Determinants of Accelerated Progression of Arterial Stiffness in Normotensive Subjects and in Treated Hypertensive Subjects Over a 6-Year Period

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Background—Elastic artery stiffness, a result of arterial aging, is an independent indicator of cardiovascular risk. The aim of the present longitudinal study was to compare the progression of aortic stiffness over a 6-year period in treated hypertensive subjects and normotensive subjects, and to evaluate the determinants of this progression.

Methods and Results—Data for the present analysis were gathered from 483 subjects who had 2 health checkups at the Centre d'Investigations Préventives et Cliniques, the first one in 1992–1993 and the second one in 1998–1999. Carotid-femoral pulse wave velocity (PWV) was used to evaluate aortic stiffness in 187 hypertensive subjects who were under treatment at the time of the first visit and throughout the follow-up period, and in 296 subjects who were classified as normotensive during the first visit and who remained treatment-free throughout the follow-up period. In both populations, PWV progression was higher in older subjects. Annual rates of progression in PWV in treated hypertensives were significantly higher than in normotensives. Only treated hypertensives with well-controlled blood pressure levels at the time of both visits had a PWV progression similar to that of normotensives. In treated hypertensives, high heart rate and high creatinine during the first visit were associated with an accelerated progression in PWV.

Conclusions—The presence of high blood pressure, high heart rate, and high serum creatinine were the major determinants of accelerated progression of aortic stiffness in treated hypertensives. This is the first longitudinal study to evaluate the determinants of arterial aging over an extended period of time. (***Circulation*. 2002;105:1202-1207.**)

Key Words: aging ■ heart rate ■ elasticity ■ hypertension

Elastic artery stiffness, resulting in high pulse pressure (PP) and accelerated pulse wave velocity (PWV), greatly increases with age and could be an independent cardiovascular risk factor.[1–4] The effects of aging are different on proximal, predominantly elastic arteries compared with distal, predominantly muscular arteries.[5–7] Central arteries stiffen progressively with age, whereas stiffness of muscular arteries changes little with age.

Several cross-sectional studies have shown that in addition to age, several other environmental and genetic factors can influence arterial stiffness.[5,7–9] Avolio et al[7] showed that high salt intake could have an independent effect on elastic artery properties contributing to increased aortic stiffness with age. Among cardiovascular risk factors, increase in blood pressure is associated with increased stiffness, and because of this hypertensives are thought to have accelerated arterial aging.[10] Among the other cardiovascular risk factors, the presence of dyslipidemia,[11] diabetes,[12] high heart rate (HR),[13] and tobacco smoking[14] are often associated with increased stiffness, but the impact of these risk factors in the development of arterial stiffness remains unclear. These observations are based on short-term pharmacological studies and on cross-sectional observational studies. The role of risk factors, especially hypertension, on the long-term progression of arterial stiffness has not yet been evaluated.

The aim of the present longitudinal study was to evaluate the determinants of PWV progression over a 6-year period in treated hypertensive subjects and in normotensive subjects.

Methods

Population

Subjects were examined at the Center d'Investigations Préventives et Cliniques (the IPC Center). This medical center, which is subsidized

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by the French national health care system (Sécurité Sociale–Caisse Nationale d'Assurance Maladie), provides all working and retired persons and their families with a free medical examination every 5 years. From June 1992 through April 1993, subjects aged 18 years or more who came to the IPC Center for a medical examination were invited to participate in a study for an evaluation of carotid-femoral PWV. Four subjects were recruited on a daily basis and included the following: the first 2 normotensive subjects of the day (systolic blood pressure [SBP] <140 and diastolic blood pressure [DBP] <90 mm Hg), the first subject with high blood pressure (≥140/90 mm Hg) and without any antihypertensive drug treatment, and the first subject with antihypertensive treatment. Six years later, we invited subjects still living in the Paris area (n=1080) to undergo the same clinical, biological, and arterial examinations. In response to this invitation, 675 subjects (63% of the invited subjects) had their second visit during the period of November 1998 through October 1999. According to the classification used in 1992–1993, 325 of the patients who had the second examination were initially normotensives, 153 were initially untreated hypertensives, and 197 were treated hypertensives. At the time of the first examination, there were no significant differences in cardiovascular risk factors between subjects who participated in the second survey and those who did not. Because the aim of this study was to evaluate the progression in arterial stiffness in treated hypertensives in comparison with normotensive subjects, data concerning untreated hypertensive subjects at the time of the first visit were not included in the present analyses. The ethics committee of Cochin Hospital approved the study protocol, and written informed consent was obtained from all study participants.

