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Early subclinical ventricular dysfunction in patients with insulin resistance

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Aims **The aim of our study was to evaluate the relationship between insulin resistance and the detection of precocious echocardiographic signs of heart failure in patients with cardiovascular risk factors.**

Methods **We enrolled 34 consecutive patients with cardiovascular risk factors. All patients underwent coronary angiography, echocardiography, and laboratory tests. Exclusion criteria were diabetes (fasting glucose greater than 126 mg/dl or treatment with insulin or oral hypoglycemic agents), coronary artery disease, creatinine above 1.5 mg/dl, left-ventricular hypertrophy, valvular heart disease, ejection fraction below 50%, atrial fibrillation, or other severe arrhythmia. The presence of insulin resistance was assessed by using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Ventricular function was investigated by echocardiography.**

Results **Distinguishing patients with insulin resistance, based on the median value of HOMA-IR (<4.06 and >4.06), we observed that in the group with higher levels of HOMA-IR, there were echocardiographic signs of subclinical ventricular dysfunction statistically more frequent (E/A in group with HOMA <4.06: 1.159 + 0.33 vs. group with HOMA >4.06: 0.87 + 0.29, $P = 0.0136$; E/E': 6.42 + 4 vs. 15.52 + 3.26, $P = 0.001$; Tei index: 0.393 + 0.088 vs. 0.489 + 0.079, $P = 0.0029$; S wave: 0112 + 0.015 vs. 0.114 + 0.027, $P = 0.0001$; ejection fraction 59.11 + 4.75 vs. 58.88 + 6.81, $P = 0.9078$). Grade II diastolic dysfunction was observed in 5 patients, grade I in 12 patients, and 17 patients had normal diastolic function. On multivariate analysis, HOMA-IR ($P = 0.0092$), hypertension ($P = 0.0287$), waist circumference ($P = 0.0009$), high-density lipoprotein ($P = 0.0004$), and fasting blood glucose ($P = 0.0003$) were variables independently associated with diastolic dysfunction. On analysis of covariance, we found that the variables that influence diastolic dysfunction are HOMA-IR, waist circumference, BMI, and age, and that the only variable that influences Tei index is HOMA-IR.**

Conclusion **Insulin resistance is frequently associated with subclinical left-ventricular dysfunction. Patients with cardiovascular risk factors and increased HOMA-IR levels, although without diabetes mellitus, overt coronary artery disease, or hypertensive cardiomyopathy, may represent a target population for screening programs, recommended changes in lifestyle, and possibly the use of pharmacological interventions to prevent the onset of heart failure.**

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Background

Heart failure is a common disease, with an estimated prevalence of 1–2% in the general population.[1] It is important to identify individuals at risk and to prevent the onset of clinically overt disease. Symptoms and signs of heart failure may also occur in patients who have normal left-ventricular systolic function [diastolic heart failure or heart failure with normal ejection fraction (HFnEF)].[2,3]

Left-ventricular diastolic dysfunction (LVDD), the precursor of diastolic heart failure, is an important predictor of cardiovascular mortality and morbidity in the general population.[4] Also, subtle and subclinical signs of ventricular dysfunction are associated with an increased cardiovascular morbidity and mortality.[5–7] Insulin resistance may precede diabetes by a decade or more, and it is a pathogenic factor for type 2 diabetes mellitus (T2DM).[8] Furthermore, insulin resistance has been shown to be an independent predictor of T2DM[9] and predicted systolic heart failure incidence independently from established risk factors including diabetes in the community.[10] Little is known about the interactions of insulin resistance and LVDD. Diastolic dysfunction can precede the development of diabetes, suggesting that it is not exclusively a complication of diabetes, but rather a coexisting condition. The aim of the present study is to explore the relationship between insulin resistance and the detection

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of echocardiographic signs of subclinical ventricular dysfunction (SVD), in patients with cardiovascular risk factors.

Methods

We enrolled 34 consecutive patients with cardiovascular risk factors, selected from 1010 patients who had been referred to our cardiology unit for suspected ischemic heart disease, in the period between May 2010 and May 2012. The protocol was approved by the local Ethics Committee, and signed, informed consent was obtained from all patients. Inclusion criteria were scheduled coronary angiography and the presence of one or more cardiovascular risk factors.

