to current standard echocardiographic measurements. In our study population the greater relative wall thickness in healthy black subjects was not accompanied by significant differences in LV systolic function or diastolic conventional echocardiographic data. Besides, the MPI geometry-dependence must be taken into consideration during the application of the Index for the evaluation of myocardial performance, and when used as a prognostic marker in cardiac disease where the LV geometry could be modified (25).

Finally, our findings regarding the association between LV geometry and myocardial performance can have significant public health implications. In fact, the pattern of increased RWT noted in black subjects may be deleterious. Koren et al (26), demonstrated that an increase of RWT is related to a higher risk of cardiovascular events, even if the calculated LV mass was normal. In this light, the MPI might represent an important adjunctive parameter in the risk stratification, and in other clinical conditions (9-13). Future prospective study could elucidate this aspect.

There are a number of limitations of the present study that must be incorporated into the interpretation of these data. First, the study population was relatively small for physiological consideration. However, the absence of confounding comorbidity, the careful methodology with multiple continuous measures and the statistical power were robust enough to counteract this. Second, this study was not a randomized controlled trial, but despite being an observational study we are able to show the differences between black and white subjects and the effect of LV geometry on the myocardial performance using the Tei Index. Third, we have speculated about risk stratification but for prognostic considerations we need an extensive follow up.

In conclusion, our findings suggest that the MPI is able to detect racial differences in the LV performance due to the LV geometry, and especially to the systolic function, even in the absence of other conventional echocardiographic changes. We discussed the possible role of this index as early marker of cardiac adaptation to racial differences.

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CHAPTER 2

MYOCARDIAL INVOLVEMENT DURING THE EARLY COURSE OF TYPE 2 DIABETES MELLITUS: USEFULNESS OF MYOCARDIAL PERFORMANCE INDEX

Source: **P Pattoneri**, FB Sozzi, E. Catellani, A. Piazza, R. Iotti, M. Michelini, D. Dall'Asta, Matteo Goldoni, Alberico Borghetti, V. Manicardi. ***Cardiovasc Ultrasound 2008. Adapted***

ABSTRACT

To evaluate whether myocardial performance index detects a subclinical impairment of left ventricular systolic and diastolic function in asymptomatic type 2 diabetic patients with short duration of disease, with or without hypertension, and whether some echocardiographic parameters are related to the metabolic control. Twenty-three type 2 diabetic and hypertensive males, mean age 57 ± 8 (mean diabetes duration 36 ± 15 months, mean hypertension duration 33 ± 13 months) and 22 type 2 diabetic normotensive males (mean age 52 ± 7, mean diabetes duration 40 ± 18 months) were compared to 20 age- and sex-matched healthy control subjects. All subjects underwent a bicycle exercise electrocardiogram test, in order to exclude the presence of coronary artery disease, a conventional Doppler echocardiography and the Doppler-derived myocardial performance index. No differences were observed in the office blood pressure, heart rate, and conventional echocardiographic parameters comparing the diabetic hypertensive pts to the diabetic normotensive pts and both groups to the controls. The mean value of E/A ratio was normal in all participants. The myocardial performance index was significantly higher in diabetic patients compared to controls, independently to the hypertension occurrence. The index was significantly correlated to HbA1c ($r=0.37$, $p<0.01$) in all diabetics. An early involvement of LV performance can be shown by MPI in asymptomatic patients with an early phase of type 2 diabetes independently of the hypertension presence, even in the absence of other conventional echocardiographic changes. These abnormalities could provide a feasible approach to detect a pre-clinical diabetic cardiomyopathy and could be useful for an indirect assessment of the metabolic control.

KEYWORDS: Diabetes Mellitus, Arterial Hypertension, Myocardial Performance Index, Diabetic Cardiomyopathy.

INTRODUCTION

A diabetic cardiomyopathy is considered a contributing factor to the high risk of heart failure in the absence of coronary artery disease, hypertension and obesity in the diabetic population (1, 2). In the early stage, diabetic cardiomyopathy is characterized by left ventricular (LV) diastolic dysfunction, while LV systolic function impairs later on the clinical course of diabetes. Indeed, LV diastolic dysfunction has been documented by means of conventional echocardiography also in subjects with impaired glucose tolerance (4) and type 2 diabetes with short duration of disease (5). Unquestionably, an early detection of LV involvement is a major goal in the prevention of cardiac disease in diabetic patients. A simple, reproducible and noninvasive Myocardial Performance Index (MPI), able to reflect both LV systolic and diastolic function, was previously described by Tei et al (6). MPI, defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by the ejection time (ET), is obtained by Doppler records performed in LV inflow and outflow tracts. MPI is a powerful independent predictor in patients with various cardiac disorders including cardiac amyloidosis (7) and myocardial infarction (8). It is able to identify individuals with heart failure (9, 10) and an early LV functional modification after drug therapy (11, 12) and it is abnormal in individuals without overt cardiac disease who have positive risk factors for coronary artery disease (13, 14). Little is known about the MPI impact in the early stage of diabetes mellitus associated or not to hypertension. The aim of this study was to evaluate whether MPI is able to detect a subclinical LV involvement in asymptomatic pts with a short duration of type 2 diabetes mellitus associated or not to hypertension, and whether echocardiographic functional parameters, in particular MPI, are related to metabolic abnormalities.

METHODS

Subjects

The study population consisted of 45 consecutive type 2 diabetic patients referred to the Operative Unit of Internal Medicine, Montecchio Emilia Hospital, IT, during the period July 2006 and December 2006. Twenty-tree males (mean age 57 ± 8) with type II diabetes mellitus (mean duration 36 ± 15 months) and systemic hypertension (mean duration 33 ± 13 months) on conventional therapy and twenty-two males (mean age 52 ± 7) with only type 2 diabetes mellitus (mean duration 40 ± 18 months) were compared to 22 sex and age matched healthy controls. Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association (15), including fasting plasma glucose level ≥ 126 mg/dl on at least two occasions. Hypertension was defined as repeated blood pressure measurements exceeding 140/90 on different occasions or treatment with antihypertensive drugs for a known diagnosis of hypertension. All included were in sinus rhythm at a 12-lead standard electrocardiogram without right or left bundle branch block or signs of ischemia. No one was smoker, with a previous history of heart disease or with heart failure symptoms. The comparison between both groups is summarized in Table 1. The Ethics Committees of the participating institution approved the study protocol. Written informed consent was obtained from all patients.

Biochemical measurement

Routine chemical method was used to determine the fasting plasma glucose. Glycated haemoglobin (HbA_{1c}) was determined by the HPLC method. Blood sample for analysis was drawn after a fasting time of 8 hours minimum and before oral antidiabetic drugs and exercise testing.

Echocardiography

Conventional and Doppler echocardiograms were obtained in all patients and controls. All subjects were examined in the standard left lateral decubitus position and in expiratory apnoea or quiet

breathing by an experienced physician (P. P.), using a commercially available equipment Sequoia 512 (Siemens Acuson, Mountain View, California) equipped with a multi-hertz sector probe (2-4 MHz). All measurements were obtained online and stored in the computer of the ultrasonic unit for later printout. LV dimensions were measured with M-mode using a leading edge-to-edge convention. The measurements included intraventricular septal thickness (IVS), posterior wall thickness (PW), left ventricular diameter measured respectively at the end of diastole and systole (LVEDD, LVESD). Left ventricular relative wall thickness was calculated as (IVS + PW) / LVEDD. Left ventricular mass (LVM) was calculated using the Penn-convention and indexed to Body Surface Area (LVM/BSA) (16-17). LV end-diastolic and end-systolic volume as well as the ejection fraction (EF) were calculated according to the biplane Simpson rule. Fractional shortening (FS) was assessed as a percent ratio: (LVDD-LVDS)/LVDD. All cardiac valves were examined to rule out significant valvular disease.

