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Salbutamol-mediated effects on arterial parameters: a tool for subclinical atherosclerosis detection in patients with metabolic syndrome submitted to a cardiac rehabilitation program

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Abstract

Introduction. Early detection of atherosclerosis is important in patients with metabolic syndrome (MetS) because cardiovascular diseases are the main cause of mortality in these patients. Cardiac rehabilitation (CR) is one of the best known and studied interventions, which has been shown to be associated with decreased morbidity and mortality of cardiovascular disease. Salbutamol-mediated effects on pulse wave represent a practical, valid and reliable non-invasive surrogate marker of subclinical atherosclerosis.

Aim of the study We assessed subclinical atherosclerosis in patients with MetS vs. a control group, by measuring aortic pulse wave velocity (PWVAo), the augmentation index and central blood pressure, before and after salbutamol administration, which allows evaluation of the hemodynamic effects of inhaled salbutamol on the arterial parameters.

Material and methods We conducted a clinical study on a representative sample of 30 subjects, 67% had metabolic syndrome and 33% did not have metabolic syndrome (control group). We measured all parameters of arterial stiffness: brachial augmentation index (Aixb), aortic augmentation index (Aixao), pulse wave velocity (PWVao), aortic pulse pressure (PPao), central blood pressure (SBPao), before and after administration of two inhalations of Ventolin® (salbutamol).

Results The analysis of arterial stiffness parameters (Table 2) showed that PWVao before salbutamol administration was 10.60 m/s in the group with MetS, and 9.11 m/s in the control group, with no significant difference. After salbutamol administration, PWVao was 10.78 m/s in the group with MetS, and significantly lower 8.2 m/s (p=0.008), in the group without MetS.

There was a significant difference between the groups regarding PPao (mmHg) before salbutamol (54.040 ± 8.5530, 66.215 ± 15.6326, p=0.03), SBPao (mmHg) before salbutamol (147.14±20.12 vs. 125.34±9.71; p<0.0001) and after salbutamol administration. (138.76±21.97 vs.121.38±8.08; p=0.005). There were no significant differences in brachial Aix (0.03±27.5 vs.-3.04±29.64, p=NS) and aortic Aix (37.72±14.04 vs.36.11±15; p=NS) between the two groups.

Conclusions. Early identification of endothelial dysfunction in subjects with metabolic syndrome is important in order to prescribe an optimal cardiac rehabilitation program.

Key words: *cardiac rehabilitation, metabolic syndrome, subclinical atherosclerosis*

Introduction

Metabolic syndrome (MetS), defined as a cluster of features such as visceral obesity, impaired glucose tolerance, dyslipidemia, hypertriglyceridemia, and elevated blood pressure, is highly prevalent all over the world. MetS has been known as a critical risk factor in the incidence of cardiovascular outcomes. People with MetS have higher all-cause or cardiovascular mortality than those without MetS [1]. Cardiac rehabilitation (CR) is one of the best known and studied interventions, which has been shown to be associated with decreased morbidity and mortality of cardiovascular diseases(CVD)[2].

CR is a complex interventional therapy, which is defined as "comprehensive long-term services involving medical evaluation, prescribed exercise, cardiac risk-factor modification, health education, counseling, and behavioral interventions" by the U.S. Department of Health and Human Services and the National Heart, Lung, and Blood Institute [3-4]. Numerous mechanisms may be responsible for improving survival associated with exercise-based CR, including cardiovascular risk factor modification

(smoking, lipids, blood pressure, and glucose metabolism) [5]. Larger volumes of exercise training (associated with higher energy expenditures) have been shown to underline regression of atherosclerosis.

On the other hand, MetS among CVD patients is associated with a higher risk of mortality and morbidity [6]. Exercise and diet are perceived not only as the key components of treatment and prevention strategies in patients with MetS or CVD [7-9], but also as essential parts of CR.

The first-line management in individuals with MetS is lifestyle modification [10]. One of the core components of lifestyle change is physical activity, which is also the most important part of a CR program for patients with CVD [11-13].