All patients underwent coronary angiography, echocardiography, and laboratory tests. Exclusion criteria were diabetes (fasting glucose greater than 126 mg/dl or treatment with insulin or oral hypoglycemic agents), coronary artery disease (CAD), creatinine above 1.5 mg/dl, left-ventricular hypertrophy, more than mild valvular heart disease, ejection fraction below 50%, and atrial fibrillation or other severe arrhythmia. Cardiovascular risk factors considered were blood pressure levels above 140/90 mmHg or antihypertensive treatment, fasting blood glucose greater than 100 mg/dl, waist circumference greater than 102 cm in men and greater than 88 cm in women, triglycerides above 150 mg/dl, high-density lipoprotein (HDL) below 40 mg/dl in men and below 50 mg/dl in women, and BMI greater than 30 kg/m^2. BMI was calculated as weight (kg)/height (m)^2.

The presence of insulin resistance was assessed by using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), a calculated parameter of insulin resistance that relates fasting glucose and insulin according to the formula proposed by Matthews *et al.* [fasting glucose (mmol/l) $\times$ Insulin (mU/ml)]/22.5,[11] and compared to the glucose clamp technique by Bonora *et al.*[12] In this study, the value of HOMA-IR chosen for threshold of insulin resistance, was higher than 2.[13] Venipuncture was performed on all patients after a 12-h fast, to determine basal glycemia and basal insulinemia in fasting state. Samples for the assay of plasma glucose were analyzed within 1 h of sampling, whereas the samples for insulin dosage were stored at -20°C and analyzed during dedicated sessions. Hemolyzed samples were excluded because the hemolysis produces enzymes that degrade the insulin, causing a dramatic underestimation. The presence of ventricular dysfunction was investigated by echocardiography. Echocardiography was performed using Acuson Sequoia equipment with a multifrequency probe following the recommendations of the American Society of Echocardiography (ASE).[14] Ejection fraction was measured by the biplane Simpson method. Transmitral flow was explored by pulsed Doppler (PWD), placing the sample volume at the distal end of the mitral leaflets in four-chamber view and by measuring the peak E wave, A wave, and E/A ratio. The tissue Doppler was recorded at the septal and lateral mitral annulus, and E1 wave, A1 wave, and S wave were evaluated. The presence of diastolic dysfunction was defined on the basis of recent recommendations by ASE/European Association of Echocardiography (EAE).[15] The Tei index was measured with tissue Doppler at the level of septal and lateral mitral annuls, adding the isovolumetric contraction time and the isovolumetric relaxation time and dividing by the ejection time.[16] The Tei index was considered to be above the norm when it exceeded a value of 0.40. The presence of SVD was defined as an impairment of diastolic function or Tei index. All echocardiographic examinations were performed by two physicians experienced in the technique, and analyses of ventricular dysfunction were double-blinded for insulin resistance. The statistical analysis was performed using the software Staview. We observed the presence of normal distribution of variables by using coefficient of skewness and coefficient of Kurtosis. Data were expressed as mean $\pm$ SD. Differences between groups were analyzed with the Student's *t*-test. Statistical significance was considered to be reached when the difference between the groups reached a P value of less than 0.05.

We assessed the relationship between HOMA-IR and echocardiographic parameters of SVD with a logistic regression model and we performed a multivariate analysis to highlight any clinical variables independently associated with SVD. We performed correlation analysis (Pearson test) between variables HOMA-IR, hypertension, HDL, fasting blood glucose, waist circumference, and presence of diastolic dysfunction. Moreover, we performed analysis of covariance (ANCOVA) for assessing the differences in dependent variable scores after statistically controlling for the covariates.

Results

We included 34 patients in the study (M : F = 23 : 11, mean age was 60.29 $\pm$ 11.59 years). Clinical, laboratory, and echocardiographic parameters of the study population are shown in Table 1. All patients had normal ventricular size; left atrium size was on average increased in the population. Distinguishing patients with insulin resistance based on the median value of HOMA-IR ($<$4.06 and $\geq$4.06) we have observed that in the group with higher levels of HOMA-IR, there were echocardiographic signs of diastolic dysfunction and subclinical systolic dysfunction was statistically more frequent (Table 2).

