

Metabolic Syndrome and Age-Related Progression of Aortic Stiffness

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OBJECTIVES	The purpose of the study was to evaluate whether a clustering of metabolic risk factors might accelerate the progression of arterial stiffness with age in subjects with metabolic syndrome (MS).
BACKGROUND	Arterial stiffness is increased in MS, but the genetic and environmental factors that might influence its progression are unknown.
METHODS	Four hundred seventy-six subjects were classified at baseline according to their number of cardiovascular (CV) risk factors (from zero to three and more), after adjustment for smoking habits. The CV risk factors were: hypertension, body mass index, dyslipidemia, hypertriglyceridemia, and hyperglycemia, classified according to traditional criteria. Subjects were followed for six years and had, at the beginning and end of the survey, determinations of blood pressure (BP), heart rate (HR), and aortic pulse wave velocity (PWV).
RESULTS	At baseline, BP, HR, plasma creatinine, and PWV were significantly higher ($p < 0.001$) in the group with three and more CV risk factors than in groups with zero to two risk factors. During the follow-up, the increase in PWV, but not in pulse pressure, was significantly higher ($p < 0.01$) in the group with three and more risk factors (i.e., metabolic syndrome) than in other groups. Results were unmodified after adjustments for age, gender, baseline values, drug treatment, smoking habits, and mean arterial pressure.
CONCLUSIONS	Metabolic syndrome is associated with an increased progression of aortic stiffness with age, supporting premature senescence in these patients. (J Am Coll Cardiol 2006;47:72–5) © 2006 by the American College of Cardiology Foundation

Systolic blood pressure (SBP), pulse pressure (PP), and aortic pulse wave velocity (PWV) are independent predictors of cardiovascular (CV) risk (see review by Safar [1]). Their increase with age contributes greatly to risk, as shown in subjects under antihypertensive therapy (2). Sodium intake and/or gene polymorphisms might contribute to PWV progression (3). Traditional CV risk factors might also play a role. Increased tobacco consumption induces only transient increases of blood pressure (BP) and arterial stiffness, occurring mainly during acute smoking (3). Dyslipidemia is inconstantly associated with increased stiffness, depending on the relative contribution of foam cells and collagen fibers to atherosclerotic plaques (3). High BP, overweight, type 2 diabetes mellitus, and metabolic syndrome (MS) are the main contributors to the development of sustained increased arterial stiffness (3–6). In subjects with either MS or type 2 diabetes mellitus, aortic PWV and brachial PP were shown to be significantly higher than in subjects with normal glucose metabolism for the same age and mean arterial pressure (MAP) (3–6). Thus, these measurements are the most appropriate for repeat determinations in large populations.

In this study, we investigated, in a cohort of 476 individuals, the clustering of metabolic CV risk factors in relation to the progression of arterial stiffness, expressed by carotid-femoral PWV, also called aortic PWV (3).

METHODS

Population. Subjects were examined in Paris, at the Center of “Investigations Préventives et Cliniques” (2). From June 1992 through April 1993, subjects ages 18 years or more were invited to participate in a study for a first measurement (visit [V]1) of aortic PWV. The choice of this population has been described in detail elsewhere (2). Six years later, subjects still living in Paris ($n = 1,080$) underwent the same examination and 675 subjects (62.3% of the invited subjects) had their second visit (V2) during the period of November 1998 through October 1999. Only 476 subjects had a complete investigation at both V1 and V2 (Table 1). In 79 normal control subjects, SBP was <140 mm Hg and diastolic blood pressure (DBP) <90 mm Hg, with no CV risk factor and no drug treatment. In the remaining population, drug treatment of hypertension involved diuretics (36.8%), beta-blocking agents (27.2%), calcium entry-blockers (12.0%), inhibitors of the renin-angiotensin system (22%), or others (2%) given alone or in association. Hypolipidemic and antidiabetic agents were given in 17% of cases. The ethics committee of Cochin Hospital, Paris,

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Manuscript received May 9, 2005; revised manuscript received July 20, 2005, accepted August 1, 2005.

Abbreviations and Acronyms

BMI	= body mass index
CV	= cardiovascular
DBP	= diastolic blood pressure
Δ	= change from V1 to V2
MAP	= mean arterial pressure
MS	= metabolic syndrome
PP	= pulse pressure
PWV	= pulse wave velocity
SBP	= systolic blood pressure
V	= visit

approved the study protocol. Written consent was obtained from all participants.

