Impact of the metabolic syndrome on aortic pulse pressure and ascending aortic pulsatility in patients with angiographically normal coronary arteries

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BACKGROUND: Large artery stiffness is a major determinant of pulse pressure (PP), and PP at baseline has been associated with future coronary events.

OBJECTIVE: To evaluate the impact of the metabolic syndrome on aortic PP and ascending aortic pulsatility (AP) in patients with angiographically normal coronary arteries.

METHODS: Forty-two patients with the metabolic syndrome and 40 age-matched control subjects without the metabolic syndrome were included in the study. All subjects had normal coronary arteries. Diagnosis of the metabolic syndrome was based on the International Diabetes Federation guidelines published in 2005. Ascending AP was estimated as the ratio of aortic PP to mean blood pressure.

RESULTS: Aortic PP (59 ± 12 mmHg versus 43 ± 10 mmHg; $P < 0.001$) and ascending AP (0.54 ± 0.10 versus 0.48 ± 0.10 ; $P < 0.001$) were significantly higher in the metabolic syndrome group. Multiple regression analysis revealed statistically independent relationships between ascending AP and fasting blood glucose, waist circumference and systolic blood pressure (model $R^2 = 0.408$; $P < 0.001$). The metabolic syndrome, as a whole, was also independently associated with both ascending AP ($P < 0.01$) and aortic PP ($P < 0.01$).

CONCLUSION: The data showed that the metabolic syndrome is independently associated with increased aortic PP and ascending AP in patients with normal coronary arteries, suggesting aortic stiffness as one of the possible mechanisms underlying the excess cardiovascular risk associated with the metabolic syndrome.

Key Words: Aortic stiffness; Metabolic syndrome

The metabolic syndrome, a cluster of atherosclerotic risk factors including impaired glucose tolerance, systemic hypertension, dyslipidemia and abdominal obesity (1,2), significantly increases the future cardiovascular risk of patients (3). Arterial stiffness is also recognized as an independent predictor of adverse cardiovascular outcomes (4,5). In fact, ascending aortic pulsatility (AP), an index of arterial stiffness, is related to the presence and extent of coronary artery disease and also has been shown to be a powerful predictor of restenosis after percutaneous transluminal coronary angioplasty (6,7). Increased arterial stiffness has been demonstrated in obese children with the metabolic syndrome (8). Furthermore, central arterial stiffness and insulin resistance have been positively correlated (9,10). Moreover, the extent of metabolic changes has been shown to predict arterial stiffness in a dose-dependent manner (11). Impaired glucose tolerance and hyperinsulinemia promote wall hypertrophy and fibrosis by increasing the local activity of the renin-angiotensin-aldosterone system (12-14). Impaired glucose tolerance also increases nonenzymatic glycation of proteins and alters the structure of the arterial wall (15).

Several components of the metabolic syndrome have been related to increased aortic stiffness (10,16,17). However, only a few studies

Impact du syndrome métabolique sur la pression aortique pulsée et la pulsatilité aortique ascendante chez des patients présentant des coronaires normales à la coronarographie

HISTORIQUE : La rigidité des grosses artères est un élément déterminant de la pression pulsée (PP) et on a pu établir un lien entre la PP au départ et d'éventuels accidents coronariens.

OBJECTIF : Évaluer l'impact du syndrome métabolique sur la PP aortique et la pulsatilité aortique (PA) ascendante chez des patients présentant des coronaires normales à la coronarographie.

MÉTHODE : Quarante-deux patients atteints de syndrome métabolique et 40 sujets témoins assortis selon l'âge et indemnes du syndrome métabolique ont été inclus dans l'étude. Tous les sujets présentaient des coronaires normales. Le diagnostic de syndrome métabolique se fondait sur les directives publiées en 2005 par la Fédération internationale du diabète. La PA ascendante a été estimée par le rapport entre la PP aortique et la tension artérielle moyenne.

