Impaired coronary flow reserve evaluated by echocardiography is associated with increased aortic stiffness in patients with metabolic syndrome: an observational study

Metabolik sendromlu hastalarda ekokardiyografik olarak gösterilen bozulmuş koroner akım rezervi artmış aort sertliği ile ilişkilidir: Gözlemsel bir çalışma

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ABSTRACT

Objective: Metabolic syndrome (MetS) is a strong predictor of cardiovascular events and coronary flow reserve (CFR), an indicator of microvascular function, has been found to be impaired in MetS. Aortic stiffness (AS) is a simple and effective method for assessing arterial elasticity. The aim of this study was to evaluate whether there is an independent association of impaired coronary flow and aortic elasticity in patients with MetS.

Methods: Forty-six patients (mean age 47.3±6.6 years) with the diagnosis of MetS according to the ATP III update criteria and 44 age and gender matched controls (mean age 46.0±6.1 years) were included into the cross-sectional observational study. Peak diastolic coronary flow velocities were measured in left anterior descending artery by pulsed wave Doppler at baseline and after adenosine infusion, and CFR was calculated as the ratio of hyperemic to baseline velocities. Aortic strain, distensibility and stiffness were calculated by M-mode echocardiography. Statistical analysis was performed by using Student t-test, Chi-square test, Pearson correlation and linear regression analyses.

Results: CFR was significantly lower in patients with MetS than in controls (2.3±0.2 vs 2.7±0.2, p<0.001). In the MetS group, aortic distensibility (10.4±3.5 $cm^2.dyn^{-1}.10^{-6}$ vs. 12.7±3.4 $cm^2.dyn^{-1}.10^{-6}$, p=0.002) was decreased and AS was significantly increased (6.5±2.0 vs. 3.2±0.8, p<0.001). In multivariate linear regression analysis, AS (β=-0.217, p=0.047), systolic blood pressure (β=-0.215, p=0.050) and waist circumference (β=-0.272, p=0.012) had an independent relationship with impaired CFR.

Conclusion: This study demonstrated that coronary flow reserve is impaired in patients with MetS and there is an independent relationship between impaired CFR and increased aortic stiffness, systolic blood pressure or waist circumference.

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Key words: Metabolic syndrome, coronary flow reserve, aortic stiffness, echocardiography, regression analysis

ÖZET

Amaç: Metabolik sendrom (MetS) kardiyovasküler olayların güçlü bir belirleyicisidir. Koroner akım rezervi (KAR) mikrovasküler fonksiyonun göstergesidir ve MetS'de bozulduğu gösterilmiştir. Arteriyel elastikiyetin değerlendirilmesinde aortik sertlik (AS) basit ve önemli bir metottur. Bu çalışmada MetS'li hastalarda bozulmuş koroner akım ve aortik elastisite arasında bağımsız bir ilişki olup olmadığının değerlendirilmesi amaçlanmıştır.

Yöntemler: Enine kesitli gözlemsel çalışmaya güncellenmiş ATP III kriterlerine göre MetS tanısı alan 46 hasta (ortalama yaş 47.3±6.6 yıl) ve 44 kontrol (ortalama yaş 46.0±6.1 yıl) hastası alındı. Pik diyastolik koroner akım, distal sol ön koroner arterden adenozin infüzyonu öncesi ve sonrasında transtorasik nabız dalga Doppler ile ölçüldü ve hiperemik pik diyastolik hızın başlangıç zirve diyastolik hıza oranı KAR olarak kabul edildi. M-mode ekokardiyografi ile aortik strain, distensibilite ve sertlik hesaplandı. İstatistiksel analizde Student t-testi, Ki-kare testi, Pearson korelasyon ve lineer regresyon analizleri kullanıldı.