Clinical Investigations

PWV measurements were taken under the same conditions during both examinations, including a constant room temperature of 19°C to 21°C. Two pressure waves were recorded transcutaneously at the base of the neck for the right common carotid artery and over the right femoral artery. PWV was determined as the foot-to-foot velocity. Pulse transit time was determined as the average of 10 consecutive beats. The distance traveled by the pulse wave was measured over the body surface as the distance between the 2 recording sites. Aortic PWV was calculated as the ratio of distance to transit time. During the 1992–1993 examination, PWV was calculated manually, whereas during the 1998–1999 examination, an automatic device was used (Complior, Colson). The validation of this automatic method and its reproducibility have been previously published.[15]

Supine blood pressure was measured using a manual sphygmomanometer. After a 10-minute rest period, blood pressure was measured 3 times, and the average of the last 2 measurements was used for statistical analyses.

All participants were administered a standardized questionnaire that provided information related to occupation, medical history, past and current medications, and personal habits such as cigarette consumption. Subjects were classified as "nonsmokers," "former smokers," or "current smokers." Total serum cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting plasma glucose were also measured.

Data Analysis

Values presented in this paper are mean±SEM. Mean initial values of the main variables were compared using a Student t test. A Student *t*-paired test was used to compare differences between the first and second visits.

The association of each variable with baseline PWV and progression in PWV (evaluated in this analysis as the residual value after adjustment for initial PWV) was assessed with Pearson correlation coefficients for continuous variables and Student *t* tests for categorical variables. The contribution of each variable was also evaluated in a multiple regression analysis by including the variables associated with PWV that had a P value <0.10 in the univariate analysis.

To assess the progression of PWV independently of the progression of mean arterial pressure (MAP), we also evaluated the determinants of the ΔPWV/ΔMAP ratio. We chose MAP rather than SBP because MAP is not directly dependent on arterial stiffness.

The roles of age, HR, and creatinine in PWV progression were also evaluated when these variables were considered as categorical variables. For the purpose of these analyses, subjects were divided into 2 age groups (≤50 and >50 years), into 3 HR categories (<60, 60 to 75, and >75 beats/min), and into creatinine tertiles. Two-way ANOVAs were carried out to evaluate the impact of each one of these 3 parameters (age, HR, and creatinine) in the progression of PWV after adjustment for covariates in normotensive and treated hypertensive subjects.

Finally, to assess the role of blood pressure control on PWV progression, treated hypertensives were classified into 4 groups according to the control of MAP at the time of the first and/or second visit. A MAP <107 mm Hg was considered as "controlled" MAP, because it corresponds to the value of the normal limits of SBP/DBP (140/90 mm Hg).

Statistical analyses were carried out using the NCSS 2000 statistical software package. A P value <0.05 was considered as statistically significant.

Results

Among normotensives, 296 (91.1%) remained treatment-free during the 6-year period, whereas an antihypertensive medication had been prescribed for the other 29. Among treated hypertensives, 187 (95%) continued their treatment and only 10 interrupted it. These 39 subjects who changed treatment status were not included in the analysis.

Table 1 shows mean values for the clinical and biological parameters assessed during the first and second visits in normotensive and hypertensive patients. At visit 1, treated hypertensive subjects, as compared with normotensive subjects, had higher body mass index (BMI), blood pressure levels, PWV, triglycerides, and serum creatinine, and they smoked less. In normotensive subjects, BMI, MAP, DBP, PWV, HDL cholesterol, and serum creatinine significantly increased between the first and the second visits, whereas SBP and total cholesterol remained unchanged, and HR and PP slightly decreased. In treated hypertensive subjects during the same period, there was an increase in BMI, SBP, PP, PWV, HDL cholesterol, and serum creatinine, whereas DBP, MAP, HR, and total cholesterol remained unchanged.

Determinants of baseline (visit 1) PWV were assessed with a multivariate analysis; age (P<0.0001), BMI (P<0.05), and MAP (P<0.001) in normotensives, and age (P<0.0001), PP (P<0.02), and HR (P<0.02) in hypertensives were independent determinants of baseline PWV. MAP was a significant determinant of PWV when PP was not included in the model (P<0.05). Total cholesterol, HDL cholesterol, glycemia, and smoking were not correlated with baseline PWV.