Clinical investigations. Aortic PWV was measured under the same conditions at V1 and V2. The foot to foot method was used, as previously described and validated (2). During the 1992 to 1993 period, PWV was calculated manually, whereas during the 1998 to 1999 period, an automatic device was used (Complior, Colson, Paris, France). Both measurements did not differ significantly, as previously shown (2).

Supine BP was measured with a manual mercury sphygmomanometer (2). A standardized questionnaire provided information related to occupation, medical history, past and current medications, and personal habits such as cigarette consumption (Table 1). Total serum cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting plasma glucose were measured with standard methods (2).

Classification of subjects. The threshold levels for the definition of MS are indicated in Table 1, according to guidelines (7,8). Body mass index (BMI) (7) was chosen, because waist circumference was not available in all subjects at V1. Both BMI and waist circumference were measured at V2, showing that 96.4% of men and 98.0% of women with a BMI >30 kg/m² had a waist circumference >102 cm in men and >88 cm in women.

The overall population was divided into four groups: zero (i.e., without any CV risk factor [control group]); one (i.e., with one CV risk factor); two (i.e., with two CV risk factors); three and more (i.e., with three or more CV risk factors). This later case corresponds to the traditional MS as described by Reaven et al. (8).

Table 1. Threshold Levels for the Definition of MS (7)

SBP ≥ 130 and/or DBP ≥ 85 mm Hg and/or presence of antihypertensive drug treatment*
Fasting serum glucose >110 mg/dl and/or presence of antidiabetic drug treatment
HDL cholesterol <40 mg/dl in men and <50 mg/dl in women
Serum triglycerides ≥ 150 mg/dl
BMI ≥ 30 kg/m ²

*Note that the metabolic syndrome (MS) classification slightly differs from that of normotensive subjects at visit 1 (1992 to 1993) with systolic blood pressure (SBP) <140 mm Hg and diastolic blood pressure (DBP) <90 mm Hg, as a consequence of international fluctuations.

BMI = body mass index; HDL = high-density lipoprotein.

Statistical analysis. In each group of CV risk factors, the mean value at baseline (V1) and the absolute change ($\Delta = V2 - V1$) of each parameter was calculated (\pm SEM). All the examined values (with the exception of plasma triglycerides, which were used as a categorical variable) had a normal distribution. Comparison between groups was performed with multivariate variance analysis by the general linear model procedure including age, gender, tobacco consumption, and, in the case of Δ values, baseline value. Adjustment, or not, for total or LDL cholesterol never modified the results. For PWV variations, adjustments involved age, gender, baseline value, tobacco consumption, and BP, which was introduced successively as MAP, SBP, DBP, and PP. Finally, in the overall population, the changes in PWV from V1 to V2 were studied as function of the change in BP (successively, MAP, SBP, DBP, PP) with a stepwise linear regression identifying the factors significantly associated with PWV variations. Statistical analyses were carried out with the SAS (version 8.02) software (SAS Institute, Cary, North Carolina). Only standard procedures were used. A p value ≤ 0.05 was considered as significant.

RESULTS

Table 2 shows, in men and women, and in the overall population, the prevalence (%) of each CV risk factor at V1. This prevalence was unmodified at V2. The repartition of tobacco consumption did not change ($<2\%$) during the six years. In 51% of subjects, either men or women, the number of CV risk factors remained stable between V1 and V2. An increase of one risk factor was observed in 21% of subjects and a decrease of a similar level in 28% of subjects. Variations of CV risk factors and their values at V2 were all taken into consideration in the statistical analysis and never influenced the results.

Table 3 indicates, in the overall population, the baseline values (V1) of brachial BP, heart rate (HR), and plasma creatinine according to the number of CV risk factors. These values were increased significantly from zero to three (and more) CV risk factors ($p < 0.0001$). The changes (Δ) in these parameters between V1 and V2 were studied as a function of the number of CV risk factors. The inter-group comparison between delta values did not reach the statistical significance for PP and HR but did reach significance for SBP, mean arterial blood pressure (MAP), plasma creatinine, ($p < 0.05$ or $p < 0.02$) and DBP ($p < 0.01$).