Early identification of subclinical atherosclerosis in subjects with metabolic syndrome is important in order to prescribe an optimal cardiac rehabilitation program.

Salbutamol-mediated effects on pulse wave represent a practical, valid and reliable non-invasive surrogate marker of subclinical atherosclerosis [14]. PWA provides useful information regarding the mechanical properties of the arterial tree and the ventricular-vascular interaction [5] and can also be used to assess endothelial function [6].

The vascular endothelium releases a number of biologically active mediators, including nitric oxide (NO), which regulate vessel tone and prevent the development of atheroma. Endothelial dysfunction, characterized by a reduced bioavailability of endothelium-derived NO, is an important step in the progression of atherosclerosis [14].

Indeed, resistance vessel, conduit artery, and coronary endothelial dysfunction independently predict all-cause and cardiovascular mortality [14,15]. A number of risk factors for cardiovascular disease, including age, hypertension, obesity, hypercholesterolemia, diabetes and smoking, are associated with systemic endothelial dysfunction [16]. Interestingly, these risk factors are also associated with increased elastic artery stiffness which is itself an important predictor of outcome in a number of patient groups [17].

Studies have confirmed that endothelial dysfunction occurs prior to atheroma formation, and assessment of endothelial function has been used as a surrogate marker for arterial damage [8]. Arterial stiffness can be measured using pulse wave velocity (PWV) [18].

Pulse wave analysis (PWA) is a non-invasive, repeatable technique that analyzes the arterial pulse wave form providing information about arterial compliance [18,19]. Recently, the changes in PWA-derived measure of wave reflection and arterial stiffness, the augmentation index (AIx), after b2-adrenoceptor agonist-induced endothelial stimulation, have been used to assess the role of endothelium in vascular responsiveness [20].

This is an alternative approach to the assessment of endothelial function, measuring the vasodilator response to b2-adrenoceptor agonists, mediated in part by endothelium-derived NO [20-23].

Aim of the study

The aim of the study was to identify metabolic syndrome patients with subclinical atherosclerosis, in order to include them in cardiac rehabilitation programs to reduce their risk of cardiovascular events.

We assessed subclinical atherosclerosis in patients with MetS vs. a control group, by measuring:

- aortic pulse wave velocity (PWVAo);
- the augmentation index and central blood pressure;
- before and after salbutamol administration, which allows evaluation of the hemodynamic effects of inhaled salbutamol on the arterial parameters.

Material and methods

Patient selection. We conducted a clinical study on a representative sample of 30 subjects.

This study was carried out in the CF University Hospital Cluj in the period spanning between February 2016 and April 2016. All patients underwent medical history taking and clinical examination, as well as anthropometric measurements; information about the habit of smoking and history of stroke was recorded; biochemical and arterial parameters were determined. All patients underwent electrocardiography; echocardiography was performed in selected cases - systolic and diastolic function, aortic and valvular atherosclerosis were assessed.

Arterial parameters were evaluated using the TensioMed^{TM} Arteriograph.

Anthropometric measurements were carried out and included weight, height and waist circumference. Based on anthropometric measurements, the body mass index (BMI) was calculated. Hypertension was diagnosed based on blood pressure measurements

performed at least twice during two or three different appointments, in a quiet room after lying down for 15 minutes. Type 2 diabetes or impaired fasting glucose was diagnosed using WHO criteria. The levels of triglycerides (TG), total cholesterol, low-density lipoproteins and high-density lipoproteins were estimated according to standard protocols. Other biochemical tests included determinations of ESR, fibrinogen (Fb), plasma urea and creatinine, hepatic enzymes – alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT).

We measured all parameters of arterial stiffness: brachial augmentation index (Aixb), aortic augmentation index (Aixao), pulse wave velocity (PWVao), aortic pulse pressure (PPao), central blood pressure (SBPao), before and after administration of two inhalations of Ventolin® (salbutamol, 400 yg).