Pulsed Doppler from the apical position was used to measure LV inflow through the mitral valve. The peak velocity and the time velocity integral of the early rapid filling (E-wave) and filling during atrial systole (A-wave) were recorded and the E/A ratio derived. The deceleration time (DT) was measured as the interval between the peak of the E-wave and the point at which the descending segment of the E-wave or its asymptote crosses the zero velocity line. These measurements were analyzed during second phase of the Valsalva manoeuvre (18) in order to discriminate subjects with normal diastolic function from subject with pseudonormalized pattern. The MPI is defined as IRT plus ICT divided by the LV ET. LV ET (interval *b*) was measured from the onset to the end of LV outflow velocity pattern. The mitral closing-to-opening time (interval *a*) was measured as the interval from the end to the onset of the mitral inflow velocity pattern (Figure 1). Mean values of three measurements were used and the myocardial performance index was calculated as $(a - b) / b$. Other aspects of this technique have been considered in a previous study (12).

Exercise ECG

A single experienced investigator (P. P.) supervised all exercise tests. Ergometric test was performed on a mechanically braked bicycle. The protocol began at a workload of 25 W and increased by 25 W every 3 minutes using maximal age-predicted heart rate as a target end point. Blood pressure was obtained in the left arm by indirect cuff-sphygmomanometer during the last minute of each stage. Computerized 12-lead ECG was continuously monitored throughout the test for rhythm, rate, and ST-T changes. Significant chest pain, ventricular arrhythmias, conduction abnormalities, ST-segment depression ≥ 3 mm, limiting symptoms such as dyspnea, dizziness, leg fatigue, etc. and excessive elevation (higher than 230 mmHg) or significant drop (≥30 mmHg) in systolic blood pressure were regarded as interruption criteria. The test was considered positive form myocardial ischemia in the case of horizontal or down sloping ST depression >1 mm or ST elevation >1 mm in non–Q-wave leads.

Statistics

The data are presented as means ± standard deviation unless otherwise specified. Comparison of all measurements were made with paired two-tailed Student's *t* test. The relationship between parameters were evaluated by means of simple linear regression data analysis. The *P*-values were considered significant at $P < 0.05$. The statistical program Microsoft Excel Win Office XP was used for the data analysis.

Table 1. Clinical and biochemical characteristics of controls and diabetic patients.

Parameters	***Diabetes mellitus***	***Diabetes mellitus with hypertension***	***Controls***
Number	22	23	22
Age (years)	52.3 ± 6.7	53.3 ± 7.7	53.2 ± 5.4
Body Mass Index (Kg/m^2)	28.6 ± 2.9	29.0 ± 2.3	26.9 ± 1.6
Body surface area (m^2)	2.02 ± 0.16	1.98 ± 0.17	1.91 ± 0.15
Systolic blood pressure (mmHg)	126.8 ± 5.1§	138.2 ± 13.8*	120.4 ± 14.5
Diastolic blood pressure (mmHg)	80.8 ± 7.1†	82.3 ± 9.2*	75.0 ±6.7
Heart rate (bpm)	74.8 ± 7.4*	76.3 ± 10.2*	66.8 ± 7.6
Fasting glucose (mg/dL)	166.8 ± 35.8§§	138.5 ± 25.4	-
HbA_{1c} (%)	7.7 ± 2.2	7.0 ± 1.0	-
Duration of diabetes (months)	40 ± 18	36 ± 15	-
Duration of hypertension (months)	-	133 ± 63	
ACE inhibitor (%)	9	65.2	-
AT II blocker (%)	0	13	-
Diuretics (%)	4.5	21.7	-
Calcium channel blockers (%)	0	17.4	-
Lipid lowering therapy (%)	13.6	21.7	-
Oral hypoglycaemic agents (%)	77.3	73.9	-
Diet theraphy (%)	22.7	26.1	-

Data are means ± SD; $^{*}p<0.01$ vs controls; $^{\dagger}p<0.03$ vs controls; $^{\S}p<0.02$ vs diabetic and hypertensive patients; $^{\S\S}p<0.03$ vs diabetic and hypertensive patients.

Table 2. Conventional echocardiographic variables in patients and controls.

Parameters	*Diabetes mellitus*	*Diabetes mellitus with hypertension*	*Controls*
LV end-diastolic diameter (mm)	49.6 ± 5.2	50.8 ± 5.1*	46.1 ± 5.2
LV end-systolic diameter (mm)	31.3 ± 5.3	32.9 ± 5.0*	28.5 ± 4.0
Septal wall thickness (mm)	10.1 ± 1.5†	11.1 ± 4.3*	9.2 ± 1.5
Posterior wall thickness (mm)	10.4 ±1.0 *	10.3 ± 1.0*	9.1 ± 1.6
Relative wall thickness	0.42 ± 0.06	0.43 ± 0.06	0.40 ± 0.07
LV mass index (g/m^2)	116.5 ± 25.3*	130.2 ± 22.3*	91.9± 23.1
LV fractional shortening (%)	36.5 ± 8.4	35.3 ± 6.3	38.8 ± 5.2
Ejection fraction (%)	63.7 ± 5.6	62.7 ± 6.4	64.3 ± 3.7
LV end-diastolic volume (ml)	96.2 ± 21.6	104.8 ± 24.1	97.3 ± 22.3
LV end-systolic volume (ml)	37.7 ± 11.1	44.0 ± 16.1	36.1 ± 12.0

Data are means ± SD; *$p< 0.01$ vs controls, †$p< 0.05$ vs diabetic and hypertensive patients. LV = left ventricle

Table 3. Myocardial Performance Index and Doppler time intervals.

Parameters	*Diabetes mellitus*	*Diabetes mellitus with hypertension*	*Controls*
LV MPI	0.49 ± 0.10*	0.49 ± 0.12*	0.39 ± 0.10
LV ICT (ms)	58.9 ± 22.5	60.0 ± 23.6	49.9 ± 11.1
LV IRT (ms)	77.9 ± 24.3†	79.7± 33.0†	62.4 ± 13.9
LV ET (ms)	281.4 ± 23.1	284.9 ± 24.8	295.5 ± 30.0
E-wave deceleration time (ms)	181.6 ± 50.8*	190.3 ± 59.2*	139.1 ± 16.5
E_{pv} (cm/s)	66.6 ± 8.8§	71.4 ± 10.8	76.2 ± 15.6
E_{tvi} (cm)	9.1 ± 1.7	9.2 ± 2.6	10.0 ± 2.0
A_{pv} (cm/s)	69.6 ± 13.4*	75.7 ± 13.9*	56.9 ± 13.4
A_{tvi} (cm)	6.3 ± 2.0	6.9 ± 1.9†	5.4 ± 2.2
E_{pv}/A_{pv} (cm/s)	0.98 ± 0.20*	0.96 ± 0.18*	1.38 ± 0.33
E_{tvi}/A_{tvi} (cm)	1.55 ± 0.45†	1.40 ± 0.46*	2.03 ± 0.60

Data are expressed as a mean value ± SD, $^{*}p< 0.01$ vs controls, $^{\dagger}p<0.03$ vs controls; $^{\S}p<0.05$ vs controls. MPI, myocardial performance index; IRT, isovolumic relaxation time; ICT, isovolumic contraction time; ET, ejection time; E, early diastolic filling wave; A, atrial contraction wave; pv, peak velocity; tvi, time velocity integral.

RESULTS

Baseline Characteristics

The main features of the studied population are shown in Table 1. There were no differences in the diabetes treatment, diabetes duration, BMI, systolic and diastolic blood pressure and resting heart rate comparing the two groups of diabetic patients. HbA_{1c} was superimposable in the two groups of diabetic patients whereas fasting blood glucose was higher in diabetic-normotensive patients compared with diabetic-hypertensive patients (Table 1).