Table 4 shows that the same profile for BP as was observed for PWV measurements, whether PWV was adjusted or not. In the overall population, baseline PWV (V1) increased significantly ($p < 0.0001$) for zero to three and more CV risk factors. The change (Δ) in PWV from V1 to V2 was negative in the group with no CV risk factor and positive and highly significant for subjects with three CV risk factors or more. This inter-group difference in V1 to V2 change was observed even after adjustment for age, gender,

Table 2. Visit 1: Age (\pm SD) and Prevalence (%) of CV Risk Factors According to Gender*

	Men	Women	Total
n	322	154	476
Age at first visit (yrs)	51.0 (10.6)	53.6 (11.0)	51.9 (10.8)
Age at second visit (yrs)	57.5 (10.6)	60.1 (11.2)	58.4 (10.8)
Obesity (%)	16.2 (n = 52)	10.4 (n = 16)	14.3 (n = 68)
Dyslipidemia (%)	9.6 (n = 31)	14.9 (n = 23)	11.3 (n = 54)
Hypertriglyceridaemia (%)	19.9 (n = 64)	11.0 (n = 17)	17.0 (n = 81)
High BP (%)	84.8 (n = 273)	72.1 (n = 111)	80.7 (n = 384)
Diabetes (%)	43.8 (n = 141)	23.4 (n = 36)	37.2 (n = 177)
Hypercholesterolemia (%)	39.1 (n = 126)	37.7 (n = 58)	38.7 (n = 184)
LDL cholesterol (%)	40.1 (n = 129)	35.1 (n = 54)	38.5 (n = 183)
Non-smokers (%)	44.1 (n = 142)	79.6 (n = 123)	55.6 (n = 265)

*Threshold levels for CV risk factors are indicated in Table 1, except for total (=240 mg/dl) and LDL (\geq 160 mg/dl) cholesterol. BP = blood pressure; CV = cardiovascular; LDL = low-density lipoprotein.

baseline value, and change in BP, mainly MAP ($p < 0.002$) (Table 4).

Stepwise linear regression analysis in the overall population showed that the progression of PWV from V1 to V2 was not influenced by baseline MAP, HR, plasma creatinine, or drug treatment. Identical results were observed when SBP, DBP, or PP was used in place of MAP.

The class and the number of antihypertensive drugs at V1 or V2 were not significantly associated with the progression of PWV (data not shown). This progression was significantly increased in subjects with three CV risk factors and more, despite a significantly higher proportion of multi-therapy (65%) by comparison with the other groups (46% and 44%, respectively). Because, in this study, we did not know the PWV values before treatment, the present study was not designed to evaluate the effects of the different class of drugs on PWV.

DISCUSSION

This report represents the first longitudinal study evaluating the progression of arterial stiffness in subjects with MS. By comparison with subjects with zero to two CV risk factors, the

increase in stiffness was significantly more pronounced in subjects with MS. In a previous investigation (2), we determined the annual increase of aortic PWV with age in an untreated normotensive population. This value (81 mm/s/year) was lower than that observed in the present population.

The treatment over the six-year period was conducted by general practitioners without any specific recommendations. Practitioners were not aware of PWV levels and, therefore, never took PWV into account in patients' management. Thus, the observed results reflect a "realistic" situation, in which the main goal was to control DBP (followed by SBP) but not PP or PWV.

Because a clustering of CV risk factors is almost synonymous with the presence of MS, an alternative classification could have been proposed, dividing the population into two groups (i.e., with and without MS). Because either two of four other factors or three of five other factors have been proposed as MS criteria in recent years (7,8), in the present study, we kept the non-rigid classification that we proposed initially. It is worth to note that, under such conditions, the effects of CV risk factors on PWV are not necessarily stepwise. Increased PWV is more frequently

Table 3. Means (SEM) of BP*, HR, and Serum Creatinine for Baseline Values, Age, and Gender-Adjusted Variations (Δ) Between the Two Visits According to the Number of Anomalies (0, 1, 2, 3)