All patients signed an informed consent for participation in the study, which was approved by the Ethics Committee.

Statistical analysis was performed using SPSS 22.0 software.

We assessed the data distribution normality using the Kolmogorov test. Data are presented as mean ± standard deviation and median values, respectively. Categorical variables are presented as numbers and percentages. Pearson's correlation test was used for quantitative variables with normal distribution, and Spearman's correlation test was employed for quantitative variables with abnormal distribution. The Student t test (independent and paired) and Mann-Whitney test were used to assess the significance of the difference between the groups. A p less than 0.05 was considered statistically significant.

Results

The study included 30 patients and, based on the new definition of metabolic syndrome according to the International Diabetes Federation (IDF), American Heart Association (AHA), National Heart Lung and Blood Institute (NHLBI) 2009 [24], 20 patients (67%) had metabolic syndrome and 10 (33%) did not have metabolic syndrome (control group).

The majority of the patients were women (57%). 70% of the MetS group and 30% of the control group were female. The mean age was 60.55 ± 7.31 years for patients with MetS and 48.8 ±12.88 years for patients without MetS, with a significant difference (p=0.02). There were 17 (85%) patients with diabetes in the MetS group, compared to 10% in the other group; in the MetS group, there were 15 (75%) obese subjects. In the group without MetS, most subjects were normal weight (80%), skinny (10%) or overweight (10%). The mean BMI among patients with MetS was 33.49 ± 4.21, compared to the other group, 22.02 ± 3.10, with a significant difference (p<0.001). The mean weight of patients with MetS was 91.4 ± 14.10 kg, compared to 64.7 ± 9.12 in the other group. All data are presented in Table 1.

Table 1. Descriptive statistics for the two groups

	Subjects with MetS	Subjects without MetS	p-value
Age (years) (mean ± SD)	60.55±7.31	48.8 ±12.88	0.02
Weight (kg)	91.4±14.10	64.7±9.12	<0.0001
BMI (W/H^2)	33.49±4.21	22.02±3.10	<0.0001
Waist circumference (cm)	113.32±13.83	77.4±11.79	<0.0001
Glycemia	152.6±63.06	81.14±10.7	0.007
Cholesterol	228.9±59.09	214.6±37.8	NS
TG	317.45±96.31	104.42±13.27	0.04

Results expressed as mean values ± SD.
Abbreviations: BMI: body mass index, TG: triglycerides.

Systolic blood pressure in the group with MetS was higher than in the control group (146.4±19.2 vs. 125.5±10.8, p-0.001), before salbutamol. Diastolic blood pressure in MetS subjects was 80.95 mmHg, higher than in the other group (71.3 mmHg, p=0.02). The analysis of arterial stiffness parameters (Table 2) showed that PWVao before salbutamol administration was 10.60 m/s in the group with MetS, and 9.11 m/s in the control group, with no significant difference. After salbutamol administration, PWVao was 10.78 m/s in the group with MetS, and significantly lower 8.2 m/s (p=0.008), in the group without MetS.

There was a significant difference between the groups regarding PPao (mmHg) before salbutamol (54.040 ± 8.5530, 66.215 ± 15.6326, p=0.03), SBPao (mmHg) before salbutamol (147.14±20.12 vs. 125.34±9.71; p<0.0001) and after salbutamol administration. (138.76±21.97 vs.121.38±8.08; p=0.005). There were no significant differences in brachial Aix (0.03±27.5 vs.-3.04±29.64, p=NS) and aortic Aix (37.72±14.04 vs.36.11±15; p=NS) between the two groups.