RÉSULTATS : La PP aortique (59 ± 12 mm Hg vs 43 ± 10 mm Hg, $p < 0,001$) et la PA ascendante ($0,54 \pm 0,10$ vs $0,48 \pm 0,10$, $p < 0,001$) étaient significativement plus élevées dans le groupe atteint de syndrome métabolique. L'analyse de régression multiple a révélé des liens statistiquement indépendants entre la PA ascendante et la glycémie à jeun, le tour de taille et la tension artérielle systolique (modèle $R^2 = 0,408$, $p < 0,001$). Dans l'ensemble, le syndrome métabolique a été associé de façon indépendante à la PA ascendante ($p < 0,01$) et à la PP aortique ($p < 0,01$).

CONCLUSION : Les données ont révélé que le syndrome métabolique est associé de façon indépendante à une PP aortique et à une PA ascendante élevées chez les patients dont les coronaires sont normales, évoquant la possibilité que la rigidité aortique soit l'un des mécanismes possibles à l'origine de l'accroissement du risque cardiovasculaire associé au syndrome métabolique.

have investigated the association of the metabolic syndrome, as a whole, with large artery stiffness (11,18,19). In the present study, we evaluated the impact of the metabolic syndrome on two determinants of large artery stiffness – aortic pulse pressure (PP) and ascending AP – in patients with angiographically normal coronary arteries.

METHODS

Study population

The study population included 42 patients with the metabolic syndrome (group 1: 16 men; mean $\pm$ SD] age 54 ± 5 years) and 40 age-matched control subjects without the metabolic syndrome (group 2: 14 men; mean age 54 ± 6 years). All participants were selected from a group of individuals who underwent coronary angiography at the Siyami Ersek Thoracic and CV Surgery Center (Istanbul, Turkey) with a suspicion of coronary artery disease and diagnosed as having angiographically normal coronary arteries. The indications for coronary angiography in patients with the metabolic syndrome were the presence of typical angina pectoris and/or abnormal noninvasive test results suggesting myocardial ischemia. The control group consisted of 40 patients with atypical chest pain admitted to the hospital for elective coronary angiography and subsequently found to have

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TABLE 1
Baseline clinical, biochemical and anthropometric findings

	Controls (n=40)	Metabolic syndrome (n=42)	P
Age, years	54±6	54±5	NS
Male, n (%)	14 (35)	16 (38)	NS
Smoker, n (%)	16 (40)	19 (45)	NS
Body mass index, kg/m ²	25±2	30±3	<0.001
Waist circumference, cm	81±8	97±10	<0.001
Total cholesterol, mmol/L	4.84±0.49	5.02±0.39	NS
LDL cholesterol, mmol/L	2.80±0.54	2.98±0.49	NS
HDL cholesterol, mmol/L	1.37±0.18	1.01±0.15	<0.001
Triglyceride, mmol/L	1.45±0.21	2.25±0.33	<0.001
Glucose, mmol/L	4.94±0.44	6.38±0.39	<0.001
Number of components of the metabolic syndrome	1.2±0.5	4.0±0.8	<0.001
Systolic BP, mmHg	118±7	148±15	<0.001
Diastolic BP, mmHg	75±6	89±8	<0.001
Mean BP, mmHg	89±7	109±11	<0.001
Pulse pressure, mmHg	43±10	59±12	<0.001
Ascending aortic pulsatility	0.48±0.10	0.54±0.10	<0.001

Data presented as mean ± SD unless otherwise specified. BP Blood pressure; HDL High-density lipoprotein; LDL Low-density lipoprotein; NS Not statistically significant

angiographically normal coronary arteries. Informed consent was obtained from each subject. The study was approved by the institutional committee on human research.

Exclusion criteria included coronary artery disease, history of myocardial infarction, left ventricular dysfunction, valvular heart disease, atrial fibrillation, history of hormone replacement therapy, uncontrolled systemic hypertension and treatment for hyperlipidemia. Diabetic patients were excluded based on self-report of diabetes or documented use of oral hypoglycemic agents or insulin. Among individuals not reporting diabetes, or not using oral agents or insulin, undiagnosed diabetes was identified using the American Diabetes Association criteria (20); these patients were also excluded.