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Bulgular: MetS'li hastalarda kontrol grubuna kıyasla KAR'ı düşük (2.3±0.2'ye karşılık 2.7±0.2, p<0.001), aortik distensibilite düşük (10.4±3.5'e karşılık 12.7±3.4, p=0.002) ve sertlik ise anlamlı yüksek saptandı (6.5±2.0'e karşılık 3.2±0.8, p<0.001). Lineer regresyon analizinde, AS (β=-0.217, p=0.047), sistolik kan basıncı (β=-0.215, p=0.050) ve bel çevresi (β=-0.272, p=0.012) ile KAR'daki bozulma arasında bağımsız bir ilişki olduğu saptandı.
Sonuç: MetS'li hastalarda koroner akım rezervi bozulmuştur ve artmış aort sertliği, bel çevresi ve sistolik kan basıncı ile azalmış koroner akım rezervi arasında bağımsız bir ilişki vardır. *(Anadolu Kardiyol Derg 2013; 13: 227-34)*
Anahtar kelimeler: Metabolik sendrom, koroner akım rezervi, aortik sertlik, ekokardiyografi, regresyon analizi

Introduction

Metabolic syndrome (MetS) is defined as a clustering of multiple cardiovascular risk factors, including dyslipidemia, obesity, hypertension and impaired glucose tolerance (1). These factors contribute to a high incidence of cardiovascular disease in patients with MetS (2, 3). MetS impairs the ability of the coronary circulation to regulate vascular resistance and balance myocardial oxygen supply and demand (4, 5). Coronary microvascular dysfunction in MetS is evidenced by reduced coronary venous PO_2, diminished vasodilation to endothelial-dependent and independent agonist and altered functional and reactive hyperemia (4-9). Alterations in coronary microvascular function could contributed to the increased cardiovascular morbidity and mortality observed in patients with MetS (10). Recently microvascular dysfunction characterized by impaired coronary flow reserve (CFR) has been identified in patients with MetS prior to overt atherosclerotic disease (7).

Aortic stiffness describes the elastic resistance that the aorta sets against its distension (11). Aortic stiffness is one of the most important cardiovascular risk factors predicting cardiovascular morbidity and mortality (12). Aortic elasticity can be assessed by various parameters measured by echocardiography, which is a non-invasive method (13). MetS causes an increase in arterial stiffness independently of other cardiovascular risk factors (14). Several components of the MetS, including high blood pressure, hyperglycemia, and abdominal fat, have been related to increased aortic stiffness (12, 15).

Aortic stiffening may cause an increase in aortic pulse pressure, left ventricular load, and ultimately left ventricular hypertrophy. This together with the decreased diastolic transmyocardial pressure gradient interacts with coronary flow and flow reserve (11). Significant correlations between coronary flow reserve and aortic stiffness parameters have been demonstrated in different populations such as hypertension, aortic valve stenosis, and hypercholesterolemia (16-19).

However, presence of an association between aortic stiffness (AS) and impaired CFR in MetS has never been evaluated.

The aim of this study was to evaluate whether there is an independent association of impaired coronary flow and aortic elasticity by utilizing transthoracic echocardiography in patients with MetS.

Methods

Study design

The present study was designed as a cross-sectional, observational study.

Study population

Forty-six patients (mean age 47.3±6.5 years) with the diagnosis of MetS according to the Adult Treatment Panel III Final Report criteria (20) without clinical coronary artery disease were included in the study. Forty-four age and gender matched healthy subjects (mean age 46.0±6.1 years) were recruited as the control group. Patients were excluded if they had coronary artery disease, severe valvular disease, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, malignancy, congenital heart disease, chronic heart failure, cardiac rhythm other than sinus, uncontrolled hypertension prior to study, systemic disease such as collagenosis, chronic autoimmune, hemolytic, hepatic and chronic renal disease, or inadequate transthoracic echocardiographic images.

The study protocol was approved by the local ethics committee and written informed consent was obtained from each subject.