Seventeen patients had HOMA-IR above 4.06, and they all had evidence of SVD. In patients with insulin resistance, the BMI, the fasting glucose, and the fasting insulin level were significantly higher compared to those without insulin resistance. Ejection fraction did not differ between patients with HOMA-IR of 4.06 or less. A higher

Table 1 Clinical, laboratory, and echocardiographic parameters of the study population (mean ± SD)

Age (years)	60.29 ± 11.59
Men (*n*)	11
MAP (mmHg)	98.33 ± 10.15
SBP (mmHg)	135.29 ± 17.53
Waist circumference (cm)	101.17 ± 20.49
Triglyceridemia	121.64 ± 41.25
HDL	50.58 ± 13.27
BMI (kg/m2)	27.565 ± 3.64
Fasting glucose (mg/dl)	101.529 ± 13.71
Fasting insulin level (mIU/ml)	17.758 ± 7.15
HOMA-IR	4.06 ± 2.23
Heart rate (bpm)	78.5 ± 12.86
EF (%)	59 ± 5.78
E/A	1.029 ± 0.33
E/E'	10.692 ± 5.79
S wave (m/s)	0.112 ± 0.02
Tei index	0.438 ± 0.09

bpm, beats per minute; EF, ejection fraction; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; MAP, mean arterial pressure.

prevalence of SVD was found in the group with HOMA-IR of at least 4.06 (lower E/A ratio, higher TEI index values, higher E/E' ratio; see Table 2).

Seventeen patients had evidence of LVDD according to the recent EAE guidelines.[16] Grade I was observed in 12 patients, grade II LVDD in 5 patients, and 17 had normal diastolic function.

We performed univariate analysis to assess the association between the presence of diastolic dysfunction and other variables such as hypertension, age, HOMA, waist circumference, BMI, heart rate, ejection fraction, triglycerides, fasting blood glucose, and HDL (see Table 3). Multivariate analysis was later performed to assess whether there were clinical variables independently associated with diastolic dysfunction. We included in the analysis only those variables that had reached statistical significance at univariate analysis. We found that HOMA-IR and fasting blood glucose were variables independently associated with diastolic dysfunction on multivariate logistic regression (Table 3). On Pearson analysis, we found that HOMA-IR, hypertension, waist circumference, HDL, fasting blood glucose, BMI, and age were significantly correlated with diastolic dysfunction (Table 4).

Among variables that showed a correlation with diastolic dysfunction, we found that at ANCOVA, those that influence diastolic dysfunction are HOMA-IR ($P < 0.001$) and waist circumference ($P < 0.001$), BMI ($P < 0.001$) and age ($P < 0.001$). The only variable that influences Tei index is HOMA-IR ($P = 0.04$).

Table 2 Clinical and echocardiographic parameters stratified by mean value of HOMA-IR (< and >4.06)

	HOMA-IR <4.06	HOMA-IR ≥4.06	*P* value
Age (years)	57.06 ± 10.90	65.23 ± 9.96	0.01
Men (*n*)	64.70 (11)	70.58 (12)	0.4128
MAP (mmHg)	90.97 ± 7.92	105.68 ± 5.92	<0.0001
SBP (mmHg)	124,70 ± 14,62	145,88 ± 13,49	0.0001
Waist circumference (cm)	91,58 ± 17,17	110,76 ± 19,38	0.0045
Triglyceridemia	99,82 ± 16,54	143,47 ± 47,16	0.0011
HDL	56,11 ± 10,51	45,05 ± 13,70	0.0127
BMI (kg/m^2)	25.824 ± 2.58	29.307 ± 3.78	0.0037
Fasting glucose (mg/dl)	91.352 ± 11.83	111.705 ± 5.28	0.0062
Fasting insulin level (mIU/ml)	12.7 ± 2.91	22.817 ± 6.522	0.0062
HOMA-IR	2.80 ± 0.67	6.292 ± 1.82	<0.001
Heart rate (bpm)	75.35 ± 10.68	81.647 ± 14.34	0.1567
EF (%)	59.11 ± 4.75	58.88 ± 6.81	0.9078
E/A	1.159 ± 0.33	0.871 ± 0.29	0.0136
E/E'	6.42 ± 4	15.52 ± 3.26	0.001
Tei index	0.393 ± 0.088	0.489 ± 0.079	0.0029
S wave (m/s)	0.112 ± 0.015	0.114 ± 0.027	0.0001

bpm, beats per minute; EF, ejection fraction; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; MAP, mean arterial pressure.