Table 2. Parameters of arterial stiffness before and after salbutamol administration

Parameter	Subjects with MetS	Subjects without MetS	p-value
Aixb before salbutamol (%)	**0.03±27.5**	**-3.04±29.64**	**NS**
Aixb after salbutamol (%)	**-2.69±31.45**	**-6.13±29.88**	**NS**
AixAo before salbutamol (%)	**37.72±14.04**	**36.11±15**	**NS**
AixAo after salbutamol (%)	**35.22±16.71**	**34.51±15.15**	**NS**
PWVAo before salbutamol(m/s)	**10.60±2.89**	**9.11±2.48**	**NS**
PWVAo after salbutamol(m/s)	**10.78±2.51**	**8.2±1.96**	**0.008**
PPao before salbutamol	**66.21±15.63**	**54.04±8.55**	**0.03**
PPao after salbutamol	**60.5±16.64**	**50.68±6.42**	**0.08**
SBPao before salbutamol	**147.14±20.12**	**125.34±9.71**	**<0.0001**
SBPao after salbutamol	**138.76±21.97**	**121.38±8.08**	**0.005**
SBP before salbutamol	**146.4±19.2**	**125.5±10.8**	**0.001**
SBP after salbutamol	**139.68±19.95**	**121.8±11.68**	**0.01**
DBP before salbutamol	**80.95±11.43**	**71.3±8.79**	**0.02**
DBP after salbutamol	**78.25±11.08**	**70.7±8.76**	**0.07**
MAP before salbutamol	**102.6±12.79**	**89.5±7.69**	**0.006**
MAP after salbutamol	**98.95±13.10**	**88.4±7.86**	**0.03**
HR before salbutamol	**71.2±10.27**	**65.8±10.09**	**NS**
HR after salbutamol	**70.26±10.01**	**65.8±9.68**	**NS**

Results expressed as mean values ± SD; Aixb: brachial augmentation index; AixAo: aortic augmentation index; PWVAo: pulse wave velocity; PPao: aortic pulse pressure; SBPao: central blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate.

Pearson's correlation coefficient (r) in absolute value showed that the correlation between pulse wave velocity (PWVao) and diastolic blood pressure, glycemia, total cholesterol was a low or non-linear correlation.

There was a good correlation between pulse wave velocity and abdominal circumference (p-0.003), body mass index (p-0.004), and age (p-0.01). (table 3)

Table 3. Pearson's correlation coefficient between arterial parameters and clinical parameters

	PWV Ao	AixAo	Aixb	PPao	SBPao
SBP	-0.027	-0.031	-0.034	0.710	0.916
DBP	0.182	0.110	0.106	0.165	0.690
Glycemia	0.105	-0.350	-0.350	0.011	0.164
Triglycerides	-0.044	-0.119	-0.117	0.138	0.015
Total cholesterol	0.145	-0.120	-0.118	0.127	-0.055
Abdominal circumference	0.518	0.0781	0.079	0.223	0.500
Weight	0.432	-0.164	-0.162	0.005	0.284
Age	0.262	-0.042	-0.047	0.280	0.276
BMI	0.509	0.003	0.004	0.218	0.356

Aixb: brachial augmentation index; AixAo: aortic augmentation index; PWVAo: pulse wave velocity; PPao: aortic pulse pressure; SBPao: central blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The brachial augmentation index (Table 4) before administration of salbutamol was 0.03±27.5% and after salbutamol it was -2.69±31.4%, with no significant difference (p=NS), both in patients with MetS and in those without MetS.

The aortic augmentation index prior to salbutamol was 37.7±14.0%, while after salbutamol it was 35.2±16.7%, showing no significant difference (p-0.087) in subjects with MetS, or in subjects without MetS; but considering the whole lot of patients the decrease of this parameter was significant (p-0.03).

The pulse wave velocity before salbutamol administration was 10.60 ± 2.89 m/s; after salbutamol administration it was 10.78 ± 2.51 m/s (p=0.684) in MetS group.

The aortic pulse pressure was 66.06 ± 16.0 mmHg before salbutamol and 60.05 ± 16.64 mmHg after salbutamol administration, evidencing a significant decrease (p=0.02), in both groups.(MetS+ , MetS-)

The central blood pressure (SBPao) was 146.5±20mmHg before salbutamol and 138.7±21.9 mmHg after salbutamol administration, with a significant difference (<0.0001) in Mets+ group. Also, there was a change in central blood pressure, from 125.34 ± 9.71 mmHg to 121.38 ± 8.08 mmHg after salbutamol administration, in MetS- group.