Standard Echocardiographic Parameters

The echocardiographic characteristics of the three study groups are listed in Table 2. Briefly, LV diameters, volumes, ejection fraction, fractional shortening and wall thicknesses were superimposable in both diabetic groups but were significantly different when compared with normal subjects.

The diastolic function, evaluated as the E/A ratios mean, and the DT were comparable between diabetic normotensive and hypertensive patients but were significantly different when compared to normal subjects, although within the normal range (Table 3). The prevalence of abnormal diastolic filling was equal in the diabetic hypertensive patients (7 patients with impaired relaxation) and diabetic normotensive patients (6 patients with impaired relaxation).

Doppler Measurements

MPI was significantly higher in both diabetic groups compared with controls (Table 3). This was primarily due to a significant prolongation of IRT. The MPI was comparable in the two diabetic independently of the diastolic dysfunction. MPI significantly correlated to HbA1c in all patients ($r = 0.37$, $p< 0.01$) (Figure 2). In particular HbA_{1c} was directly correlated with ICT ($r = 0.29$, $p< 0.05$) and inversely with ET ($r = - 0.29$, $p< 0.05$). No correlations were found between some clinical (diabetes duration, systolic and diastolic blood pressure, patients age) and echocardiographic

parameters (LV mass index, wall thickness, age, systolic and diastolic blood pressure, LV ejection fraction or fractional shortening, E/A ratios and DT were found.

Figure 1.

Measurements of the time intervals of the flow Doppler Myocardial Performance Index (MPI). The interval "a" is measured from the end to the onset of mitral inflow waveforms; the interval "b" is the left ventricular outflow velocity tracing (ET). The MPI was calculated as (a – b) / b.

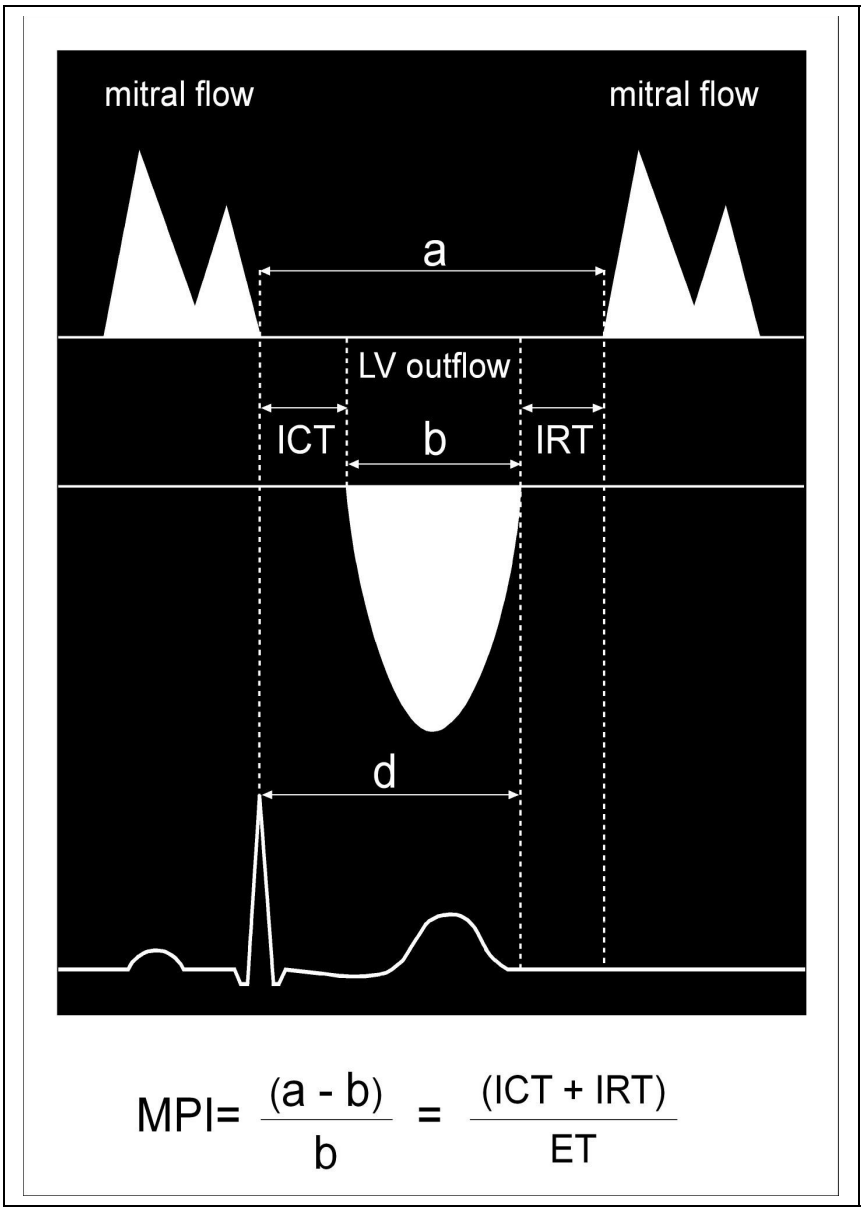
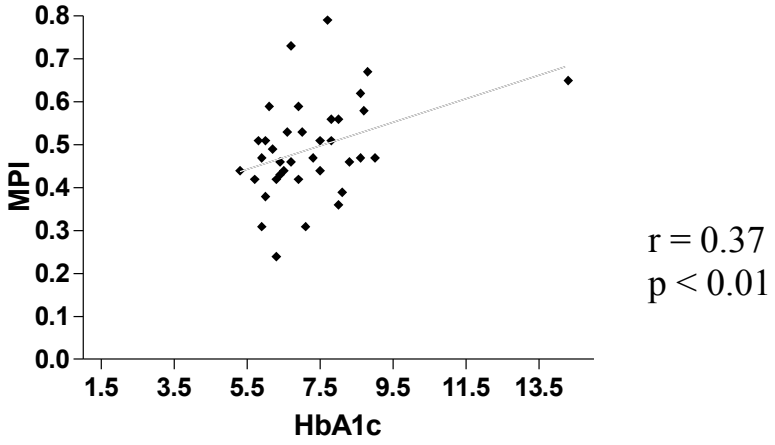


Figure 2.

Relationship between Myocardial Performance Index and glycated haemoglobin A1c in all diabetic patients.



DISCUSSION

To our knowledge this is the first study that identify the earliest abnormalities of cardiac performance at echocardiography in a homogeneous group of uncomplicated asymptomatic type 2 diabetic patients with very short duration of disease with or without hypertension. In our diabetic patients the E/A ratios were lower than in controls, although within normal limits. The MPI was comparable between the two diabetic groups independently of the diastolic function. The MPI increase was mainly due to a prolongation of IRT. Our data show that the global myocardial performance dysfunction may precede the diastolic dysfunction, representing the earliest echocardiographic evidence of diabetic cardiomyopathy. The mechanisms behind LV performance dysfunction in our patients remains largely unknown. As the patients were normotensive and free of ischaemic heart disease, it is likely that metabolic abnormalities may play a major role. We found a relation between myocardial performance index and HbA_{1c} in type 2 diabetic patients (Figure 2), suggesting that metabolic control may contribute to the pathogenesis of cardiac dysfunction. There is experimental evidence that short-term hyperglycaemia is able to alter cardiomyocite contraction and relaxation (19). In addition, in human some data indicate that the diabetic milieu, i. e. hyperglycaemia and insulin resistance, is able to induce functional and structural changes of cardiomyocites, which lead to progressive deterioration of regional and global myocardial dynamics (20).