Unadjusted annual progression of PWV in treated hypertensives was significantly higher than in normotensives (147±22 versus 81±18 mm/s per year, P=0.02), and this difference remained significant after adjustment for age, sex, and initial PWV values (171±20 versus 66±16 mm/s per year, P=0.0003, Figure 1).

The role of baseline clinical and biological parameters on the progression in PWV over the 6-year period was assessed in univariate and multivariate analyses (Table 2). The univariate analysis showed that in both normotensives and treated hypertensives, PWV progression was more pronounced in men than in women, but the contribution of sex was not

TABLE 1. Demographic and Clinical Characteristics of Normotensive and Hypertensive Subjects During the First (1992–1993) and Second (1998–1999) Visits

	Normotensive Subjects (n=296; 64.5% male)		Treated Hypertensive Subjects (n=187; 63.1% male)	
	1st Visit	2nd Visit	1st Visit	2nd Visit
Age, y	47.6±0.6	54.1±0.6†	56.9±0.7‡	63.6±0.7†
BMI, kg/m^2	24.5±0.2	25.3±0.2†	26.6±0.3‡	27.9±0.4†
SBP, mm Hg	128.0±0.7	129.5±0.9	144.5±1.0‡	149.7±1.3†
DBP, mm Hg	78.4±0.5	82.4±0.6†	88.3±0.7‡	87.2±0.7
MAP, mm Hg	94.9±0.5	98.1±0.6†	107.1±0.7‡	108.0±0.8
PP, mm Hg	49.6±0.4	47.1±0.7*	56.2±0.7‡	62.5±1.2†
HR, bpm	67.8±0.7	65.5±0.5†	67.8±0.9	65.8±0.7*
PWV, m/s	9.84±0.13	10.35±0.10†	11.40±0.19‡	12.23±0.18†
Cholesterol, mg/dL	228±3	231±3*	226±3	229±3
HDL, mg/dL	59.1±1.0	64.8±1.1†	58.4±1.2	60.3±1.6
Glucose, mg/dL	101.9±1.1	97.3±0.8	106.2±1.4	102.0±1.7
Triglycerides, mg/dL	89.2±4.2	100.2±4.6†	113.7±9.3‡	118.1±4.7†
Creatinine, mg/L	9.37±0.09	9.95±0.08†	9.90±0.13‡	10.53±0.14†
Current smokers	20%	22%	12%‡	10%

*P<0.01 and †P<0.001, second vs first visit; ‡P<0.001 normotensive vs treated hypertensive subjects.

significant after adjustment for blood pressure and creatinine. Age was a significant determinant of PWV progression in both groups, and its contribution remained significant in the multivariate analysis (Table 2). Age was also a significant determinant of the progression of PWV/MAP ratio in normotensives (P<0.02) and in treated hypertensives (P<0.05).

In normotensives, PWV progression was positively correlated with SBP, DBP, and cholesterol, and negatively correlated with HDL. However, in the multivariate analysis, none of these variables was significantly related to PWV progression.

In treated hypertensives, visit 1 values of HR and creatinine were positively correlated with PWV progression, and the contribution of these 2 variables remained significant in the multivariate model (Table 2). These 2 variables were also significant independent determinants of the progression in PWV/MAP ratio, explaining respectively 7.2% (P=0.0001) and 5.2% (P=0.0002) of its variability. By contrast, we did not find any association between initial HR and creatinine, and the progression of SBP or DBP levels.

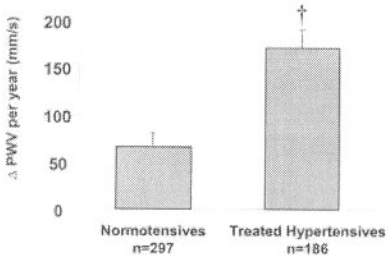

Figure 1. Annual PWV progression in normotensive and treated hypertensive subjects (adjusted for initial PWV, age, and sex); †P=0.0003.

Figures 2 through 4 show the role of baseline values of age, HR, and serum creatinine in PWV progression when these parameters were considered as categorical variables (see Patients and Methods). After multivariate adjustments including sex and initial PWV, the annual PWV progression was higher in subjects >50 years of age, in both normotensives (0.8±20 mm/s per year in younger subjects versus 114±27 mm/s per year in older subjects, P<0.0001) and treated hypertensives (102±41 mm/s per year in younger subjects versus 244±23 mm/s per year in older subjects, P<0.001) (Figure 2). Complementary adjustments for initial HR and creatinine did not change this result.