Table 4. Comparison of the values of arterial parameters before and after administration of salbutamol

Parameter	Subjects with MetS			Subjects without MetS			All patients		
	Before salbutamol	After	p	Before salbutamol	After	p	Before salbutamol	After	p
Aixb	0.03±27.5	-2.69±31.4	NS	-3.04±29.6	-6.1±29.8	0.07	-0.9±27.6	-3.7±30.4	NS
AixAo	37.7±14.0	35.2±16.7	0.08	36.1±15.0	34.5±15.1	0.07	37.2±14.0	35.0±15.9	0.03
PWVao	10.6±2.8	10.7±2.51	NS	9.1±2.4	8.2±1.9	NS	10.1±2.8	9.9±2.6	NS
PPao	66.06±16.	60.5±16.6	0.02	54.0±8.5	50.6±6.4	0.02	61.9±14.9	57.1±14.6	<0.0001
SBPao	146.5±20	138.7±21.9	<0.0001	125.3±9.7	121.3±8.0	0.03	139.2±20	132.7±20	<0.0001
HR	71.0±10.5	7.2±10.0	NS	65.8±10.0	64.5±9.8	NS	69.2±10.4	68.7±9.9	NS

Aixb: brachial augmentation index; AixAo: aortic augmentation index; PWVAo: pulse wave velocity; PPao: aortic pulse pressure; SBPao: central blood pressure; HR: heart rate.

Discussion

The aortic pulse pressure and central blood pressure of subjects with metabolic syndrome decreased after the administration of salbutamol, unlike the value of pulse wave velocity which was almost constant, similarly to the values of the brachial augmentation index and the aortic augmentation index. The change of their values was not statistically significant after salbutamol administration, which is an indicator of endothelial dysfunction and arterial stiffness. A recent study shows that the lowering influence of salbutamol on augmentation index may be largely explained by increased heart rate, suggesting that this effect may not predominantly reflect endothelial function. [25]

Pulse wave velocity in controls decreased after salbutamol administration, which evidences a good endothelial function. Regarding the brachial and aortic augmentation index there were no significant differences between subjects with metabolic syndrome and controls, before salbutamol and after salbutamol. The Student test evidenced no statistically significant difference in pulse wave velocity before salbutamol administration between the two groups, but instead, after salbutamol administration there was a statistically significant difference in the p value. Thus, salbutamol improves assay sensitivity for the diagnosis of atherosclerosis.
Although β2-adrenoceptors mediate vasorelaxation at the level of vascular smooth muscle, the stimulation of β2-adrenoceptors is known to increase endothelial release of NO and cause largely endothelium-mediated vascular relaxation [26]. Therefore, the effect of the β2-adrenoceptor agonist salbutamol on the PWA-derived measure of wave reflection and arterial stiffness, the Aix, has been applied as a method to evaluate the influence of endothelial stimulation in the whole arterial tree [20, 27, 28]. In a recent study, inhaled salbutamol has induced an 8–12% decrease in the Aix in healthy subjects, but in many studies the effects on other haemodynamic variables have not been determined [26]. Waring, in contrast to a number of studies, showed that endothelial function (Aix after Salbutamol) is preserved in patients with hypertension. [20]. In other study [29], the inhalation of salbutamol reduced systemic vascular resistance and BP and increased heart rate already before the decrease in Aix was observed. In this study, was no significant differences for heart rate, before and after salbutamol.

Conclusions

The asses of endothelial dysfunction and arterial stiffness in patients with metabolic syndrome allow the early identification of subclinical atherosclerosis. PWA is a simple technique capable of assessing systemic arterial stiffness and endothelial function.
Perspectives
Early identification of subclinical atherosclerosis in subjects with MetS will allow their early inclusion in cardiac rehabilitation programs.

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