Our findings may have important clinical implications to the early identification of subclinical myocardial performance abnormalities with normal cardiac function with conventional echocardiography. First, this index could provide an easy approach to detect an earliest phase of diabetic cardiomyopathy that precede diastolic dysfunction, and to monitor the natural history of the diabetic disease. Second, MPI could be useful for indirectly assess the metabolic control or suggest an early start of specific pharmacological treatments that may help the clinical course of diabetic cardiomyopathy. Most importantly, whether such abnormalities may be reverted by optimal

metabolic control and/or pharmacologic treatments could be determined. Diagnosing pre-clinical diabetic cardiomyopathy early through MPI is not only important but also may turn out to be essential for the appropriate clinical testing of new therapeutic approaches to diabetic disease.

Several reports have attempt to determine the prevalence of LV diastolic dysfunction in middle-aged asymptomatic subjects with type 2 diabetes (21-23). However, these studies, which used Doppler assessment of transmitral flow velocity, could have underestimated the prevalence of LV diastolic dysfunction (21-23), because they neglected to account for pseudonormal patterns of ventricular filling, which are often noted in the evaluation of LV diastolic function (24).

A study limitation is represented by the patients sample, which is limited in size. In addition, the diabetes therapy was different in the two groups of patients although according the guidelines. No outcome data are available at the moment.

In conclusion, subtle abnormalities of LV myocardial performance are detected by means of MPI during the early stage of type 2 diabetes, independently of the hypertension presence, and it broadens the spectrum of preclinical diabetic cardiomyopathy. A correlation between MPI and the HbA_{1c} value, was found indicating its role as an early marker of metabolic control, supporting the use of this index in the initial clinical evaluation and in follow-up of subjects with type 2 diabetes mellitus.

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CHAPTER 3

EVALUATION OF THE MYOCARDIAL PERFORMANCE INDEX FOR EARLY DETECTION OF MITOXANTRONE-INDUCED CARDIOTOXICITY IN PATIENTS WITH MULTIPLE SCLEROSIS

Source: **P Pattoneri,** G Pelà, E Montanari, I Pesci, P Moruzzi, A Borghetti. ***Eur J Echocardiogr 2007***. ***Adapted***

ABSTRACT

Aims. Multiple sclerosis is the most common cause of neurological disability in young adults. Mitoxantrone is a synthetic anthracenedione, recently approved for the treatment of worsening multiple sclerosis, which is known to induce cardiotoxicity. This study was designed to evaluate the early alterations in left ventricular function in patients with multiple sclerosis receiving mitoxantrone, by the use of the myocardial performance index, a new parameter of global (systolic and diastolic) ventricular function.

Methods and Results. The study included 29 caucasian patients with multiple sclerosis (mean age 41.8 ± 9.3 years, 12 males and 17 females) treated with mitoxantrone (mean cumulative dose 30.8 ± 18.2 mg/m^2) compared to 28 healthy subjects (mean age 37.8 ± 11.8 years, 13 males and 15 females). Both groups underwent a complete two-dimensional and Doppler-echocardiography including assessment of the mitral inflow and left ventricular outflow patterns for estimation of the Doppler-derived Myocardial Performance Index. This parameter is defined as the sum of isovolumic contraction time and isovolumic relaxation time, divided by ventricular ejection time.

No differences were observed in blood pressure, heart rate, left ventricular diameters, mass and ejection fraction in multiple sclerosis patients compared to the controls. The mitral flow pattern showed a significant decrease of E wave calculated as peak velocity (E_{pv}) (63.3 ± 13.4 vs 77.2 ± 17.2, $p< 0.002$) and time velocity integral (E_{tvi}) (8.8 ± 1.9 vs 10.3 ± 2.4, $p < 0.02$), with a significant decrease of E_{pv}/A_{pv} ratio and a non significant decrease of E_{tvi}/A_{tvi} ratio in the patients. In addition, E-wave deceleration time was significantly increased in multiple sclerosis patients compared to controls (178.2 ± 30.2 vs 137.9 ± 14.7, $p < 0.0001$). The mean value of myocardial performance index was 0.55 ± 0.1 in patients compared to 0.37 ± 0.06 in the controls ($p < 0.0001$). A significant correlation between the given cumulative dose of mitoxantrone and myocardial performance index ($r = 0.67$, $p < 0.001$) and E-wave deceleration time ($r = 0.45$, $p < 0.001$) respectively were demonstrated.

Conclusion. The myocardial performance index represent a parameter of combined systolic and diastolic myocardial performance strongly correlated with the given cumulative dose of mitoxantrone. The myocardial performance index may be an adjunctive parameter to the conventional echocardiography for detecting sub-clinical cardiotoxicity of mitoxantrone in the clinical management of the multiple sclerosis patients.

INTRODUCTION

Multiple sclerosis (MS) is a neurological disorder that typically results in significant disability and has a negative impact on the patient's quality of life. Treatment options, recently approved by the FDA, specifically target the inflammatory phase of MS and include immunomodulators and an immunosuppressant, mitoxantrone. Mitoxantrone hydrochloride is an anthracenedione that has been used as one of the latest in a long line of general immunosuppressive agents studied in worsening MS. Although there is increasing evidence for the beneficial effects of mitoxantrone in the treatment of patients with MS, there is controversy concerning the potential cardiotoxicity effects of this therapy (1, 2). The potential for myocardial damage resulting in congestive heart failure is the factor limiting the total dose in MS patients. The risk for chronic cardiomyopathy limits the approved cumulative dose of mitoxantrone for treatment of worsening MS to 140 mg/m2. The drug is taken up by myocardial cells, in which it chelates with iron and forms complexes. Cardiomyopathy is thought to result from intracellular generation of reactive oxygen intermediates via iron or enzyme-mediated oxidation–reduction reactions. Cardiac myocytes appear to be selectively susceptible to mitoxantrone-induced damage due to their relative lack of defence mechanisms such as catalase and superoxide dismutase (3, 4).

A relatively new Doppler-derived index, able to assess the global left ventricular function including components from both systole and diastole, was proposed by Tei and co-workers (5, 6). This myocardial performance index (MPI, also denoted the TEI-Doppler index), which is defined as the sum of isovolumic contraction time and isovolumic relaxation time divided by the ejection time, was reported to be simple, noninvasive, reproducible and independent of the heart rate and blood pressure (5). The MPI has been shown to have significant clinical utility. It is prolonged in many cardiac diseases even in the absence of clinical signs. Studies have demonstrated that MPI correlates well with invasive measures of both systolic and diastolic function in adults (7) and provides prognostic information about morbidity and mortality in patients with ischemic heart disease (8), cardiac amyloidosis (9), dilated cardiomyopathy (10) and primary pulmonary

hypertension (11). The aim of the present study was to investigate whether conventional 2-dimensional and Doppler echocardiography can detect early alterations in left ventricular function induced by mitoxantrone therapy, and in particular, whether MPI can contribute to the assessment of subtle changes of myocardial function.

SUBJECTS AND METHODS

Subjects

We examined 29 caucasian patients (12 males and 17 females, mean age 41.8 ± 9.8, range 24 – 58 years), 12 with relapsing–remitting MS and 17 with secondary progressive MS, treated whit mitoxantrone in the Operative Unit of Neurology, Hospital of Fidenza, during the period from September 2004 to June 2005.

A control group of 28 healthy subjects, matched for age and gender were considered. All subjects enrolled in the study underwent a 12-lead standard electrocardiogram, a clinical examination and blood pressure evaluation before the echocardiogram. Nobody subject was smoker and had a history of arterial hypertension, heart disease or clinical symptoms of heart failure. The comparison of both groups is summarized in Table 1.

