Metabolic Syndrome Is Associated With Aortic Stiffness in Untreated Essential Hypertension

Giuseppe Schillaci, Matteo Pirro, Gaetano Vaudo, Massimo R. Mannarino, Gianluca Savarese, Giacomo Pucci, Stanley S. Franklin, Elmo Mannarino

Abstract—Metabolic syndrome is a powerful predictor of cardiovascular disease in hypertension, and large-artery stiffness is increasingly recognized as a cardiovascular risk factor. We hypothesized that the adverse prognostic significance of the metabolic syndrome in hypertension might be explained in part by its association with aortic stiffness. A total of 169 newly diagnosed, never treated, nondiabetic patients with essential hypertension (men 55%, 48±11 years) were classified by the presence (n=45) or absence (n=124) of the metabolic syndrome. All patients underwent aortic and upper limb pulse wave velocity determination by means of an applanation tonometry-based method. Aortic pulse wave velocity had a direct correlation with office and 24-hour systolic pressure (r=0.42 and 0.31, respectively), as well as with waist circumference (r=0.35, all P<0.001), but not with body mass index (r=0.10, P=not significant). Aortic pulse wave velocity was higher in the subgroup with the metabolic syndrome (10.0±2.7 versus 8.8±2.1 m/s; P=0.003), whereas upper limb velocity did not differ in the 2 groups (8.6±1.4 versus 8.7±1.5 m/s; P=not significant). In a multiple regression, aortic pulse wave velocity was independently associated with age, systolic blood pressure, and the metabolic syndrome. Only diastolic BP independently predicted upper limb pulse wave velocity. We conclude that in untreated hypertension, the metabolic syndrome is independently associated with a higher aortic, but not upper limb, pulse wave velocity. Central, but not general, adiposity is an important determinant of aortic stiffness in hypertension.

Key Words: aortic stiffness ■ hypertension ■ metabolic syndrome ■ pulse wave velocity

The metabolic syndrome, a cluster of cardiovascular risk factors closely linked to insulin resistance,1 is associated with a high risk of cardiovascular disease in hypertensive patients,2 as well as in other clinical conditions.3–6 The mechanisms through which this syndrome increases cardiovascular risk are only partially understood but might involve increased large-artery stiffness, which is increasingly recognized as an important predictor of cardiovascular morbidity and mortality.7–9 Several of the individual components of the syndrome, including high blood pressure,10 hyperglycemia,11 and abdominal fat,12,13 have been related to increased aortic stiffness, and an association between the metabolic syndrome and reduced large-artery elasticity has been reported in healthy populations.14–16 However, the link between the metabolic syndrome and arterial stiffness in hypertension has received little attention.

Hypertension tends to cluster with metabolic risk factors17 and is considered one of the key features of the metabolic syndrome. Of note, coronary risk is higher in drug-treated hypertensive patients than in normotensive individuals,18 and some of this difference might be caused by the presence in hypertensive patients of additional metabolic risk factors, which have been collectively identified as the metabolic syndrome. A possible mechanism by which metabolic syndrome affects cardiovascular health in hypertensive patients2 is through its association with large artery stiffness. To investigate this hypothesis, the present study was undertaken to evaluate the influence of the metabolic syndrome on carotid–femoral pulse wave velocity (PWV), a measure of aortic stiffness, in a group of untreated, nondiabetic patients with essential hypertension.

Methods

We examined 169 consecutive patients with essential hypertension (men 55%, age 48±11 years) who had been referred to our outpatient hypertension clinic between January 2003 and June 2004. Patients with uncomplicated essential hypertension were included in the study if they had received a diagnosis of hypertension within the previous 3 years and had never received antihypertensive drug treatment. Hypertension was defined as clinic blood pressure (BP) ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on at least 3 visits at 1-week intervals. Exclusion criteria were: clinical or laboratory evidence of heart failure, coronary heart disease, cerebrovascular disease, valvular defects, secondary causes of hypertension, serum creatinine ≥136 μmol/L (1.5 mg/dL) in men and ≥120 μmol/L (1.4 mg/dL) in women, major noncardiovascular

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disease, dyslipidemia requiring pharmacological treatment, known diabetes or fasting glycemia ≥126 mg/dL, and treatment with any cardiovascular drug, including nitrates. Written informed consent was obtained from each patient, and the study protocol was reviewed and approved by the institutional ethics committee.