Diagnostic criteria for the metabolic syndrome

The diagnosis of the metabolic syndrome was based on the International Diabetes Federation clinical definition of the metabolic syndrome (21). This requires the presence of abdominal obesity (waist circumference greater than 94 cm in men and greater than 80 cm in women), plus two of the following factors: a high triglyceride level (1.695 mmol/L or greater); a low high-density lipoprotein (HDL) cholesterol level (less than 1.04 mmol/L for men and less than 1.30 mmol/L for women); high blood pressure (systolic 130 mmHg or greater, or diastolic 85 mmHg or greater, or on antihypertensive medication); and a high fasting plasma glucose concentration (5.6 mmol/L or greater). Control subjects had fewer than two of these properties.

Biochemical analysis

The study group was asked to fast for 12 h before blood sampling. Serum concentrations of total cholesterol and triglycerides were measured by full enzymatic techniques. HDL cholesterol was determined after precipitation of apolipoprotein B-containing lipoproteins with nonchloride and dextran sulphate. Low-density lipoprotein (LDL) cholesterol was calculated as described by Friedewald et al (22). Plasma glucose was measured with the glucose oxidase technique.

Anthropometric measurements

Height, weight and waist circumference were measured according to a standardized protocol (23). Body mass index was calculated by dividing weight in kilograms by height in metres squared (kg/m²). The waist circumference was measured at its smallest point with the abdomen relaxed.

Measurement of hemodynamic parameters

Hemodynamic measurements were obtained during cardiac catheterization with the patient supine. Aortic pressure was measured using a fluid-filled system (pigtail catheter) placed at the ascending aorta. Systolic and diastolic aortic pressures were obtained from pressure tracings at a paper speed of 25 mm/s. In each patient, an average of six to nine blood pressure curves were used for analysis. Aortic mean pressure was calculated using the following formula:

$$1/3 \text{ systolic pressure} + 2/3 \text{ diastolic pressure}$$

AP (fractional PP) was defined as the ratio of aortic PP to mean blood pressure (24).

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables are expressed as percentages. Comparison of categorical and continuous variables between the two groups was performed using the χ^2 test and paired *t* test, respectively. Multiple regression analyses were performed to further quantify the relationships between aortic PP and ascending AP, and the components of the metabolic syndrome. Specifically, aortic PP and ascending AP were regressed for waist circumference, body mass index, HDL cholesterol, LDL cholesterol, total cholesterol, fasting plasma glucose, triglyceride level, and systolic and diastolic blood pressure. The models were run again after adding the metabolic syndrome as a dummy explanatory variable. To confirm the significance of the metabolic syndrome, another set of models including the individual components of the metabolic syndrome (but without the metabolic syndrome) and all of the possible interactions among these components was constructed. To demonstrate the contribution of the metabolic syndrome to ascending AP and aortic PP, these values were calculated with the least-squares method after adjusting for sex, LDL cholesterol and the individual components of the metabolic syndrome. The values were then computed in the presence and absence of the metabolic syndrome in the model and compared by analysis of covariance.

RESULTS

Baseline clinical, biochemical and anthropometric findings of patients with the metabolic syndrome and control subjects are presented in Table 1. As expected, patients with the metabolic syndrome had a greater waist circumference, higher serum triglycerides and fasting plasma glucose, and lower HDL cholesterol than control subjects. All of the female patients in the study population were postmenopausal (cessation of menses for at least one year). In terms of smoking, 25% of patients in the control group and 26% of patients in the metabolic syndrome group were light smokers (less than five cigarettes/day). In the metabolic syndrome group, 38 patients (90%) were hypertensive and taking antihypertensive medications that included angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (n=28), calcium channel blockers (n=12), beta-blockers (n=4) and diuretics (n=12). In addition, 24 patients (57%) in the metabolic syndrome group were on fenofibrates.

Patients with the metabolic syndrome had higher systolic and diastolic blood pressures than the control group (Table 1). Aortic PP (59±12 mmHg versus 43±10 mmHg, *P*<0.001) and ascending AP (0.54±0.10 versus 0.48±0.10, *P*<0.001) were found to be significantly higher in patients with the metabolic syndrome than in age-matched control subjects (Table 1). The overall relative frequency of each component of the metabolic syndrome is presented in Table 2.

