ORIGINAL ARTICLE

Asymptomatic Left Ventricular Dysfunction and Metabolic Syndrome: Results from an Italian Multicenter Study

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ABSTRACT

Context: Metabolic syndrome (MS) is a cluster of interrelated common clinical disorders, including obesity, insulin resistance, glucose intolerance, hypertension and dyslipidemia, associated with a greater risk of atherosclerotic cardiovascular disease than any of its individual components. Although MS is associated with increased cardiovascular risk (CVR), its relationship with heart failure (HF) and left ventricular (LV) dysfunction is not fully understood. **Aims:** We sought to determine whether MS is associated to LV systolic and diastolic dysfunction in a sample of patients with MS and no symptoms for HF. **Subjects and Methods:** We enrolled 6422 consecutive asymptomatic patients admitted to echo-lab for a routine echocardiogram. We calculated LV systolic and diastolic function, by Simpson biplane method and validated Doppler parameters, respectively. MS was diagnosed if three or more CVR factors were found. **Results:** LV systolic function was evaluated in 6175 patients (96.2%). In the group of patients without MS (n = 5630), the prevalence of systolic dysfunction was 10.8% (n = 607) while in the group of patients with MS (n = 545) it was 12.5% (n = 87), (RR1.57; CI 95% 1.2-2.0; P < 0.001). Diastolic function was evaluated in 3936 patients (61.3%). In the group of patients without MS (n = 3566) the prevalence of diastolic dysfunction was 33.3% (n = 1187), while in patients with MS (n = 370) it was 45.7% (n = 169), (RR1.68; CI95% 1.3-2.0; P < 0.001). After adjustment for age and gender, MS proved to be an independent predictor of LV systolic and diastolic dysfunction. **Conclusions:** Our data show that asymptomatic LV systolic and diastolic dysfunction, is correlated with MS and demonstrate that echocardiography is a useful tool to detect patients at high risk for HF. Echocardiography in asymptomatic patients with MS may lead to a therapy initiation at early stages to prevent future cardiovascular events and HF.

Key Words: Diastolic ventricular dysfunction, echocardiography, metabolic syndrome, systolic ventricular dysfunction

INTRODUCTION

Congestive Heart failure (HF) is classified according to clinical and instrumental findings into four stages. Stage A and B being the first two are characterized by the presence of clinical risk factors and structural abnormalities, respectively, asymptomatically.[1,2]

These silent abnormalities may lead over a time to symptomatic left ventricular dysfunction (LVD) (stage C and D).[3-6] Early detection of subclinical form of LVD may lead to establish an early *protective* treatment and potentially delay the development into overt HF.[7,8] Metabolic syndrome (MS) is a cluster of several risk factors for cardiovascular diseases associated with an higher incidence of symptomatic HF and cardiovascular events.[9-12] Data from Third National Health and Nutrition Examination Survey (NHANES III) showed that patients with MS had nearly twice the likelihood of self-reported HF, suggesting that MS may serve as a surrogate indicator for the association

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between insulin resistance and HF.[13] Moreover, each individual marker of MS is inferior to MS itself in identifying subtle cardiac dysfunction.[14] However, the prevalence of asymptomatic LV systolic and/or diastolic dysfunction is not well established in patients with MS at stage A or B of HF.

Aim of this study is to evaluate left ventricular systolic and/or diastolic abnormalities in a large sample of patients with MS and without symptoms of HF.

SUBJECTS AND METHODS

Study population

Total of 6422 consecutive patients (median age 59 years, interquartiles range: 48-68; men 3364) referred for a routine transthoracic examination to 75 national echocardiographic laboratories, were enrolled in the study. All laboratories were selected according to the competence level of the operators, which is level 3 in agreement with the American Society of Echocardiography (ASE) requirements.[15] Detailed history of all the patients were taken, with focus on cardiovascular risk factors. Exclusion criteria were: Dyspnoea, valvular heart disease at least of moderate degree, previous valvular heart surgery, coronary artery by-pass surgery within the previous six months.