All subjects underwent a careful clinical examination. Regular physical activity (at least 30 minutes 3 times or more per week) was assessed by questionnaire. Total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined by enzymatic–colorimetric method (Dimension Autoanalyzer; DADE Inc), and low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. Waist circumference was measured at the midpoint between the bottom of the rib cage and the top of iliac crest from patients at minimal respiration. After the subject had been resting in a supine position for 5 minutes, 3 consecutive measurements of clinic BP and heart rate were obtained and averaged, and fasting blood samples were taken to perform routine blood chemistry. Ambulatory BP was recorded with an oscillometric device (model 90207; SpaceLabs) that was set to take a reading every 15 minutes throughout the 24 hours, as reported previously.16

The metabolic syndrome was defined on the basis of the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) guidelines1 by the presence, in addition to hypertension, of ≥2 of the following criteria: (1) serum triglyceride levels ≥1.69 mmol/L (150 mg/dL); (2) serum HDL cholesterol <1.04 mmol/L (40 mg/dL) in men and <1.30 mmol/L (50 mg/dL) in women; (3) fasting plasma glucose ≥6.11 mmol/L (110 mg/dL); and (4) waist circumference >102 cm in men or >88 cm in women.

After measuring BP, aortic PWV was determined with an automatic device, the SphygmoCor Vx system (AtCor), which uses a single-lead ECG and a high-fidelity applanation tonometer to measure the pressure pulse waveform sequentially in 2 peripheral artery sites, one at the base of the neck for the common carotid artery and the other over the femoral artery. The distance between the 2 sites was measured using a standard compass system, which avoided the measure to be influenced by thoracic and abdominal profiles. The average of 10 different cardiac cycles on each of the sites was used for the analysis. Aortic PWV was then automatically calculated from measurements of pulse transit time and the distance between the 2 sites, according to the following formula: PWV (m/s)=distance (m)/transit time (s). Similarly, upper limb PWV was calculated from common carotid and radial artery waveforms. The same observer, unaware of the patient’s clinical and biochemical data, performed all measurements.

Statistical Analysis
Continuous variables were given as means±SD, except for serum triglycerides, which, because of their skewed distribution, were expressed as median and interquartile range, and were log-transformed before statistical analysis. Differences between groups were tested using Student t test for unpaired data, analysis of variance, and χ2 test when appropriate. Pearson correlation coefficients examined the degree of association between examined variables, and the bivariate normal ellipse (P=0.95), ie, the contour enclosing 95% of the observations in the population, was reported. Multiple regression analyses were used to evaluate the relations between the metabolic syndrome, or its components, and aortic and upper limb PWV, after adjustment for potential confounders, including age, sex, smoking habits, body height, physical activity, office and 24-hour mean arterial pressure, office heart rate, and LDL concentration.

Results
Selected clinical and demographic characteristics of the 169 study patients, divided by the presence or absence of the metabolic syndrome, are given in Table 1. Within the group of patients with the metabolic syndrome, 100% had hypertension (by selection), 84% had abdominal obesity, 76% had elevated triglyceride levels, 53% had low HDL cholesterol concentration, and 22% had high fasting plasma glucose. By definition, all of the anthropometric and metabolic variables used to define the metabolic syndrome were significantly different in the 2 groups. Subjects with the metabolic syndrome were also slightly older. The 2 groups did not differ by sex distribution, smoking habits, BP values, and total cholesterol concentration.

As reported in Table 1, patients with the metabolic syndrome had a greater aortic PWV (10.0±2.7 versus 8.8±2.1 m/s; P=0.003). This difference held after controlling for the confounding effect of age and mean arterial pressure, taken as a measure of distending pressure (9.7±2.0 versus 9.0±2.0, P=0.03; Figure 1). When the patients were subdivided into those with 1, 2, and 3 or more components of the metabolic syndrome, aortic PWV increased progressively from the first to the last group (8.7±2.2 m/s, 9.0±1.9 m/s, 10.0±2.7 m/s, respectively; P for linear trend=0.004). In contrast, upper limb PWV was not significantly different in the groups with and without the metabolic syndrome (Table 1). Aortic PWV in hypertensive patients with and without the individual components of the metabolic syndrome is illustrated in Figure 2.

Aortic PWV had significant direct correlations with age (r=0.52, P=0.001) and with clinic and 24-hour systolic BP (r=0.43 and r=0.32, respectively; both P<0.001), whereas no associations were found with diastolic BP (r=0.10 and r=0.03 for clinic and 24-hour values; both P=not significant). When the components of the metabolic syndrome were considered separately, aortic PWV showed direct associations with waist circumference (r=0.35, P<0.001), blood glucose concentration (r=0.19, P=0.014), and triglyceride concentration (r=0.17, P=0.028), whereas no significant relation was found with HDL cholesterol concentration (r=−0.08, P=not significant). At variance with waist circumference, body mass index had no significant association with aortic PWV (Figure 3).