Echocardiography

An experienced sonographer examined the subjects in the left lateral decubitus position utilizing Acuson Sequoia (Acuson Corp., Mountain View, California) ultrasound imaging systems, equipped with a multi-hertz sector probe (2-4 MHz).

The systolic and diastolic thickness of the septum and posterior wall, systolic and diastolic left ventricle short-axis dimensions were measured according to the Penn-convention in the parasternal view (12). Left ventricular mass was calculated using the Penn-convention and indexed to the body surface area (12). Left ventricle end-diastolic and end-systolic volume as well as the ejection fraction were calculated according to the biplane Simpson's rule. Endocardial border detection was enhanced by use of Coded second harmonic imaging (13).

The blood flow across the mitral valve was monitored by the pulse-Doppler technique in the apical 4-chamber view. The sample volume of 3-5 mm was placed at the tip of the valve leaflets with the Doppler beam aligned perpendicular to the plane of the mitral annulus. The blood flow profile

contains a diastolic early filling (E) wave and atrial contraction (A) wave in diastole. For each wave the peak velocity and its time integral were measured. In the text and table 3, peak velocities and time velocity integrals are often abbreviated with the *pv and tvi* subscripts, respectively (e.g. E_{pv}, A_{tvi}).

Deceleration time was measured as the time from E-wave peak velocity to the intercept of the deceleration of flow with the baseline (14).

Doppler time intervals were measured from mitral inflow and left ventricle outflow Doppler tracings, as described by Tei et al (5). Specific time intervals measured to derive MPI are shown in Figure 1. MPI is defined as the sum of isovolumic contraction time (ICT) and isovolumic relaxation time (IRT) divided by ventricular ejection time (ET). To obtain the sum of ICT and IRT, the left ventricular ET (interval "*b*"), measured from the apical 5-chamber view in the left ventricle outflow tract, was subtracted from the interval from cessation to onset of mitral valve inflow (interval "*a*") obtained from the apical 4-chamber view. This difference was then divided by the ET to derive the MPI. IRT was measured by subtracting the interval *d,* between the R wave and cessation of left ventricle outflow, from the interval *c,* between the R wave and the onset of mitral inflow. ICT was calculated by subtracting the IRT from *a-b* interval. Three consecutive beats were measured and averaged for each parameter. Twenty random Doppler recordings were analyzed to determine the inter and intra-observer variability in measurement of MPI. The mean inter-observer difference in the measurement of MPI was 3.9%, whereas the mean intra-observer variability was 3.2%.

Statistics

Data were expressed as mean ± standard deviation. The statistical analysis was based on the paired two-tailed Student's t test. The relationship between parameters were evaluated by means of Linear regression data analysis. Values were considered significantly different at P value < 0.05. We used the statistical program Microsoft Excel Win Office XP for the purpose of statistical data analysis.

Table 1. Clinical data.

Parameters	Patients	Controls
Number	29	28
Age (years)	41.8 ± 9.3	37.8 ± 11.8
Sex (male/female)	12/17	13/15
Body surface area (m^2)	1.77 ± 0.3	1.78 ± 0.2
Body mass index (Kg/ m^2)	23.3 ± 3.9	22.9 ± 1.6
Mitoxantrone cumulative dosage (mg/m^2)	30.8 ± 18.2	0
Heart rate (beats/min)	70.5 ± 10.5	68.4 ± 10.3
Systolic blood pressure (mmHg)	116.2 ± 9.7	122.1 ± 14.1
Diastolic blood pressure (mmHg)	75.3 ± 7.2	75.4 ± 7.2

Data are expressed as a mean value ± SD (p = NS for all comparisons).

Table 2. Comparison of basic echocardiographic parameters between controls and patients.

Parameters	Patients	Controls	Significance
LV end-diastolic diameter (mm)	44.6 ± 4.1	46.7 ± 4.9	NS
LV end-systolic diameter (mm)	28.3 ± 4.0	28.9 ± 3.9	NS
Septal wall thickness (mm)	8.9 ± 1.3	8.9 ± 1.5	NS
Posterior wall thickness (mm)	9.1 ± 1.2	8.8 ± 1.6	NS
LV fractional shortening (%)	36.9 ± 6.2	38.4 ± 5.3	NS
Ejection fraction (%)	62.4 ± 3.92	64.1 ± 4.4	NS
LV mass index (g/m^2)	92.6 ± 18.3	96.7 ± 20.5	NS
Relative wall thickness	0.40 ± 0.05	0.38 ± 0.07	NS

LV, left ventricle;
Data are expressed as a mean value ± SD.

Table 3. Summary of Doppler Time intervals and mitral flow patterns.

Parameters	Patients	Controls	Significance
LV MPI	0.55 ± 0.1	0.37 ± 0.06	p < 0.0001
LV ICT (ms)	65.6 ± 11.8	47.2 ± 6.5	p < 0.0001
LV IRT (ms)	82.0 ± 14.7	59.2 ± 8.2	p < 0.0001
LV ET (ms)	267.0 ± 20.6	288.0 ± 30.0	p < 0.004
ICT/ET	0.25 ± 0.04	0.16 ± 0,03	p < 0.0001
IRT/ET	0,31 ± 0.05	0.21 ± 0,04	p < 0.0001
E-wave deceleration time (ms)	178.2 ± 30.2	137.9 ± 14.7	p < 0.0001
E_{pv} (cm/sec)	63.3 ± 13.4	77.2 ± 17.2	p < 0.002
E_{tvi} (cm)	8.8 ± 1.9	10.3 ± 2.4	p < 0.02
A_{pv} (cm/sec)	56.6 ± 14.0	56.5 ± 13.2	NS
A_{tvi} (cm)	5.4 ± 1.6	5.4 ± 2.2	NS
E_{pv}/A_{pv} (cm/sec)	1.17 ± 0.33	1.41 ± 0.36	P < 0.02
E_{tvi}/A_{tvi} (cm)	1.75 ± 0.57	2.07 ± 0.60	NS

LV, left ventricle; *MPI*, myocardial performance index; *IRT*, isovolumic relaxation time; *ICT*, isovolumic contraction time; *ET*, ejection time; *E*, early diastolic filling wave; *A*, atrial contraction wave; *PV*, peak velocity; *TVI*, time velocity integral.
Data are expressed as a mean value ± SD.

RESULTS

Baseline Characteristics of Patients

As table 1 shows, MS patients and controls did not differ significantly with respect to age, body surface area (BSA), body mass index (BMI), heart rate and systolic and diastolic blood pressure. ECG tracings did not indicate any pathological pattern in all subjects. The MS patients received a mean cumulative dose of mitoxantrone of 30.81 ± 18.17 mg/m^2 (range 3 – 68 mg/m^2).

Standard Echocardiography Study

In terms of basic echocardiography no significant differences were observed in the cavity dimensions of left ventricle. The thickness of septum and posterior wall as well as the relative wall thickness and LVM/BSA were similar in MS patients and controls. The left ventricular systolic function, evaluated as ejection fraction (range from 55 to 70 %) and fractional of shortening, were superimposable in the two groups (Table 2). In 7 patients a mild mitral insufficiency was detected whilst in 4 a slightest aortic insufficiency was found. In the control group, a mild mitral insufficiency was found in 3 subjects.

Doppler Measurements

The left ventricular diastolic function, assessed by mitral inflow, showed a significant decrease of E_{pv} and E_{tvi}, with a significant decrease of the E_{pv}/A_{pv} ratio and a non significant decrease of E_{tvi}/A_{tvi} ratio (Table 3). However, all these parameters were within the normal limits in both groups. The E-wave deceleration time was significantly increased in MS patients compared to controls (Table 3).