Study variables

The baseline variables of study were as following: age, sex, smoking status, systolic (SBP) and diastolic (DBP) blood pressure, history of diabetes mellitus (DM), hypertension (HT), body mass index (BMI), waist circumference, fasting plasma glucose (FPG), total cholesterol, triglycerides, high-density (HDL) and low-density (LDL) lipoprotein cholesterol, high sensitive C-reactive protein (hsCRP), and echocardiographic measurements. In our study, presence of MetS was a primary predictor variable, the outcome variables were CFR and aortic stiffness and confounding variables were age, waist circumference, SBP, FPG, HDL-cholesterol, triglycerides, hs-CRP, and left ventricular mass index (LVMI).

Clinical and laboratory examinations

All patients underwent clinical and laboratory examinations. Demographic data including classical risk factors of atherosclerosis (HT, dyslipidemia, smoking) were noted. Blood samples were obtained after overnight fasting. Plasma glucose, total cholesterol, HDL and LDL cholesterol, triglyceride levels were measured using standard methods (HITACHI MODULAR EVO P800, Roche Diagnostics GmbH, Mannheim, Germany). The levels of hsCRP were measured with immunonephelometric method (IMMAGE Immunochemistry Systems; Beckman Coulter, California, USA).

Definitions

Metabolic syndrome was diagnosed if three or more of the followings were present according to the Adult Treatment Panel III Final Report criteria (20): (i) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; (ii) plasma triglycerides: ≥150 mg/dL; (iii) plasma HDL cholesterol:<40 mg/dL in men and <50 mg/dL in women; (iv) SBP ≥130 mmHg or DBP ≥85

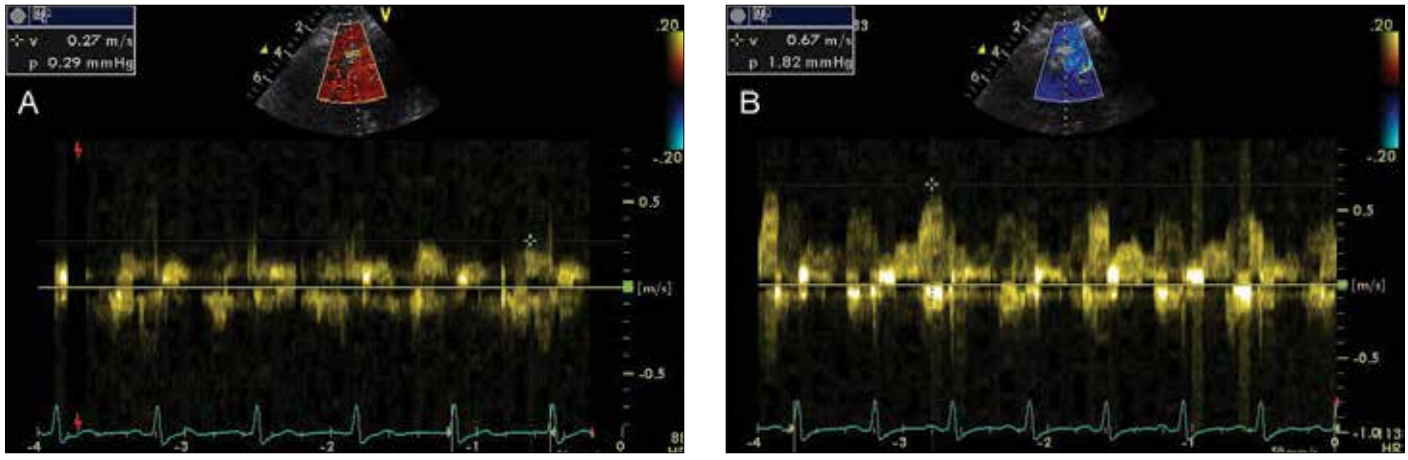

Figure 1. Demonstration of coronary flow velocity at (A) baseline and (B) hyperemia obtained by transthoracic pulsed wave Doppler echocardiography in the distal left anterior descending coronary artery