In a multiple regression model in which metabolic syndrome was included as a dummy explanatory variable together with age, sex, smoking habits, body height, physical activity, office and 24-hour mean arterial pressure, office heart rate, and LDL concentration, the metabolic syndrome was independently associated with aortic PWV along with age and office mean arterial pressure (Table 2, model 1). When metabolic syndrome was replaced by its individual anthropometric and metabolic components (waist circumference, glycemia, triglycerides, and HDL cholesterol), only waist circumference turned out to be independently associated with aortic PWV together with age and office mean arterial pressure (Table 2, Model 2). When the metabolic syndrome was forced in the multivariate model together with each of its components, the results did not change materially. In this extended model, age, office mean arterial pressure, and the metabolic syndrome (regression coefficient 0.712, P<0.03) were independently associated with aortic PWV.

Upper limb PWV had significant direct relations with systolic BP (r=0.21 and r=0.23 for office and average 24-hour values, respectively) and diastolic BP (r=0.23 and r=0.38; all P<0.01), whereas no association was found with age (r=0.10, P=0.20) or other cardiovascular risk factors. In a multivariate regression analysis, only diastolic BP was
Discussion

The present study demonstrates that metabolic syndrome is associated with aortic stiffness, measured as carotid–femoral PWV, in a group of patients with uncomplicated, untreated essential hypertension. In our study, the link between metabolic syndrome and aortic stiffness was confirmed regardless of the confounding effect of age, sex, distending pressure, and other major cardiovascular risk factors. Because aortic stiffness has been identified as an independent predictor of cardiovascular mortality in the specific setting of essential hypertension,7,8 changes in arterial stiffness may, in part, mediate the association between metabolic syndrome and cardiovascular risk in patients with hypertension.2

Relationships between arterial stiffness and individual components of the metabolic syndrome have been examined previously, sometimes with inconsistent results.20 In contrast,

Figure 1. Age-adjusted and mean arterial pressure-adjusted aortic pulse wave velocity (PWV) in never-treated essential hypertension in patients with (gray bars) and without (open bars) the metabolic syndrome. Mean (standard error).

Figure 2. Aortic PWV in hypertensive patients with (hatched bars) and without (open bars) the individual components of the metabolic syndrome, defined according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III).4 See text for details. Median value for systolic blood pressure (BP) was 147 mm Hg. Mean (standard error).

TABLE 1. Clinical Characteristics of 169 Hypertensive Subjects With and Without the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Data</th>
<th>Metabolic Syndrome</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=124)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>47 (11)</td>
<td>0.11</td>
</tr>
<tr>
<td>Men, %</td>
<td>57</td>
<td>0.34</td>
</tr>
<tr>
<td>Body mass index, kg×m⁻²</td>
<td>26.8 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body height, m</td>
<td>1.67 (0.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Regular physical activity, %</td>
<td>29</td>
<td>0.23</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>91 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>28</td>
<td>0.19</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>148 (16)</td>
<td>0.49</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>95 (9)</td>
<td>0.25</td>
</tr>
<tr>
<td>Office mean arterial pressure, mm Hg</td>
<td>112 (10)</td>
<td>0.30</td>
</tr>
<tr>
<td>Office heart rate, beats/min</td>
<td>77 (10)</td>
<td>0.61</td>
</tr>
<tr>
<td>24-hour systolic BP, mm Hg</td>
<td>130 (10)</td>
<td>0.08</td>
</tr>
<tr>
<td>24-hour diastolic BP, mm Hg</td>
<td>83 (9)</td>
<td>0.68</td>
</tr>
<tr>
<td>24-hour mean arterial pressure, mm Hg</td>
<td>99 (10)</td>
<td>0.42</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.44 (0.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.55 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.30 (0.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.19 (0.87–1.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>4.8 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic pulse wave velocity, m/s</td>
<td>8.7 (1.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>Upper limb pulse wave velocity, m/s</td>
<td>8.7 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

Independent associations to upper limb PWV (data not shown).
only few studies have explored the association of metabolic syndrome, as a whole, with arterial stiffness. In a group of 180 healthy women, carotid arterial distensibility was associated with several variables of metabolic syndrome, as well as with their clustering. More recently, clustered components of the metabolic syndrome have been associated with the risk for increased aortic PWV in middle-aged Japanese men, and with carotid artery stiffness in the Baltimore Longitudinal Study on Aging.

To the best of our knowledge, this is the first evaluation of the influence of metabolic syndrome on aortic stiffness in untreated patients with essential hypertension. Our findings confirm in part these observations, obtained in different clinical settings. Our study identifies for the first time to our knowledge a strong association between metabolic syndrome and aortic stiffness in a group of newly diagnosed, never-treated hypertensive patients without diabetes.