Multiple regression analysis revealed statistically independent relationships between ascending AP and fasting blood glucose, waist circumference and systolic blood pressure (model *R*²=0.408; *P*<0.001) (Table 3). In addition, fasting blood glucose, waist circumference and systolic blood pressure were each independently associated with aortic PP (model *R*²=0.438; *P*<0.001) (Table 4). When the model was run again after adding the metabolic syndrome as a dummy variable, the

TABLE 2
Relative frequency of each component in the metabolic syndrome group

	n (%)
Waist circumference (>94 cm in men; >80 cm in women)	42 (100)
Blood pressure (systolic $\geq$ 130 mmHg; diastolic $\geq$ 85 mmHg)	38 (90)
High fasting plasma glucose ($\geq$ 5.55 mmol/L)	35 (83)
High triglyceride level ($\geq$ 1.695 mmol/L)	30 (71)
Low HDL cholesterol level (<1.04 mmol/L for men; <1.30 mmol/L for women)	32 (76)
<i>HDL High-density lipoprotein</i>	

variables remained independently associated with ascending AP and aortic PP, respectively. The metabolic syndrome, as a whole, was also found to be independently associated with both ascending AP ($P<0.01$) and aortic PP ($P<0.01$) (Tables 3 and 4).

When the model was run after including all of the possible interactions among the individual components as independent variables, the model R^2 (0.46 for both) was modestly increased by the addition of these interaction terms. By analysis of covariance, the addition of the metabolic syndrome to the models significantly increased the values of ascending AP ($P=0.04$) and aortic PP ($P=0.02$). When treated hypertensive and normotensive patients were combined, the significance of the same predictors persisted on multiple regression analyses, and the model R^2 was reduced by only 1%.

DISCUSSION

The present study had two main findings. First, aortic PP and ascending AP are significantly higher in patients with the metabolic syndrome than in age-matched control subjects. Second, even after considering each individual component of the metabolic syndrome, the clustering of at least three components of the metabolic syndrome is independently associated with increased aortic PP and ascending AP in patients with angiographically normal coronary arteries.

There is growing evidence that large artery stiffness is a significant predictor of adverse cardiovascular outcomes (4,5). In the Framingham Heart Study (25), increased PP, an index of large artery stiffness, was shown to be strongly related to the risk of coronary artery disease in middle-aged and elderly populations without clinical evidence of coronary artery disease at baseline, during a 20-year follow-up period.

The metabolic syndrome, a cluster of atherosclerotic risk factors, has also been associated with a high risk of cardiovascular events (3) and the number of metabolic syndrome criteria and mortality from cardiovascular causes has been shown to have a linear relationship (26). A possible mechanism by which the metabolic syndrome affects cardiovascular outcomes may be through its association with large artery stiffness. Indeed, several of the individual components of the syndrome, including systemic hypertension (16), hyperglycemia (17) and visceral adiposity (10), have been related to increased aortic stiffness.

However, only a few studies have investigated the association of the metabolic syndrome, as a whole, with arterial stiffness. In a cohort of 180 nondiabetic, healthy, middle-aged women, carotid artery distensibility was associated with several components of the metabolic syndrome, as well as with their clustering (18). More recently, the clustering of multiple components of the metabolic syndrome have been associated with increased aortic pulse wave velocity in middle-aged Japanese men (19) and with carotid artery stiffness in the Baltimore Longitudinal Study on Aging (11).

Our study confirmed these findings and extended them. We used a different index of stiffness (ascending AP) that has been associated with angiographic coronary artery disease and shown to be a powerful predictor of restenosis after percutaneous transluminal coronary angioplasty (6,7). Despite the fact that the control subjects were age-matched, both aortic PP and ascending AP were found to be higher in the metabolic syndrome group, suggesting the metabolic syndrome as an accelerant of vascular aging. The metabolic syndrome, as a whole,

TABLE 3
Multiple regression models evaluating the independent determinants of ascending aortic pulsatility (fractional pulse pressure)