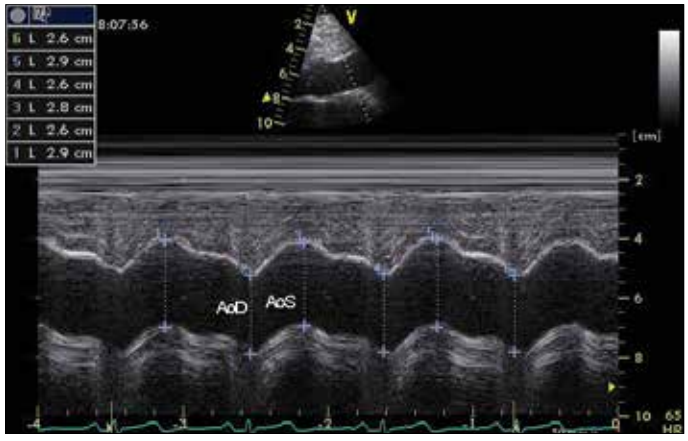

Figure 2. Measurements of aortic diameters shown on the M-mode tracing obtained at a level 3 cm above the aortic cusps
AoD - diastolic aortic diameter, AoS - systolic aortic diameter

mmHg or use of an anti-hypertensive medication; (v) FPG ≥110mg/dL. Hypertension was defined as SBP >140 mmHg or DBP >90 mmHg or use of an antihypertensive medication (21). Diabetes mellitus was defined in case of a history of oral antidiabetics, insulin medication or fasting blood glucose ≥126 mg/dL at study entrance (22). Coronary artery disease was defined as the presence of 1 of the following: a past history of a myocardial infarction/revascularization, typical angina, ST-segment or T-wave changes specific to myocardial ischemia, Q waves on electrocardiogram, wall motion abnormality on echocardiography, a non-invasive stress test demonstrating ischemia or any perfusion abnormality, coronary artery stenosis on angiography. Height and weight were measured according to a standardized protocol. BMI was calculated as body weight divided by height squared (kg/m^2). Waist circumference was measured on bare skin during mid-respiration at the natural indentation between the tenth rib and the iliac crest to the nearest 0.5 cm.

Transthoracic echocardiography

All the patients underwent transthoracic echocardiography using a Vivid 7 Dimension Cardiovascular Ultrasound System (GE Healthcare, USA) with a 3.5 MHz transducer. Two dimensional, M-mode and transthoracic Doppler echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography (23) and images were digitally stored and analyzed by an experienced echocardiographer blinded to the study protocol. Left ventricular mass was calculated from M-Mode records taken on parasternal long-axis images according to Devereux's formula (24). The LVMI was calculated as LVM/body surface area.

CFR determination

Left anterior descending (LAD) coronary artery was visualized using a modified, foreshortened, 2-chamber view, and an optimal alignment to the interventricular sulcus was obtained. The color gain was adjusted to provide optimal images and coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall. By placing the sample volume on the color signal, spectral Doppler of the LAD showed the characteristic biphasic flow pattern with larger diastolic and smaller systolic components. Hyperemia was induced by intravenous infusion of adenosine at a rate of 0.140 µgr/kg/min over 4 minutes. Coronary diastolic peak velocities were measured at baseline and after adenosine by averaging the highest 3 Doppler signals for each measurement. CFR was calculated as the ratio of hyperemic to baseline diastolic peak velocities (Fig. 1) (25).

Assessment of aortic stiffness

Aortic elasticity was assessed using a two-dimensional guided M-mode evaluation of systolic aortic diameter (AoS) and diastolic aortic diameter (AoD), 3 cm above the aortic valve (13, 26). AoD was obtained at the peak of the R wave on the simultaneously recorded electrocardiogram, while AoS was measured at the maximal anterior motion of the aortic wall; for each diameter, 3 measurements were averaged (Fig. 2). The following indexes of aortic elasticity were calculated: % aortic strain=100xAoS-AoD/AoD, aortic distensibility= [2x (AoS-AoD) /

AoD (pulse pressure)] (10^{-6}.cm^{-2}.dyn^{-1}); and aortic stiffness (AS)=ln (SBP / DBP) / [(AoS-AoD) / AoD], where SBP and DBP refer to brachial systolic blood pressure and diastolic blood pressure, measured in millimeters of mercury; pulse pressure was calculated as SBP-DBP, and ln (SBP / DBP) refers to the natural logarithm of the relative pressure (13, 26).