Several potential mechanisms can explain our observation of an association between metabolic syndrome and arterial stiffness in hypertension. First, patients with the metabolic syndrome were older and had a marginally higher systolic BP than patients without the syndrome, and advancing age and BP are both well-known determinants of aortic stiffness. BP is both cause and consequence of large-artery stiffness. Large-artery distensibility, as evaluated by carotid–femoral PWV, is a major determinant of systolic BP. However, increased distending pressure tends to reduce the elasticity of a given arterial segment through the recruitment of collagen fibers. Nevertheless, in our study the associations between metabolic syndrome and aortic stiffness held after proper adjustment for age and BP values.

Second, hyperglycemia, a key component of the metabolic syndrome, might increase arterial stiffness through the non-enzymatic glycation of matrix proteins and the accumulation of advanced glycation end products, which may induce arterial stiffening. Aortic PWV is increased in type 2 diabetes mellitus, and increased arterial stiffness in patients with type 2 diabetes mellitus has been hypothesized as a mechanism for increased cardiovascular risk. Impaired fasting glucose was associated with a greater aortic PWV in our study (Figure 2), although the relation was no longer significant in a fully adjusted multivariate model.

Third, adipocytes, in particular from visceral abdominal regions, produce several bioactive peptides, such as angiotensin, interleukin-6, plasminogen activator inhibitor-1, leptin and adiponectin, which in turn impact on vascular structure and function. Elevated leptin levels may be found in patients with the metabolic syndrome and have been associated with impaired brachial artery distensibility in healthy adolescents. Low adiponectin levels, which are commonly found in association with the metabolic syndrome, have been linked with endothelial dysfunction and atherosclerosis. Because leptin and adiponectin were not measured in our study, the role of these factors remains to be explored. In agreement with a recent study by Ferreira et al., we observed that abdominal adiposity as measured by waist circumference was strongly and adversely associated with aortic stiffness, whereas body mass index as a measure of general adiposity was not (Figure 3). These data support the view that abdominal obesity, rather than obesity per se, defines the metabolic syndrome and the risk for increased arterial stiffness.

In our study, metabolic syndrome was an independent predictor of aortic PWV, whereas it was unrelated to upper limb PWV. It is known that different arterial segments respond differently to aging. Aorta, an elastic artery, loses its compliance with advancing age, whereas compliance in the peripheral, predominantly muscular, arteries appears less closely related to age. Our results support the view that metabolic syndrome might selectively contribute to increase aortic stiffness, which is in turn recognized as the predomin-

**TABLE 2. Independent Determinants of Aortic Pulse Wave Velocity in a Stepwise Multiple Linear Regression Analysis**

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Coefficient</th>
<th>Multiple r</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.091</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic mean arterial pressure, mm Hg</td>
<td>0.057</td>
<td>0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic syndrome, yes/no</td>
<td>0.741</td>
<td>0.38</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2</th>
<th>Coefficient</th>
<th>Multiple r</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.110</td>
<td>0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>0.037</td>
<td>0.34</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clinic mean arterial pressure, mm Hg</td>
<td>0.058</td>
<td>0.36</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Constant was \(-1.359\) in Model 1 and \(-2.483\) in Model 2. Metabolic syndrome was included as a dummy variable in model 1 and was replaced by its components (waist circumference, high-density lipoprotein cholesterol, glycemia, triglycerides) in model 2. Only variables that entered the final model are reported.
nant cause of increased PP, a more sensitive measure of risk than other indexes of BP in middle-aged and older persons.

Our study has several limitations. Its cross-sectional design does not allow us to draw conclusions in terms of causality. Moreover, our results were obtained in a middle-aged, white, uncomplicated, untreated hypertensive population, and inferences with regard to other ethnicities, older individuals, treated subjects, and high-risk populations should be made with caution.

Perspectives

By showing that metabolic syndrome influences arterial functional properties that are related to cardiovascular risk, our findings provide a pathophysiological framework for understanding the associations between metabolic syndrome and arterial stiffness-related cardiovascular morbidity and mortality. As a matter of fact, in this hypertensive population, the presence of the metabolic syndrome was a stronger determinant of large-artery stiffness than either BP values or LDL cholesterol concentration. The present findings of a joint effect of hypertension and the metabolic syndrome on large-artery stiffness support the need for a metabolic screening in all hypertensive patients and for a more intense therapeutic approach in hypertensive patients with the metabolic syndrome.

Acknowledgments

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References

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