Figure 3 shows that annual PWV progression was more pronounced in hypertensives with higher initial HR (49±37, 167±32, and 290±47 mm/s per year in the 3 HR groups [P<0.001]). No such association was observed in normotensives. The 2-way ANOVA showed a significant difference in the association between HR and PWV progression in normotensive and hypertensive subjects (interaction term, P<0.05). An additional adjustment for the type of medication at the time of the first and second visits did not modify the results.

Classifying subjects into tertiles for serum creatinine showed significantly higher PWV progression in treated hypertensives with higher serum creatinine (Figure 4). The annual PWV increase was 34±48, 142±39, and 248±31 mm/s per year in the first, second, and third tertiles, respectively (P<0.001). The 2-way ANOVA showed that the association between creatinine and PWV progression was observed in hypertensives but not in normotensives (interaction term, P<0.001).

Figure 5 shows that in well-controlled hypertensives, at both visits (group 1; see Subjects and Methods for classification), the annual progression in PWV was significantly lower than in the other treated patients (49±40 mm/s per year in group 1 versus 213±47 and 223±44 mm/s per year in groups 3 and 4,

TABLE 2. R^2 Regression Coefficients of Univariate and Multivariate Analyses Between Baseline (1st Visit) Clinical and Biological Parameters and Progression in PWV*

	Univariate Analysis		Multivariate Analysis	
	Normotensive Subjects	Hypertensive Subjects	Normotensive Subjects	Hypertensive Subjects
Sex (M>F)	**0.015‡**	**0.037‡**	0.025 (P=0.13)	NS
Age (+)	**0.041§**	**0.020‡**	**0.041‡**	**0.025‡**
BMI	0.014	0.017		
SBP (+)	**0.032‡**	0.003	0.013 (P=0.10)	
DBP (+)	**0.028‡**	0.000		
HR (+)	0.000	**0.068§**		**0.084§**
Cholesterol (+)	**0.017‡**	0.001		
HDL (−)	**0.032‡**	0.009	0.015 (P=0.06)	
Creatinine	0.008	**0.110§**		**0.097§**
Plasma glucose	0.003	0.013		
Triglycerides (+)	**0.035‡**	0.002		
Smoking status†	0.009	0.003		
Model R^2	...	...	**10%**	**22%**

All variables were considered as continuous variables except for sex and smoking status.

Significant correlations are in bold. (M>F) indicates that the progression in PWV is more important in men than women; (+), positive correlation; and (−), negative correlation.

*Residual value after adjustment for initial PWV.

†Current smokers vs others.

‡P<0.05; §P<0.001.

respectively, P<0.01). Patients in group 2 presented intermediate values of PWV progression (145±57 mm/s per year). Progression in PWV in controlled, treated hypertensives was similar to that of normotensives (49±40 versus 81±18 mm/s per year, respectively).

The type of treatment and the number of antihypertensive drugs at the time of the first and second visits were not significantly associated with the progression of PWV (data not shown). However, because we did not know the PWV values before treatment, this study was not designed to evaluate the effects of the different drugs on PWV.

Discussion

To our knowledge, this is the first longitudinal study to evaluate the determinants of the progression of arterial stiffness over an extended period of time. Results of the present study show that the increase in stiffness over a period of 6 years is more marked in treated hypertensives than in normotensives, indicating accelerated arterial aging among treated hypertensives. Three factors were identified as being responsible for accelerated progression in PWV in treated hypertensive patients, as follows: uncontrolled blood pressure values, increased HR, and increased serum creatinine. By contrast, no association between other major cardiovascular risk factors and progression in aortic stiffness was found.

Accelerated Aging in Treated, Uncontrolled Hypertensives

The annual increase in PWV with age that we observed in the normotensives (81 mm/s per year) was very similar to that

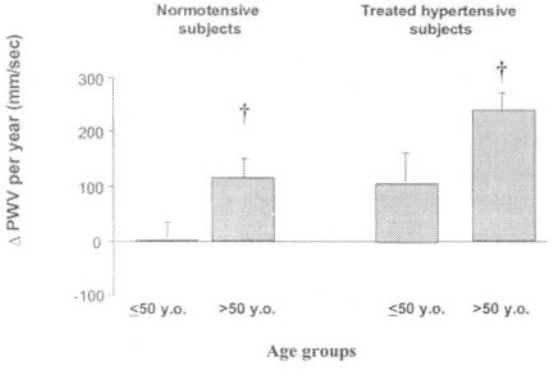

Figure 2. Annual PWV progression in younger (≤50 years) and older (>50 years) normotensive (left) and treated hypertensive (right) subjects (adjusted for initial PWV and sex); †P<0.001 vs younger subjects.