Table 3 Association between the presence of diastolic dysfunction and clinical parameters (univariate analysis), and clinical variables independently associated with diastolic dysfunction (multivariate analysis)

	Univariate		Multivariate	
Variables	Coefficient	*P*	Coefficient	*P*
Age	0.01894	0.0106	0.00771	0.0677
SBP	0.01774	0.0001	0.00306	0.3496
Waist circumference	0.01176	0.005	0.003230	0.2175
Triglyceridemia	0.0066	0.0011	0.00104	0.4447
Fasting blood glucose	0.02787	0.0001	0.01279	0.0056
HDL	−0.01617	0.0127	−0.00359	0.3391
BMI	−0.00006171	0.3754		
HOMA-IR	0.18	0.001	0.07877	0.0118
Heart rate	0.009801	0.1567		
EF	−0.001808	0.9078		

bpm, beats per minute; EF, ejection fraction; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

Discussion

Our study aimed to evaluate the relationship between insulin resistance and precocious echocardiographic signs of ventricular dysfunction in patients with cardiovascular risk factors. Insulin resistance can contribute to the diastolic dysfunction by different mechanisms; the alteration of the insulin signaling, the enhanced deposition of nonenzymatic glycation end products in the extracellular matrix, the increase of the deposition of myocardial collagen with down-regulation of metalloproteinases (MMPs) and tissue inhibitor of up-regulation MMP,[17] altered metabolism of fatty acids,[18] and endothelial

Table 4 Pearson test (correlation analysis between variables and presence of diastolic dysfunction)

Variables	Correlation coefficient *r*	*P*
SBP	0.6129	0.0001
Waist circumference	0.4748	0.0045
Fasting blood glucose	0.7531	<0.0001
HDL	−0.4229	0.0127
HOMA-IR	0.7941	<0.0001
BMI	0.4848	0.0037
Age	0.4326	0.0106

HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

dysfunction.[19] In particular, the alteration of fatty acids metabolism can contribute to the impaired relaxation of the left ventricle, inhibiting the oxidation of glucose and consequently the availability of ATP.[20]

In addition, insulin resistance and the consequent hyperinsulinism may promote the activation of the sympathetic nervous systems,[21] and increase the activation of the rennin–angiotensin–aldosterone system and consequently the production of collagen,[22,23] which can lead to fibrosis and diastolic dysfunction. Hyperinsulinemia can also lead to increased myocardial mass through its growth-stimulating function and probably differential organ-specific levels of insulin resistance.[24] These observations suggest a theoretical basis for our observation of subtle changes in myocardial, specifically diastolic, function in prediabetes.

To avoid the possible influence of confounding factors on the development of SVD in our study, we excluded patients with diabetes, CAD, renal impairment, left-ventricular hypertrophy, more than mild valvular heart disease, reduced ejection fraction, atrial fibrillation, or other severe arrhythmias as stated in the method section.

Only a limited number of studies in the literature have shown the presence of such an association. Recently, it was shown that insulin resistance and glucose abnormalities are predictors for incident heart failure independently from diabetes.[10,25,26] However, most of these studies have methodological limitations regarding the identification of LVDD. The criteria used to define LVDD were highly variable and predominantly did not consider the diagnostic echocardiographic guidelines. Furthermore, most of these studies did not screen for the presence of CAD using coronary angiography.

An important limitation of our study is the small, although well selected, sample size and the unbalanced sex distribution. Moreover, we did not use the gold standard in the assessment of insulin sensitivity, that is the glucose clamp. However, previous studies have shown that HOMA-IR is strongly related to clamp-measured insulin resistance in both diabetic and nondiabetic patients.

A possible clinical implication of our study is that patients with insulin resistance constitute a population at risk of heart failure that need to undergo screening programs for early detection of the disease, life style changes, and early therapeutic intervention.

In all patients with insulin resistance, weight loss, in cases of obesity, and aerobic exercise to improve insulin resistance is therefore recommended. Furthermore, drugs that reduce the activation of the renin–angiotensin–aldosterone system, and drugs that increase insulin sensitivity and improve glucose utilization may be suggested early to groups with insulin resistance. In these patients, early intervention in the subclinical phase may allow the reversibility of the damage and thus prevent the progression to overt and often irreversible clinical disease.

Conclusion

Our results demonstrated that insulin resistance is associated with SVD. Patients with cardiovascular risk factors without diabetes mellitus, without overt CAD, and without hypertensive cardiomyopathy may represent a target population for screening programs, recommended changes in lifestyle, and possibly use of pharmacological interventions to prevent the onset of heart failure. However, our study is a pilot study and large prospective epidemiological studies are needed to confirm our results.

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