Statistical analysis

Statistical analysis was performed using SPSS software (Version 15.0, SPSS Chicago, USA). Continuous data were presented in median±IQR (interquartile range) or mean±standard deviation (SD). Comparisons of multiple mean values were carried out by student t test or Mann-Whitney U test. To test the distribution pattern, the Kolmogorov-Smirnov test was utilized. Categorical variables were summarized percentages and compared with the Chi-square test or Fisher's exact test. Correlations were sought by the Spearman's and Pearson correlation test. The multivariate linear regression analysis was performed to determine independent relationship between CFR and aortic stiffness and other potential confounding variables. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics

Demographic and clinical characteristics and laboratory results of the study population are summarized in Table 1. The mean age of the study population was 47.3±6.47 years. Gender and mean age were similar between the groups (p>0.05). As expected, the prevalence of HT was significantly higher in patients with MetS. The mean values for BMI and waist circumference were significantly higher in patients with MetS (p<0.05 for all). The mean values hsCRP and FPG levels were significantly higher in patients with MetS than in controls. Patients with MetS had significantly higher LDL cholesterol and triglyceride concentrations, and lower HDL cholesterol levels (p<0.05 for all). Twenty of MetS patients underwent coronary angiography and found normal coronary arteries within last 6 months. All patients in both groups had exercise stress test, which revealed as negative for all.

CFR and aortic distensibility

During adenosine infusion, no major adverse reactions were observed. The mean baseline diastolic peak velocity (DPV) value was similar in both groups (26.3±1.5 cm/s vs. 26.6±1.8 cm/s, p=0.430) but the mean hyperemic DPV was significantly lower in patients with MetS compared with control subjects (60.1±4.5 cm/s vs. 67.7±5.2 cm/s, p<0.001). When CFR was compared between groups, patients with MetS had significantly lower CFR values than did those without MetS (2.3±0.2 vs. 2.7±0.2, p<0.001).

There were no significant differences with regard to end-diastolic volume, end-systolic volume and ejection fraction between the groups. LVMI was significantly higher in patients with MetS than in control subjects (p<0.001). Aortic distensibility was significantly decreased, and aortic stiffness (AS) was increased significantly in patients with MetS compared to controls (10.4±3.5 / 10^{-6}.cm^{-2}.dyn^{-1} vs. 12.7±3.4 / 10^{-6}.cm^{-2}.dyn^{-1}, p=0.002, 6.5±2.0 vs. 3.2±0.8, p<0.001) (Table 2).

Table 1. Comparison of clinical, laboratory and transthoracic and Doppler echocardiography findings

Variables	MetS (n=46)	Controls (n=44)	*p
Age, years	47.3±6.5	46.0±6.1	0.215
Men, n (%)	25 (54.3)	18 (40.9)	0.214
Smoker, n (%)	20 (43.5)	13 (29.5)	0.195
Hypertension, n (%)	29 (63.0)	0 (0)	<0.001
Diabetes mellitus, n (%)	3 (3.3)	0 (0)	0.242
BMI, kg/m^2	31.9±4.1	24.0±3.4	<0.001
Waist circumference, cm	107.1±8.7	84.9±8.7	<0.001
Fasting glucose, mg/dL	106.1±18.3	90.0±7.8	<0.001
Total cholesterol, mg/dL	213.1±33.2	186.2±33.1	<0.001
LDL cholesterol, mg/dL	127.7±35.7	114.2±26.6	0.046
HDL cholesterol, mg/dL	37.7±8.3	53.1±10.6	<0.001
Triglyceride, mg/dL	243.6±64.3	95.8±32.7	<0.001
hs-CRP, mg/L	3.6±3.0	2.1±2.1	0.008
Baseline PDV, cm/s	26.3±1.5	26.6±1.8	0.430
Hyperemic PDV, cm/s	60.1±4.5	67.7±5.2	<0.001
CFR	2.3±0.2	2.7±0.2	<0.001
LVMI, g/m^2	107.5±17.2	80.7±10.6	<0.001
LV EF, %	64.1±2.1	65.1±1.6	0.214