MPI was easily obtained in all study subjects. MPI was significantly increased in MS patients treated with mitoxantrone (0.55 ± 0,1 vs 0.37 ± 0.06). This was due to a significant prolongation of IRT and ICT and a shortening of the ET in MS group (Table 3).

Correlations

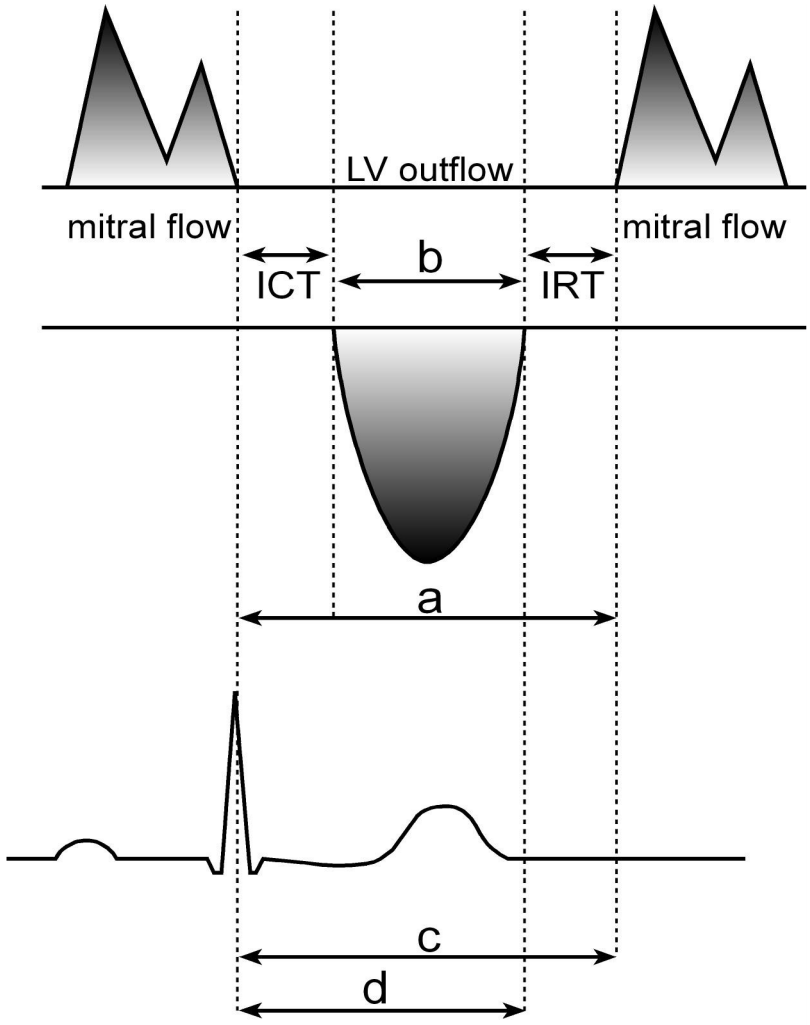
In all patients MPI significantly correlated to the cumulative dose of mitoxantrone ($r = 0.67$, $p < 0.001$) (Figure 2, top left) and with E-wave deceleration time ($r = 0.39$, $p < 0.01$) (Figure 2, top

right). In addition, a significant correlation was found between E-wave deceleration time and cumulative dose of mitoxantrone ($r = 0.45$, $p < 0.001$) (Figure 2, bottom right) and IRT and cumulative dose of mitoxantrone ($r = 0.70$, $p < 0.001$) (Figure 2, bottom left).

MPI correlated inversely with E_{pv} ($r = -0.42$, $p < 0.001$) and E_{tvi} ($r = -0.34$, $p < 0.05$). No significant correlation was detected between MPI and E_{pv}/A_{pv} and E_{tvi}/A_{tvi} ratios. MPI did not correlate with age, BSA, heart rate, blood pressure and the systolic function parameters.

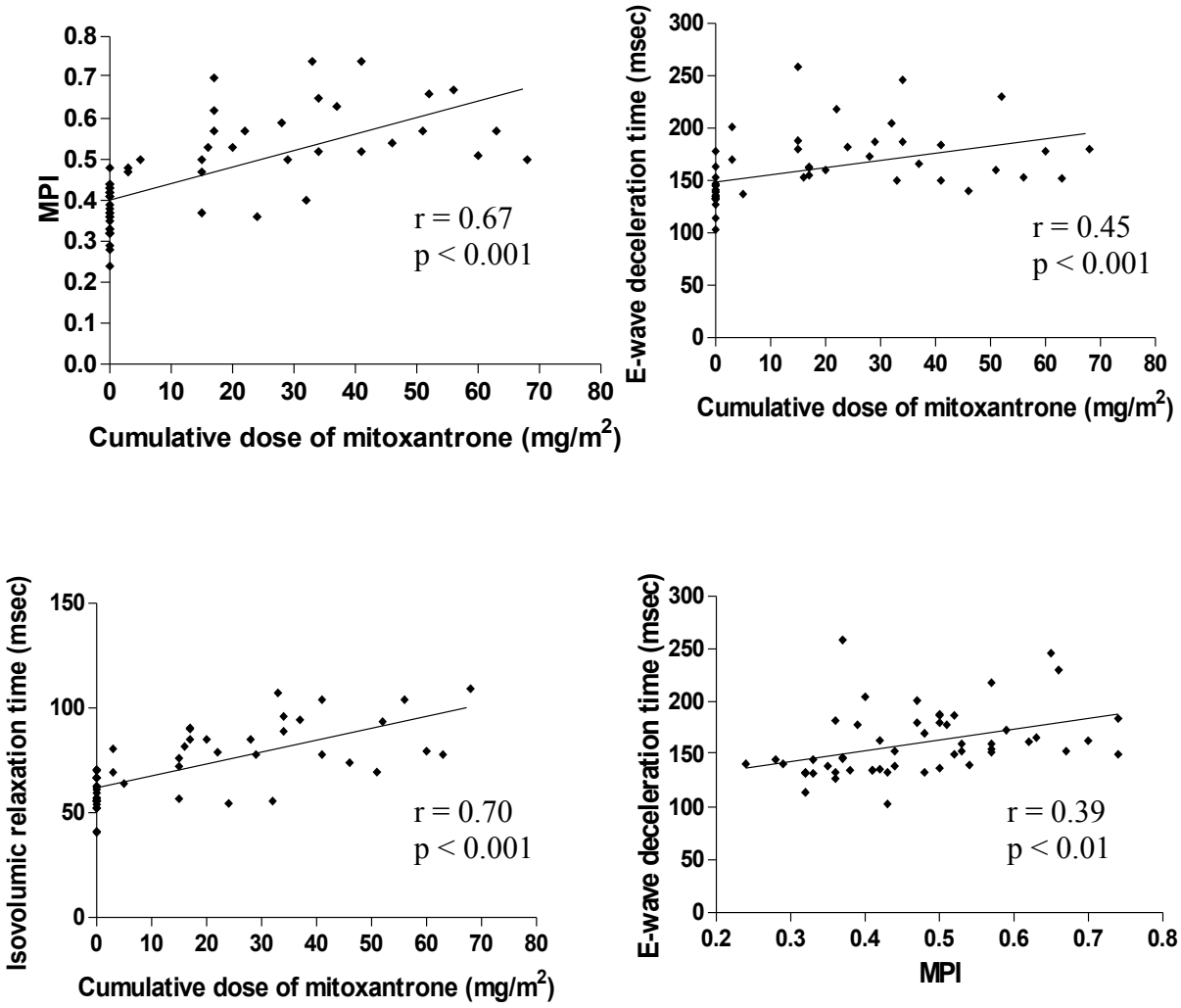
Figure 1.