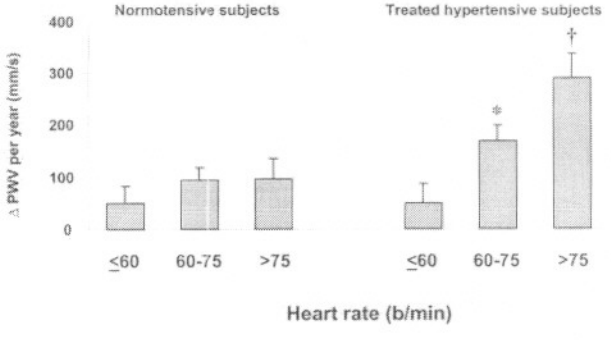

Figure 3. Annual PWV progression according to HR levels in normotensive (left) and treated hypertensive (right) subjects (adjusted for initial PWV, age, MAP, and sex); *P<0.05; †P<0.001 vs HR ≤60 bpm.

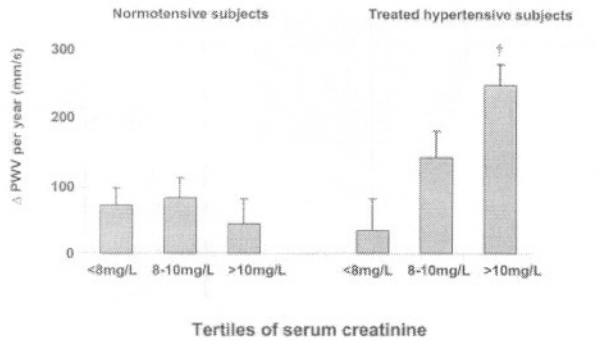

Figure 4. Annual PWV progression according to creatinine levels in normotensive (left) and treated hypertensive (right) subjects (adjusted for initial PWV, age, MAP, and sex); †$P<0.001$ vs serum creatinine <8 mg/L.

reported in a large cross-sectional study in an urban Chinese population (92 mm/s per year) composed essentially of normotensive subjects.[7] As was the case for the Chinese urban population, this Parisian population presents a higher progression in PWV than the Chinese rural population.

In the present study, treatment over the 6-year period was conducted by the patients' general practitioners without any study-specific recommendations. It is important to note that the general practitioners were not aware of PWV levels and therefore did not take into account this parameter in the management of patients at any time during the 6 years. Therefore, the observed results reflect a "realistic" situation in treated hypertensives in whom the main goal is to control DBP (followed by SBP), but not PP or PWV, which better reflect arterial aging. The absence of any association between baseline blood pressure levels and PWV progression in treated hypertensives (Table 2) does not negate the impact of blood pressure levels in PWV progression. Actually, when blood pressure levels remain elevated over an extended period of time despite treatment, arterial aging is accelerated. One might suggest that accelerated progression of PWV in uncontrolled subjects does not reflect accelerated aging but rather only increased distension pressure (leading to higher

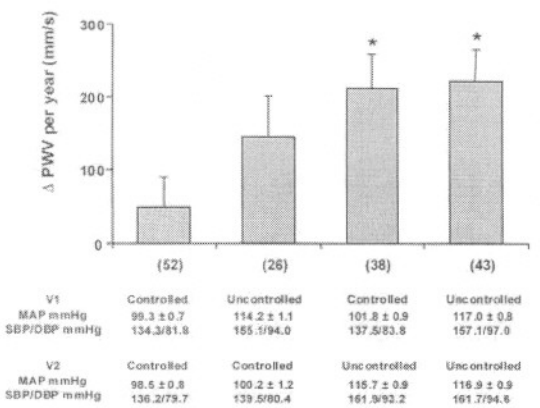

Figure 5. Annual PWV progression (adjusted for initial PWV, age, HR, and sex) in treated hypertensive subjects as a function of MAP control (controlled=MAP<107 mm Hg) at the time of the initial visit (V1) and the last visit (V2); *$P<0.01$ vs controlled in both visits.