Data are presented as mean±SD and number (percentage)
*Student's t-test and Chi-square test
BMI - body mass index, CFR - coronary flow reserve, HDL - high-density lipoprotein, hs-high sensitive, hsCRP - high-sensitive C - reactive protein, LDL - low-density lipoprotein, LVEF - left ventricular ejection fraction, LVMI - left ventricular mass index, MetS - metabolic syndrome, PDV - peak diastolic velocity

Association of CFR with clinical and echocardiographic variables

In correlation analysis, CFR was significantly correlated with age (r=-0.220, p<0.0001), systolic blood pressure (r=-0.596, p<0.001), diastolic blood pressure (r=-0.216, p=0.042), waist circumference (r=-0.642, p<0.001), total cholesterol (r=-0.251, p=0.018), HDL-cholesterol (r=0.514, p<0.001), triglyceride (r=-0.507, p<0.001), fasting glucose (r=-0.358, p<0.001), hsCRP (r=-0.227, p=0.033), LVMI (r=-0.396, p<0.001), and AS (r=-0.604, p<0.001).

In multivariate linear regression analysis in which CFR was taken as a dependent variable and age, waist circumference, SBP, FPG, HDL-cholesterol, triglyceride, LVMI and AS were taken as independent variables, we found that AS (β=-0.217, p=0.047), SBP (β=0.215, p=0.050) and waist circumference (β=-0.272, p=0.012) have an independent association with impaired CFR (Table 3).

Table 2. Comparison of aortic elastic properties of the groups

Variables	Metabolic syndrome (n=46)	Controls (n=44)	*p
Systolic blood pressure, mmHg	131.4±15.3	110.0±10.6	<0.001
Diastolic blood pressure, mmHg	74.6±10.8	68.4±7.5	0.002
Aortic systolic diameter, cm	3.40±0.23	3.28±0.31	0.035
Aortic diastolic diameter, cm	3.12±0.23	2.90±0.31	<0.001
Aortic strain, %	10.5±2.9	12.1±5.1	0.08
Aortic distensibility,$cm^2.dyn^{-1}.10^{-6}$	10.4±3.5	12.7±3.4	0.002
Aortic stiffness	6.5±2.0	3.2±0.8	<0.001

Data are presented as mean±SD
*Unpaired Students` t-test

Table 3. Independent relationship between CFR and confounding variables by multivariate linear regression analysis (r^2=0.571, p<0.001)

Independent variables	Beta regression coefficient	p
Age	-0.067	0.413
Waist circumference	-0.272	0.012
Systolic blood pressure	-0.215	0.050
Fasting glucose	0.045	0.625
HDL-cholesterol	0.133	0.202
Triglyceride	-0.117	0.229
hsCRP	0.004	0.959
LVMI	-0.028	0.746
Aortic stiffness	-0.217	0.047

Multivariate linear regression analysis
CFR - coronary flow reserve, HDL - high-density lipoprotein, hsCRP - high- sensitive C - reactive protein, LVMI - left ventricular mass index

Discussion

This study demonstrated that coronary flow reserve is impaired in patients with MetS and there is an independent relationship between impaired CFR and increased aortic stiffness evaluated by echocardiography.