In this study, we adopted the main definition of MS in accordance with the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) scientific statements.[16] We diagnosed MS with the presence of at least three of the following: Hypertension, dyslipidemia, glucose intolerance and obesity with cutoff points consistent with the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) report, modified with body mass index (BMI) in place of waist circumference.[12]

Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥ 90 mm Hg, or self-reported antihypertensive medication use during the 2-week period before the clinical examination.[17] Dyslipidemia was defined as a low HDL cholesterol level (<40 mg/dL in men and <50 mg/dL in women) or as an elevated triglyceride level (≥150 mg/dL).[18] Glucose intolerance was defined by the presence of diabetes (self-reported physician diagnosis of diabetes, use of insulin or oral hypoglycemic medication, or fasting glucose level ≥126 mg/dL) or impaired fasting glucose (fasting glucose level ≥110 mg/dL) according to American Diabetes Association criteria.[19] Subjects having three or more of the above mentioned criteria were classified as having MS.

Consistently with other major studies, we used BMI because we could not obtain waist circumference measurements for the entire study sample.[20,21] The waist circumference criteria used in the ATP III definition were replaced with cutoff points for BMI (28.8 kg/m^2 for men and 26.7 kg/m^2 for women), as in previous studies.[22]

All patients underwent physical examination, 12-lead electrocardiography, and a complete transthoracic echocardiographic examination, according to the standardized protocol based on the recommendations of the ASE.[23]

Echocardiograms were analyzed when at least 80% of the endocardium was visible. Quantitative analysis was performed for each laboratory, by the same expert operator. Measurements of left ventricular ejection fraction (LVEF) were performed using the modified biplane Simpson's rule as a mean of three cardiac cycles. In patients with atrial fibrillation, the average value was obtained from six cardiac cycles. Left ventricular diastolic function was evaluated by measuring mitral valve and pulmonary venous flow Doppler parameters; the mitral flow was recorded in basal condition and during valsalva manoeuvre, according to the standard criteria.[24] The following echocardiographic parameters were evaluated: LVEF, mitral inflow [E wave velocity, A wave velocity, E/A, Δ E/A (changes from basal to valsalva manoeuvre), E wave deceleration time (DT), A wave duration (A_{dur})], pulmonary venous flow [(systolic velocity (S), diastolic velocity (D), a reverse wave duration (AR_{dur})].

Systolic LVD was defined as LVEF equal or less than 50%.[24] Diastolic function was classified, according to the progression of dysfunction, as follows: Normal (0.75<E/A<1.5, DT>140 msec, ΔE/A<0.5 during Valsalva manoeuvre, S≥D, AR_{dur}<A_{dur}); mild (E/A≤0.75, DT >140 msec, ΔE/A<0.5, S>D, AR_{dur}<A_{dur}); moderate (0.75<E/A<1.5, DT>140 ms, ΔE/A≥0.5, S<D or AR_{dur}>A_{dur}+30 ms) and severe dysfunction (E/A>1.5, DT<140 ms, ΔE/A≥0.5, S<D or ARdur>Adur+30 ms).[24] Participants were required to have at least two concordant Doppler criteria to be classified and patients with atrial fibrillation were excluded from evaluation of diastolic dysfunction.

The study was approved by the local research ethic committees and all patients gave a written informed consent.

Statistical analysis

All analyses were performed by using SPSS for Windows (version 12.0.1, Chicago Ill). Continuous variables are expressed as mean ± SD or as median and 25th through 75th interquartiles when appropriate. The association between age and presence of MS was evaluated using nonparametric Mann-Whitney U test. Categorical variables were compared by the chi-square test. Stepwise logistic regression analysis was used to determine the association between MS and left ventricular systolic and diastolic dysfunction adjusting for age and gender. A two-tailed *P* value of <0.05 was considered significant.

RESULTS

A total number of 6422 patients were eligible for the study. Clinical characteristics of patients are shown in Table 1. Patients were divided according to the absence or presence of MS into Group A and Group B [Table 2]. Prevalence of MS was higher in man (9.1%) than in women (8.5%), but not statistically significant (*P* = 0.37).

Left ventricular systolic function was evaluated in 6175 patients (96.2%); in the remaining 247 patients (3.8%) LVEF was not calculated because of poor acoustic window. In the group of patients with MS (group B), the prevalence of systolic dysfunction was significantly higher than in patients without MS (group A), 12.5% vs 10.8% (RR 1.57; CI 95% 1.2-2.0; *P* < 0.001) [Table 3].