PWV). However, a counter-argument is the fact that in patients with uncontrolled blood pressure levels at both visits, MAP did not significantly increase throughout the follow-up, but PWV progression was more than 3 times higher than in well-controlled hypertensives. Therefore, permanent blood pressure elevation in treated subjects appears to promote accelerated aging, at least partly independently from the evolution of MAP itself. The present study cannot, however, answer the question whether the relation between MAP and PWV progression is linear or whether there is a threshold value for MAP versus change in PWV. These results reinforce recent data from the Framingham cohort showing that people with high blood pressure are more likely to present an excessive increase in SBP and a decrease in DBP later in life, which suggests accelerated arterial aging in subjects with high blood pressure levels.[16]

HR and Acceleration of Arterial Stiffness

In treated hypertensives, the presence of increased HR during the first visit was an additional factor for accelerated PWV progression. Increased HR is associated with high cardiovascular disease mortality, independently of other risk factors.[17,18] In cross-sectional studies, it has been shown that HR was a significant determinant of arterial stiffness in hypertensives.[13,19] The results of the present longitudinal study are complementary to results showing that chronic increase in HR contributes to arterial fatigue and to atherosclerotic lesions.[20] Previous studies have suggested that people with increased HR have an increased risk of developing hypertension later in life.[21] In the present study, this particular result was not found. This may be explained by the fact that, as we mentioned in the previous paragraph, the evolution of blood pressure was directly influenced by physician intervention. However, our results pertaining to the influence of high HR in the progression of PWV (which was not taken into account in the therapeutic strategies in this study) are in concordance with the concept that increased HR may be a determinant of accelerated arterial aging and may have deleterious effects on patient outcome.

Serum Creatinine and Arterial Stiffness

Our study shows that serum creatinine levels were a strong independent determinant of the progression of aortic stiffness. Previous studies have clearly shown that subjects with end-stage renal failure present a marked increase in aortic stiffness independently of mean blood pressure values and other cardiovascular disease risk factors. In a cross-sectional analysis in a large population, we recently showed that increased stiffness was significantly associated with creatinine clearance.[22] A new finding from the present study is that serum creatinine levels during the first visit were a strong predictor for the long-term progression of PWV, indicating that kidney alterations may accelerate elastic artery aging. It is interesting to note that, as for HR, serum creatinine was a determinant of PWV progression in hypertensive but not in normotensive subjects. This result suggests that hypertensives are more vulnerable than normotensive subjects to the deleterious effects of certain risk factors.

Age and Progression in PWV

In a previous cross-sectional study,[9] we reported the same observation, suggesting a more pronounced increase in PWV with age, after the age of 50 years. The present longitudinal results confirm that in both normotensive and treated hypertensive subjects, the progression in arterial stiffness is more pronounced in older subjects. This result corroborates the epidemiological observation of a more pronounced increase in SBP and PP, the main clinical manifestations of elastic artery stiffness, after the age of 55 years.[16]

However, some previous cross-sectional studies have reported a linear age/PWV relationship.[7,23] A possible explanation for this is that in cross-sectional studies, the older patients with the higher aortic stiffness may be "absent" as a result of a higher mortality rate in this subgroup of subjects.

Limitations of the Study

A limitation of the present study is that the determinants of blood pressure evolution could not be assessed because of treatment modifications—oriented by blood pressure levels—made by patients' general practitioners. This limitation, however, does not concern PWV, because practitioners were not aware of PWV.

Another limitation of this study could be the small number of subjects with diabetes and severe dyslipidemia, possibly leading to a type II error, ie, the inability to detect a possible contribution of these metabolic parameters on PWV progression because of the weak number of affected patients.

Finally, it is important to point out that in the present study the direct distance between the common carotid and femoral arteries was measured to determine PWV. However, there was no consensus on which distance should be chosen for carotid-femoral PWV measurements. Although this is of limited importance for the present study, given that all measurements were taken the same way, this is important when comparisons with other studies are made.

In conclusion, the present longitudinal study shows that accelerated arterial aging in treated hypertensive subjects is in large measure explained by uncontrolled blood pressure levels, high HR, and altered renal function. Controlling blood pressure and lowering HR could reduce age-related progression of arterial stiffness.

Acknowledgments

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