MetS is a group of risk factors including obesity, dyslipidemia, insulin resistance/impaired glucose tolerance, and/or hypertension and is accompanied by pro-inflammatory and thrombotic states (27). Since all components of MetS have unfavourable effects on the endothelium, endothelial dysfunction more prevalent in patients with MetS and could play a role in the increased risk for cardiovascular disease and type 2 DM in this population (28). Many reported studies have used several modalities to investigate the relationship MetS and coronary microvascular circulation. Turhan et al. (29) reported an impaired coronary blood flow using the Thrombolysis in Myocardial Infarction frame count method in MetS patients with angiographically normal coronary arteries. Pirat et al. (7), using transthoracic echocardiography, have reported an impaired vasodilatory response to pharmacologic agents in the LAD of coronary arteries in patients with MetS. In present study, we also evaluated CFR, the magnitude of the increase in blood flow at maximal coronary vasodilation, by using transthoracic Doppler echocardiography as a reliable and reproducible way to assess CFR (30) and found that there is a coronary microvascular endothelial dysfunction in MetS patients.

MetS impairs the ability of the coronary circulation to regulate vascular resistance and balance myocardial oxygen supply and demand (9). All the components of MetS (hypertension, dysglycemia, dyslipidemia, and obesity) can individually impair microvascular function (10, 28, 31). Exact mechanisms underlying impaired pharmacologic coronary vasodilation in MetS have not been clearly defined, but are likely related to altered functional expression of receptors and ion channels, endothelial and vascular smooth muscle function, paracrine and neuroendocrine influences, structural remodeling of coronary arterioles and/or microvascular rarefaction (9). Coronary vasomotor dysfunction in the MetS is related to chronic activation of the renin-angiotensin and sympathetic nervous system that leads to augmented angiotensin II tip 1 and alpha 1-adrenoceptor mediated coronary vasoconstriction (5, 32).

Aortic stiffness describes the elastic resistance that the aorta sets against its distension (11). Many methodologies, both invasive and non-invasive, have been applied to the assessment of arterial elasticity (33). To evaluate aortic stiffness, two important variables should be noted: the change in volume due to blood injection in the aorta, and the pressure change caused by this volume change (11). Noninvasive measures fall into three board groups:1) measuring pulse wave velocity (PWV), 2) relating change in diameter (or area) of an artery to distending pressure, and 3) assessing arterial pressure waveforms (11, 34). PWV, which is defined as the velocity of the arterial pulse for moving along the vessel wall, plays an important clinical role in defining patients under high cardiovascular risk and it is inversely correlated with arterial elasticity and relative arterial compliance (35). Measurement of aortic stiffness by applanation tonometry with pulse-wave velocity has been the gold-standard method and is well validated in large populations as a strong predictor of adverse cardiovascular outcomes (34). Additionally, pulse wave velocity can also be assessed noninvasively by echocardiography with pulse wave Doppler. Although this method has not been as commonly used, it seems to have good correlation (r=0.83) with the applanation tonometry (36). The main advantage of ultrasound techniques is their wide availability, and the main limitation is the incomplete visualization of the aortic arch (34). To non-invasively quantity aortic stiffness measurement of systolic blood pressure, diastolic blood pressure and changes in aortic diameters are necessary. Aortic diameters can be measured noninvasively with echocardiography, computed tomography, and magnetic resonance imaging. Stefanadis et al. (13) demonstrated that the noninvasively evaluated aortic stiffness is comparable with invasive methods with a high degree of accuracy. There is growing evidence that large artery stiffness is a significant predictor of adverse cardiovas-

cular outcome (12). MetS causes an increase in arterial stiffness independently of other cardiovascular risk factors (14). Several components of the MetS, including high blood pressure, hyperglycemia, and abdominal fat, have been related to increased aortic stiffness (12, 15).