Diastolic function was evaluated in 3936 patients (61.3%). The overall prevalence of diastolic LVD was 33.3% (*n* = 1187) and was significantly higher in patients with MS, 45.7% vs 33.3% (RR 1.68; CI 95% 1.3-2.0; *P* < 0.001) [Table 4].

Moreover, logistic regression analysis showed that after adjustment for age and gender, MS was an independent predictor of both systolic and diastolic LVD [Tables 5 and 6].

DISCUSSION

In our study, we sought to determine if MS is associated with LVS and/or diastolic dysfunction in patients without symptoms for HF.

In previous studies, we demonstrated that echocardiography can detect preclinical functional or structural myocardial abnormalities in asymptomatic subjects with two or more CVRs and without electrocardiogram abnormalities,[3] and can improve the prognostic impact in comparison to other settings (clinical, ECG).[25] In this survey, asymptomatic patients having diagnosed for MS, were presented with significantly higher prevalence of systolic than patients with only one or two risk factors. More importantly, after adjustment for age and gender, MS proved to be a strong independent predictor of early LV systolic and diastolic dysfunction in this subset of patients.

Table 1: Study population characteristics

	Metabolic syndrome		Overall	*P*
	Group A no MS *N* (%)	Group B MS *N* (%)		
Female	2,798 (47.8	260 (45.9)	3,058 (47.6)	0.202
Male	3,057 (52.2)	307 (54.1)	3,364 (52.4)	
Diabetes	395 (6.7)	334 (58.9)	729 (11.4)	<0.001
Hypertension	2,905 (49.6)	552 (97.4)	3,457 (53.8)	<0.001
Dyslipidemia	1,556 (26.6)	496 (87.5)	2,052 (32)	<0.001
Obesity	575 (9.8)	387 (68.3)	962 (15)	<0.001
Smokers	1,173 (20)	106 (18.7)	1,279 (19.9)	0.241
Family history of cardiovascular disease	1,858 (31.7)	228 (40.2)	2,086 (32.5)	<0.001
Previous Myocardial infarction	493 (8.4)	95 (16.8)	588 (9.2)	<0.001
Angina	249 (4.3)	57 (10.1)	306 (4.8)	<0.001
Atrial Fibrillation	248 (4.2)	19 (3.4)	267 4.2)	0.186
Stroke	77 (1.3)	14 (2.5)	91 (1.4)	0.028
Transient Ischemic cerebrovasculopary	59 (1)	10 (1.8)	69 (1.1)	0.080

Group A = No metabolic syndrome; Group B = Metabolic syndrome

Table 2: Risk factors and MS prevalence

Total population n 6422	Risk factors (*n*)	*n* (%)	Median age y (interquartiles) *P* (<0,001)
Group A *n* 5855 (91,2%)	0	2024 (31.5)	58 (47-68)
	1	2231 (34.7)	
	2	1600 (24.9)	
Group B *n* 567 (8,8%)	3	499 (7.8)	63 (55-71)
	4	68 (1,1)	

Table 3: Systolic left ventricular dysfunction (LVD) in the two groups

	Patients *n* 6175 (96% total population)	
LV Systolic function	Group A *n* 5630	Group B *n* 545
Normal EF *n* (%)	5022 (89,2)	477 (87,5)
Low EF *n* (%)	608 (10,8)	68 (12,5)

P < 0.0001

Table 4: Diastolic left ventricular dysfunction (LVD) in the two groups

	Patients n 3936 (61.3% of total population)	
LV diastolic function	Group A *n* 3566 (%)	Group B *n* 370 (%)
Normal	2379 (66.7)	201 (54.3%)
Abnormal	1187 (33,3)	169 (45,7)

P < 0.0001

Table 5: Logistic regression: Predictors of systolic LVD

	OR (CI 95%)	*P* value
Age	1.01 (1.01-1.02)	<0.001
Gender (m)	2.20 (1.85-2.61)	<0.001
MS	1.45 (1.13-1.86)	0.001