Schema for measurements of Doppler time intervals. The index is derived as (*a-b/b*), where *a* is the interval between cessation and onset of the mitral inflow, and *b* is the ejection time (ET) of left ventricular outflow.



$$MPI = \frac{(a - b)}{b} = \frac{(ICT + IRT)}{ET}$$

Figure 2



Relations between MPI and cumulative dose of mitoxantrone (top panel), E-wave deceleration time and cumulative dose of mitoxantrone (middle panel) and E-wave deceleration time and MPI (bottom panel).

DISCUSSION

Few systematic echocardiographic reports are available in patients with MS receiving mitoxantrone. Some studies suggest no adverse cardiac effects, but others have documented a decrease in the left ventricular systolic function estimated by either shortening fraction or ejection fraction in patients receiving mitoxantrone (15, 16). In a previous paper Spindler and co-workers found that all the echo parameters of systolic and diastolic performance (E/A-ratio, isovolumic relaxation time, and E-wave deceleration time) were not different in fifteen multiple sclerosis patients treated with mitoxantrone compared with 15 matched control multiple sclerosis patients (17). On the other hand, a number of studies have shown that the diastolic parameters of left ventricular function were affected before systolic indexes (18, 19, 20, 21). The risk for myocardial toxicity increases with cumulative doses >100 mg/m^2, and the total approved dose for use in worsening MS is 140 mg/m^2. Consequently, cardiac function monitoring is required periodically and is recommended before every infusion once a cumulative dose of 100 mg/m^2 has been reached. In spite of the fact that the incidence of early cardiotoxicity when the doses of mitoxantrone are under 100 mg/m^2 is small, there is the problem of subclinical consequences of this treatment. There is a growing interest in detecting the early signs of left ventricular damage. In this study we tested if MPI was able to identify an initial myocardial involvement in a group of MS patients treated with low cumulative dose of mitoxantrone which were asymptomatic for cardiac disease. In one preliminary study, MPI appeared to be a more sensitive noninvasive parameter for detecting subclinical left ventricle dysfunction than current standard echocardiographic measurements (22). Our data support these suggestions. In the current investigation, we report for the first time that a significant increases in the left ventricular MPI occurred before changes in other conventional echocardiographic measures of left ventricular function in MS patients receiving mitoxantrone, and we proved the good correlation between this index and the given cumulative dose of mitoxantrone. These changes occurred at mean cumulative dosages as low as 40 mg/m^2. Our data agree with previously

mentioned studies that demonstrated left ventricular diastolic function to be mainly impaired before systolic function after mitoxantrone therapy. In fact, we have found an impaired left ventricular relaxation characterized by an increase of the isovolumic relaxation time and the deceleration time and decreasing of E_{pv} and E_{tvi}, with a significant decrease of the E_{pv}/A_{pv} ratio, when compared with the control group. Besides, we have found a significant increase of ICT in MS patients, but without significant correlations with echocardiographic conventional indexes of systolic function.

Our study had several limitations. For the evaluation of diastolic function only the mitral valve inflow parameters were determined. The mitral valve inflow represent the cornerstone of the conventional echocardiographic assessment of diastolic function but is now clear that it is indeed limited. Besides, our study was observational. Longitudinal follow-up of these patients is essential to define outcomes. Future research could evaluate if MPI can be used to monitoring the impact of treatment in MS patients receiving mitoxantrone.

In conclusion, MPI appears to be a sensitive noninvasive technique for detecting significant subclinical left ventricular dysfunction, occurred at a substantially low dose of mitoxantrone, than current standard echocardiographic measurements. We expect that MPI may be an adjunctive parameter to the conventional echocardiography for detecting sub-clinical cardiotoxicity of mitoxantrone.

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PRELIMINARY STUDIES - 1

BI-VENTRICULAR MYOCARDIAL PERFORMANCE: A NEW APPROACH TO EVALUATE INTERVENTRICULAR DELAY

Source: **P Pattoneri**, E Cassinerio,S Ariotti, G Pelà, A Borghetti, MD Cappellini MD. ***SIC 2008.***

Background. Patients with idiopathic or ischemic dilated cardiomyopathy frequently exhibit prolongation of the QRS complex associated with disease progression and impaired prognosis. The delayed ventricular activation leads to asynchronous ventricular contraction with negative effects on left ventricular systolic and diastolic performance. There is not consensus about the best approach and ultrasound parameters for estimate the myocardial dyssynchrony and for selecting candidates to cardiac resynchronization therapy (CRT), and electrocardiogram representation of abnormal cardiac conduction still remains as the main criterion in guidelines. A relatively new Doppler-derived index, the Myocardial Performance Index (MPI), able to assess the global left ventricular function including components from both systole and diastole, was proposed by Tei and co-workers. The MPI has been shown to have significant clinical utility. Studies have demonstrated that MPI correlates well with invasive measures of both systolic and diastolic function in adults and provides prognostic information about morbidity and mortality in patients with ischemic heart disease, cardiac amyloidosis, dilated cardiomyopathy and primary pulmonary hypertension. We sought to evaluate whether the MPI, calculated as ratio between left and right ventricle (LV, RV), represent an early marker of interventricular delay.

Methods. The study included 20 male patients (mean age 66.7 ± 14.3) with NYHA functional class II and III, chronic heart failure of any origin who had been taking optimal drug therapy for at least three months. All patients underwent a clinical examination, 12-lead electrocardiogram and a complete two-dimensional and Tissue Doppler Echocardiography (TDE), including assessment of the isovolumetric Doppler time intervals for the estimation of the Doppler-derived MPI, both in LV and RV.

Results. Strong correlations were found between LV-RV and QRS duration ($r = 0.73$, $p < 0.001$), with NYHA functional class ($r = 0.70$, $p < 0.001$), with Pitzalis Index ($r = 0.65$, $p < 0.01$), and with conventional echocardiographic parameters as the LV end-diastolic diameter ($r = 0.55$, $p < 0.01$), the LV end-diastolic volume ($r = 0.49$, $p < 0.01$) and with LV ejection fraction ($r = -0.66$, $p < 0.001$).

Conclusion. MPI calculated as ratio between LV and RV, seems to be a sensible marker able to identify interventricular myocardial dyssynchrony. A longitudinal follow-up and future studies could explain if this Doppler-time-difference represents a prognostic marker and an useful index for select patient responders to CRT before the procedure.

PRELIMINARY STUDIES - 2

EVALUATION OF MITOXANTRONE-INDUCED CARDIOTOXICITY IN PATIENTS WITH MULTIPLE SCLEROSIS: PROGNOSTIC VALUE OF THE MYOCARDIAL PERFORMANCE INDEX

Source: **P Pattoneri**, G Pelà, E Montanari, I Pesci, M Goldoni, P Moruzzi , A Borghetti, MD, Cappellini. ***SIC 2008.***

Aim. This study sought to investigate the ability of the Doppler-derived myocardial performance index (MPI) to predict cardiotoxicity in patients with multiple sclerosis (MS) under mitoxantrone therapy.

Methods. We prospectively evaluated 20 caucasian patients with MS (mean age 41 ± 9 years, 11 males and 9 females) treated with low-dose of mitoxantrone (basal mean cumulative dose 20 ± 14 mg/m^2, end of follow-up mean dose 41 ± 17 mg/m^2). All patients underwent two-dimensional and Doppler-echocardiography at baseline and after a mean follow-up of 19 ± 11 months. Doppler-derived MPI was estimated using mitral inflow and left ventricular (LV) outflow pattern.