	Number CV Risk Factors				p
	0	1	2	\geq 3	
n	57	178	163	78	
Age (yrs)	51.3 (10.7)	54.5 (11.0)	53.8 (10.9)	58.9 (11.8)	<0.0001
Baseline PP (mm Hg)	44.3 (7.3)	54.7 (11.0)	53.6 (10.9)	59.0 (11.8)	<0.0001
Δ PP (mm Hg)	-3.07 (1.8)	2.25 (0.96)	0.71 (1.00)	2.54 (1.48)	0.06
Baseline SBP (mm Hg)	118.2 (4.6)	143.2 (18.4)	144.8 (16.0)	152.5 (15.7)	<0.0001
Δ SBP (mm Hg)	-7.10 (2.4)	-0.34 (1.2)	0.20 (1.3)	1.00 (1.9)	0.05
Baseline DBP (mm Hg)	72.1 (6.1)	87.3 (11.6)	89.1 (11.2)	93.9 (11.9)	<0.0001
Δ DBP (mm Hg)	-3.53 (1.4)	-1.30 (0.70)	1.20 (0.73)	-0.54 (1.09)	0.01
MAP initiale (mm Hg)	87.5 (4.9)	106.0 (13.2)	107.7 (12.3)	113.4 (12.0)	<0.0001
Δ MAP (mm Hg)	-4.78 (1.56)	-0.47 (0.78)	0.87 (0.81)	-0.005 (1.21)	0.02
Creatininemia (mg/l)	9.04 (1.44)	9.46 (1.52)	9.66 (1.51)	10.01 (1.71)	<0.0001
Δ Creatininemia (mg/l)	0.42 (0.14)	0.73 (0.08)	0.63 (0.08)	0.92 (0.12)	0.05
Baseline HR (beats/min)	65.1 (10.1)	68.8 (11.1)	70.5 (12.5)	76.0 (14.3)	<0.0001
Δ HR (beats/min)	-4.31 (2.92)	-1.01 (1.56)	-2.90 (1.63)	-4.12 (2.43)	0.6

*Using mercury manometer.

HR = heart rate; MAP = mean arterial pressure; PP = pulse pressure; all other abbreviations as in Tables 1 and 2.

Table 4. Baselines Adjusted Values and Change (Δ) in PWV According to the Number of Anomalies (0, 1, 2, 3 . . .)

	Number CV Risk Factors				P
	0	1	2	≥ 3	
No. of subjects	57	178	163	78	
PWV (m/s)	9.4 (2.1)	10.7 (2.6)	11.2 (2.9)	12.2 (3.0)	0.0001
Δ PWV*	-0.29 (0.31)	0.62 (0.17)	0.33 (0.18)	0.96 (0.29)	0.01
Δ PWV (1)	-0.38 (0.30)	0.64 (0.17)	0.35 (0.18)	1.00 (0.25)	0.003
Δ PWV (2)	-0.27 (0.31)	0.63 (0.17)	0.35 (0.18)	0.99 (0.25)	0.01
Δ PWV (3)	-0.44 (0.31)	0.65 (0.25)	0.35 (0.18)	1.02 (0.25)	0.002

*Age, gender, baseline pulse wave velocity (PWV) value, tobacco consumption at visit 2 adjusted means (SEM). 1 = Means (SEM) adjusted on age, gender, tobacco consumption at visit 2, baseline PWV value, and SBP variation; 2 = Means (SEM) adjusted on age, gender, tobacco consumption at visit 2, baseline PWV value, and pulse pressure (PP) variation; 3 = Means (SEM) adjusted on age, gender, tobacco consumption at visit 2, baseline PWV value, and mean blood pressure variation.

Abbreviations as in Tables 1 and 2.

observed in subjects with obesity and diabetes mellitus than in subjects with hyperlipemia (3-6).

The accelerated progression of PWV with age in subjects with MS might result from the progressive increase of distension BP with age, thus causing a higher PWV with age. In our multiple regression analysis involving the overall population, however, the observed changes in MAP did not significantly correlate with the changes in PWV. Furthermore, the level of PWV progression was, firstly, adjusted for age, MAP, and baseline value; and secondly, not attenuated by the use of increased amounts of antihypertensive agents. Therefore, the increased progression of PWV in subjects with MS represents an accelerated aging process, rather related to the CV risk factors themselves than to the increase of MAP with age. Identical results were observed when SBP or DBP were used in place of MAP. The progression of PP with age was less sensitive than that of PWV, because PP represented only brachial and not central PP and was measured in a relatively young population (mean age at baseline: 51.9 ± 10.8 years), where PP was influenced both by arterial stiffness and ventricular ejection.

Our results are consistent with data from the Framingham Study showing that young people with high BP are more likely to present an excessive increase in SBP and a decrease in DBP later in life, suggesting accelerated arterial aging in subjects with high BP levels (1-3). Cardiovascular risk factors are usually responsible for endothelial dysfunction, which, in turn, might cause reduced nitric oxide bio-availability and increased oxidative stress, with resulting accelerated PWV progression. This hypothesis requires that other independent measurements, such as those related to flow dilatation, should be performed.

In conclusion, the present longitudinal study has shown that accelerated arterial aging is observed in populations

with MS. The best marker for this process is PWV and not MAP or brachial PP. Central PP or carotid augmentation index could have been proposed to be determined in parallel. They have not yet been measured in long-term follow-up. Specific therapies remain to be explored for such alterations but require further investigations.

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