Determinant	Metabolic syndrome added to model			
	No		Yes	
	Regression coefficient	P	Regression coefficient	P
Fasting glucose	0.034	<0.02	0.032	<0.03
SBP	0.046	<0.01	0.038	<0.01
Waist circumference	0.062	<0.01	0.060	<0.01
Metabolic syndrome	—	—	0.840	<0.01
Model R^2	0.408	<0.001	0.416	<0.001

Only variables that remained significant after backward stepwise elimination are shown. SBP Systolic blood pressure

TABLE 4
Multiple regression models evaluating the independent determinants of aortic pulse pressure

Determinant	Metabolic syndrome added to model			
	No		Yes	
	Regression coefficient	P	Regression coefficient	P
Fasting glucose	0.040	<0.01	0.036	<0.02
SBP	0.044	<0.01	0.042	<0.01
Waist circumference	0.068	<0.01	0.062	<0.01
Metabolic syndrome	—	—	0.780	<0.01
Model R^2	0.438	<0.001	0.446	<0.001

Only variables that remained significant after backward stepwise elimination are shown. SBP Systolic blood pressure

was found to be independently associated with both aortic PP and ascending AP, suggesting aortic stiffness as one of the possible mechanisms underlying the excess cardiovascular risk associated with the metabolic syndrome.

Several potential mechanisms may underlie our observation of an association between the metabolic syndrome and aortic stiffness. The first potential mechanism by which this syndrome could adversely affect large artery function may be through altering blood pressure. Blood pressure and blood flow are important determinants of circumferential wall stress and flow-mediated shear stress that act on arterial wall function (27,28). In the present study, we found a statistically independent relationship between ascending AP and systolic blood pressure.

Impaired fasting glucose might also increase arterial stiffness through the glycation of matrix proteins and the accumulation of advanced glycation end products (29,30). The advanced glycation end products tend to accumulate on collagen and elastin, and induce arterial stiffening (29). The results of our multiple regression analysis showed that fasting blood glucose was associated with ascending AP.

In addition, central adiposity may increase the secretion of several peptides such as leptin, which in turn, may alter arterial wall motion (31,32). In our study, central adiposity, as measured by waist circumference, was significantly associated with ascending AP, whereas body mass index was not. Therefore, our data suggest that central adiposity, rather than general adiposity, may be associated with a higher risk for aortic stiffness, in agreement with a recent study by Schillaci et al (33).

Invasive measurements of blood pressure are more accurate than sphygmomanometer-measured brachial blood pressure (34,35). Aortic PP increases physiologically from central to peripheral arteries; therefore, invasively derived aortic PP may be regarded as a more reliable index for assessing arterial stiffness. A large aortic PP relative to mean blood pressure is the characteristic waveform of stiffened arteries.

The most important limitation of the present study was that the angiographic definition of normal coronary arteries may have underestimated the total atherosclerotic burden, which could be better evaluated with intravascular ultrasonography. Another limitation of the study might be the use of different classes of antihypertensive agents by our study group. Previous studies have shown that angiotensin-converting enzyme inhibitors and calcium channel blockers, to a lesser extent, exert direct effects on arterial wall stiffness and cause alterations independent of the blood pressure-lowering effect (36). In addition, to clarify the potential influence of hypertension on the relationship between aortic stiffness and the metabolic syndrome, another analysis was performed. When data from treated hypertensive and normotensive patients were combined, the significance of the same predictors persisted on multiple regression analyses, and the model R^2 was reduced by only 1%. These findings excluded a hypertension selection bias.

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CONCLUSIONS

Our findings indicate that even after considering each individual component of the metabolic syndrome, the clustering of at least three components of the metabolic syndrome is independently associated with increased aortic PP and ascending AP in patients with angiographically normal coronary arteries, suggesting aortic stiffness as one of the possible mechanisms underlying the excess cardiovascular risk associated with the metabolic syndrome. Furthermore, although patients with diabetes and uncontrolled systemic hypertension were excluded from the study, the influence of obesity risk together with subclinical metabolic disturbances remained independently related to the two determinants of arterial stiffness. Future studies should be planned to determine whether strategies to reduce aortic stiffness can decrease the adverse cardiovascular outcomes related to the metabolic syndrome.