Relations between microvascular function and aortic stiffness have been reported (37, 38). In the Framingham Heart Study offspring cohort increased aortic stiffness was associated with higher forearm vascular resistance at baseline and during reactive hyperemia, and with blunted flow reserve during hyperemia (39). Aortic stiffening may cause an increase in aortic pulse pressure, left ventricular load, and ultimately, left ventricular hypertrophy (LVH). This LVH, together with the decreased diastolic transmyocardial pressure gradient caused by the decrease in diastolic blood pressure, interacts with coronary flow and flow reserve (17, 40). Besides the aortocoronary hemodynamic relationship, aortic stiffness may be a marker of a more generalized vascular disease or coexists with microvascular disease (13). Another interpretation is that abnormalities in the microcirculation and, therefore, in peripheral vascular resistance, lead to the perturbations in aortic stiffness (41). The hypothesis that coronary flow may be influenced by aortic elastic properties was introduced by Bouvrain et al. (42), and was confirmed by experimental studies (37, 38). In previous studies, significant correlations between CFR and aortic stiffness assessed by pulse wave velocity have been demonstrated in patients with hypertension and coronary artery disease (43, 44). Aortic stiffness has been described to reduce the improvement in hyperemic coronary blood flow after a successful percutaneous coronary intervention (45). Nemes et al. (46) described reduced CFR and increased indices of aortic stiffness [E(p) and E(s)] in patients with LAD coronary artery disease as compared with patients with normal epicardial coronary arteries. In addition to these findings in patients with coronary artery disease, Nemes et al. demonstrated significant correlations between CFR and aortic stiffness in patients without coronary artery disease, but with hypertension, aortic valve stenosis, type-2 diabetes and hypercholesterolemia (16-19). However, presence of an association between aortic stiffness and impaired CFR in MetS has never been evaluated.

Each of components of the MetS has been independently associated with vascular dysfunction (6, 47). In hypertension, the structure and function of the microcirculation are altered (48). As the vasoconstriction takes place with the decreases in vasodilatation, wall to lumen ratio of precapillary arterioles increases (41). The obese patients have similar alterations in microcirculation (49). Insulin resistance is also associated with impaired capillary recruitment and microvascular vasodilation (41). In addition, obesity is associated with insulin resistance and insulin resistance leads to endothelial dysfunction (31). Endothelial and microvascular dysfunction are present in obese subjects even in the absence of hypertension or hyperglycemia, and it is better correlated to waist/hip ratio than BMI (50). Additionally, endothelial dysfunction may lead to functional stiffening of large arteries as the reduced availability of nitric oxide and increased activity of vasoconstrictors (51). Endothelial dysfunction may lead to smooth muscle cell proliferation and increased synthesis of structural proteins such as collagen. The insulin resistance of obesity is known to be associated with arterial stiffness (52). Our study revealed an independent relationship of decreased coronary flow reserve with increased aortic stiffness, waist circumference or systolic blood pressure.

Study limitations

Our study has several limitations. The most significant of all is the small number of patients in both groups. Another major concern is the measurement method of aortic stiffness, which was not performed with pulsed wave velocity analysis. Owing to the lack of clinical indications and the invasive nature of the procedure, we did not perform coronary angiography in all patients. Also we did not assess invasively CFR. However, transthoracic Doppler echocardiography with pharmacological stress for the assessment of CFR has been demonstrated to be a useful and highly reproducible tool to evaluate CFR (30). The cross-sectional design of this study, causation cannot be established. Although our data suggest that these echocardiographic properties are related to overall effect of MetS on the aorta and coronary arteries, confirmatory longitudinal work is necessary.

Conclusion

The cluster of metabolic and hemodynamic abnormalities present in metabolic syndrome is associated with impaired coronary flow reserve. Waist circumference, systolic blood pressure or aortic stiffness has an independent association with coronary microvascular dysfunction. These results can suggest the overall effect of MetS on the function and structure of the aorta and coronary arteries. Using a noninvasive and readily available tool, transthoracic Doppler echocardiography, aortic stiffness and coronary flow reserve can easily be simultaneous evaluated. However, future research is warranted to provide more robust information on direct evaluation of aortic stiffness and CFR in patients with MetS.

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