Results. Comparing data at baseline and at the end of follow-up a significant decrease in ejection fraction was observed (60.2 ± 4.7 vs 56.3 ± 4.3, $p < 0.03$). The mean value of MPI was 0.52 ± 0.1 at baseline and 0.60 ± 0.1 at the end of follow-up ($p < 0.04$). Such difference was mainly due to a isovolumic relaxation time prolongation (80.0 ± 21.5 at baseline and 97.7 ± 30.0 at the end of follow-up, $p = 0.07$). The area under the receiver operating characteristic curve, calculated for a MPI cut point value of 0.57, in identifying a significant reduction of LV ejection fraction ≤50% was 0.94 with sensitivity and specificity of 97.5% and 90% respectively. MPI was significantly related to relative wall thickness ($r=0.45$, $p<0.05$) and to cumulative dose of mitoxantrone ($r=0.43$, $p<0.05$).

Conclusion. In conclusion MPI appear to be able to predict cardiotoxicity secondary to mitoxantrone therapy in MS patients.

PRELIMINARY STUDIES - 3

EVALUATION OF THE LEFT VENTRICULAR MYOCARDIAL PERFORMANCE IN NORMOTENSIVE OFFSPRING OF HYPERTENSIVE PARENTS

Source: **P Pattoneri**, Cassinerio E, Ariotti S, Pelà G, Borghetti A, Cappellini MD. ***SIC 2008***.

Background. Offspring of hypertensive parents are at increased risk of developing hypertension. Abnormalities of the left ventricular morphology and function may occur very early in development of essential hypertension and even in the pre-hypertensive period.

This study was designed to evaluate the influence of genetic predisposition to essential hypertension on left ventricular function by the use of myocardial performance index (MPI), a relatively new parameter of global (systolic and diastolic) function.

Methods. The study included 15 healthy normotensive male subjects, (mean age 28 ± 5 years), of normal weight, offspring of hypertensive parents (HY+); HY+ were compared to 10 aged-matched normotensive subjects without any family history of hypertension (HY-). All subjects were sedentary and none of them received pharmacological treatment and was smoker. All subjects underwent a conventional Doppler Echocardiography including the assessment of MPI defined as the sum of isovolumic contraction time and isovolumic relaxation time, divided by ventricular ejection time. Doppler Tissue Echocardiography (DTE) was also applied at the mitral and tricuspid annulus, at the lateral site, to evaluate the systolic and diastolic function of both ventricles. **Results.** HY+ showed a significant increase in the office blood pressure (BP) with statistical significance in diastolic BP (85 ± 9.2 vs 71.7 ± 2.9 mmHg; $p<0.02$). A tendency to an increase in the relative wall thickness (RWT) was observed in HY+ compared to HY- (0.37 ± 0.04 vs 0.31 ± 0.02; $p=0.05$) whilst the left ventricular mass was unchanged (84.3 ± 13.8 vs 80.1 ± 6.6 gr/m^2; p= NS). Systolic and diastolic function, assessed by conventional and DTE parameters in both ventricles, were superimposable in the two groups**.** The MPI was higher in HY+ subjects compared to controls (0.48 ± 0.10 vs 0.41 ± 0.04; p= NS), mainly due to significant prolongation of isovolumic contraction time (61.9 ± 9.2 vs 51.0 ± 10.0; $p<0.04$). The index was significantly correlated to RWT ($r=0.44$, $p<0.05$).

Conclusion. In conclusion this study showed that offspring of hypertensive parents have an higher clinical BP associated to a tendency to left ventricular concentric remodelling and a different myocardial performance. MPI seems attractive and useful to identify those subjects with genetic

predisposition to future hypertension who develop early morphological and functional changes of the cardiovascular system.

CONCLUSION

Myocardial performance index (MPI) is a numeric value calculated as the sum of the isovolumic relaxation time (IRT) and isovolumic contraction time (ICT) divided by the left ventricular (LV) ejection time (LVET), has been utilized as a combined systolic-diastolic index and could be calculated for each ventricle individually. MPI has prognostic value in patients with dilated cardiomyopathy (1) and post myocardial infarction (2) and in various clinical settings. In the original description of this index in patients with normal LV function and dilated cardiomyopathy, MPI was correlated with indices of systolic performance and contractility but was unrelated to heart rate, preload, LV geometry and mean arterial pressure (3). It has been further demonstrated that contractility and systolic performance were related to MPI in studies which utilize dobutamine in the normal left ventricle (4, 5), in the left ventricle with reduced LV function (6, 7) with contractile reserve, with the ischemic production of LV dysfunction (8), or in groups with differing LV function (1, 3). Of importance, dobutamine was demonstrated to shorten all components of MPI but specifically ICT and prolonged the diastolic filling period both in the normal ventricle (5) and in the left ventricle with dysfunction and contractile reserve (6, 7). Systematic evaluations of MPI in the normal and abnormal left ventricle have recently been performed using a canine model of chronic ischemic LV dysfunction. MPI was demonstrated to be preload and afterload dependent but not heart rate dependent (9, 10). In this model, improved systolic performance with afterload reduction with LV dysfunction was associated with shortening of the isovolumic indices and lengthening of the LVET (11). Although clinical studies (6, 7) have been performed assessing the effect of dobutamine stress on MPI with LV dysfunction, the focus has been on ischemia or contractile reserve. Limited work has been performed assessing the effect of contractility on MPI and its components with LV dysfunction without the obfuscating effects of intraventricular conduction delay or ischemic provocation (6, 7). MPI has been identified as a useful prognostic parameter following acute myocardial (2, 11, 12) infarction, with dilated cardiomyopathy (1), amyloid heart disease (13), and pulmonary hypertension (14). Its prognostic capabilities appear to be mediated by

increased values due to longer isovolumic indices and a lower LVET. In this thesis, clinical applications of MPI are scrutinized.

In the first study, we demonstrated that LV geometry represents an important determinant of the myocardial performance. In fact, our data demonstrates a correlation between MPI and RWT but not with LVM/BSA. The MPI geometry-dependence must be taken into consideration during the application of the Index for the evaluation of myocardial performance, and when used as a prognostic marker in cardiac disease where the LV geometry could be modified.

In the second study the MPI has been confirmed able to identify the earliest abnormalities of cardiac performance at echocardiography in a homogeneous group of uncomplicated asymptomatic type 2 diabetic patients with very short duration of disease with or without hypertension. The MPI increase was mainly due to a prolongation of IRT. A correlation between MPI and the HbA_{1c} value, was found indicating its role as an early marker of metabolic control. Our findings may have important clinical implications. First, this index could provide an easy approach to detect an earliest phase of diabetic cardiomyopathy that precede diastolic dysfunction, and to monitor the natural history of the diabetic disease. Second, MPI could be useful for indirectly assess the metabolic control or suggest an early start of specific pharmacological treatments that may help the clinical course of diabetic cardiomyopathy. Most importantly, whether such abnormalities may be reverted by optimal metabolic control and/or pharmacologic treatments could be determined. Diagnosing pre-clinical diabetic cardiomyopathy early through MPI is not only important but also may turn out to be essential for the appropriate clinical testing of new therapeutic approaches to diabetic disease.

Finally, the MPI appears to be a sensitive noninvasive technique for detecting significant subclinical left ventricular dysfunction, in patients with multiple sclerosis treated with low dose of mitoxantrone, an antracenedione antineoplastic agent. Besides, provides important prognostic information for the risk of future cardiotoxicity, beyond other conventional echocardiographic measurements. We expect that MPI may be an adjunctive parameter to the conventional echocardiography in monitoring cardiac side effects and for detecting sub-clinical cardiotoxicity of

mitoxantrone.

In conclusion, a simple measure of Doppler index, combining systolic and diastolic time interval as an expression of global myocardial performance, correlates with overall cardiac function, seem to be a useful predictor of clinical outcome and could be an adjunctive index for the diagnosis and for the clinical management of patients with many cardiac and systemic disease.

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