Table 6: Logistic regression: predictors of diastolic LVD

	OR (CI 95%)	*P* value
Age	1.06 (1.05-1.07)	<0.001
Gender (m)	1.10 (0.95-1.27)	0.17
MS	1.44 (1.15-1.81)	0.001

Our results are consistent with other data available in literature, suggesting that MS leads to an higher risk of ventricular dysfunction involving the myocardium in early stages, before clinical signs of HF.[26] Individual MS markers are inferior to MS in identifying subtle cardiac dysfunction, emphasizing the importance of synergistic effect of these clinical conditions in identifying organ damage. Particularly, among MS criteria, the coexistence of MS and type 2 diabetes exhibits the highest risk for biventricular dysfunction, requiring more aggressive therapeutic strategies to prevent HF.[14]

Furthermore, the number of coexisting characteristics of metabolic syndrome (arterial hypertension, central obesity, hyperglycemia and hypertriglyceridemia) can strongly influence not only the presence, but also the degree of diastolic dysfunction.[27]

It has also been demonstrated that the impact of MS on LV remodeling and diastolic LVD is significantly influenced by gender, since the effects of MS on preclinical LVD were found to be more pronounced in women.[28] However, these data were not confirmed in our study, in which no statistically significant differences were found between sex categories.

In a community-based sample of middle-aged men, metabolic syndrome proved to be a significant predictor of HF, independent of established risk factors for HF, during two decades of follow up.[29] Moreover, data from a large trial on 9306 participants with impaired glucose tolerance and at least one or more CVR, reveal that traditional risk factors and novel indices of central adiposity and increased urinary albumin-creatinine are good predictors of incident hospitalization for HF.[30] This implies that MS provides important risk information beyond that of established risk factors for HF. However, the exact mechanisms are still not clear. Previous data supported the role of insulin resistance, as an important risk factor for the development of hypertension, atherosclerotic heart disease, left ventricular hypertrophy and HF, reflecting that a disturbance of glucose metabolism may potentially worsen metabolic efficiency of both skeletal muscle and cardiac muscle.[30,31] Some authors proposed that insulin resistance might be promoted by a sympathetic nervous system over activity, characterizing chronic HF and that this neurohormonal disregulation could be potentiated by obesity and MS.[32] Recently, it has been pointed out that superobesity is associated with insulin resistance, with a worse impact on cardiac remodeling and LV diastolic function than morbid obesity.[33]

Consistently with an early myocardial damage, metabolic syndrome was recently found to be associated with decreased mechanical properties of the myocardium, particularly of sub-endocardial fibers, as demonstrated by an impairment of longitudinal myocardial diastolic and systolic functions, but preserved circumferential functions and twist mechanics.[34]

However, our study is the first large national multicenter study providing a real prevalence of asymptomatic LVD in a population with CVR and no symptoms for HF.

Limitations

Limitation of this study is the selection of a sample of patients not representative of entire population, but a selected population with more prone to CVR. Another limitation is that we used BMI rather than waist circumference to define metabolic syndrome. However, this parameter has been accepted by other major studies, in which a close correlation was found between BMI and waist circumference. Moreover, being a national multicenter study, involving more than 75 centers, our protocol did not include tissue Doppler imaging (TDI) or 2-dimensional (2D) strain for longitudinal function and myocardial deformation evaluations, as they are not easily available in all echolabs within the territory. These data might have revealed an early left ventricular dysfunction also in patients with normal EF, unmasking the earliest stages of systolic LVD.

CONCLUSION

Our data show that in a large sample of asymptomatic patients, the presence of MS is an independent predictive risk factor for asymptomatic systolic and diastolic LVD.

Echocardiographic examination is a useful tool to detect left ventricular alterations in high risk patients, and may help to identify subset of patients prone to develop overt

HF.[3,25] The presence of these alterations may help to introduce lifestyle changes aimed to reducing single risk factors, or lead to establish a prompt pharmacological treatment to prevent future cardiovascular events and/or the progression to symptomatic congestive HF.

Considering the epidemiologic implication of the disease, patients who are at risk for MS, should be screened aggressively for cardio-vascular parameters with the aim of reducing morbidity and mortality, improving quality of life, and also reducing the financial burden.

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