Abstract—Several studies have shown that aortic stiffness was an independent predictor for cardiovascular events. However, data are less consistent concerning carotid stiffness. We analyzed the determinants of the discrepancies between aortic and carotid stiffness in different populations with contrasting cardiovascular risk factors: 94 healthy normotensives (NT), 243 nondiabetic hypertensives (HT), and 126 patients with hypertension and type 2 diabetes (T2D). Aortic stiffness was measured with carotid-femoral pulse wave velocity. Common carotid stiffness was determined from the relative stroke change in diameter (measured with a high-resolution echotracking system) and carotid pulse pressure (measured with applanation tonometry) and was expressed in the same dimensions as pulse wave velocity (m/s). We identified the various factors explaining the discrepancies between aortic and carotid stiffness by multivariate analysis of the residuals of the correlation between aortic and carotid stiffness. The strength of the correlation between aortic and carotid stiffness became weaker as the number of cardiovascular risk factors increased (NT, \( r^2 = 0.41 \); HT, \( r^2 = 0.16 \); and T2D, \( r^2 = 0.11 \)), whereas we observed the opposite for the discrepancies (residuals) between aortic and carotid stiffness, of which an increasing part was explained (11% in NT, 22% in HT, and 45% in T2D) primarily by aging. In conclusion, although carotid-femoral pulse wave velocity and carotid stiffness provided similar information on the impact of aging on large artery stiffness in normal subjects, this was not the case for high blood pressure and/or diabetes. In these cases, the aorta stiffened more than the carotid artery with age and other cardiovascular risk factors. (Hypertension. 2006;47:371-376.)

Key Words: aorta ■ carotid arteries ■ elasticity ■ diabetes mellitus ■ arteriosclerosis

Aortic stiffness is an independent predictor of all-cause mortality, fatal and nonfatal coronary events, and fatal strokes in patients with uncomplicated essential hypertension,\(^1\) type 2 diabetes,\(^2\) end-stage renal disease (ESRD),\(^3\) and in elderly subjects.\(^4\) However, data are less consistent for arterial stiffness measured at other arterial sites. Unlike carotid-femoral pulse wave velocity (PWV), which is a direct and robust index of aortic stiffness, neither brachial artery nor femorotibial artery PWV were able to predict CV outcome in ESRD patients.\(^5\) We have reported previously that central elastic arteries, such as the aorta and the common carotid artery (CCA), stiffen with aging and hypertension, whereas peripheral muscular arteries, such as the brachial radial and the femoral arteries, do not stiffen.\(^6\)–\(^10\)

Although carotid stiffness (CS) could be used to predict CV events in patients with ESRD\(^11\) and after renal transplantation,\(^2\) this was less evident for patients with manifest arterial disease.\(^13\) The intima-media thickness of the common carotid artery has been consistently shown to be predictive of CV events in various populations.\(^14\)–\(^15\) Therefore, it was important to determine the relationship between the arterial stiffness, measured locally in the CCA, and aortic stiffness, measured with carotid-femoral PWV. We included 3 different populations with contrasting CV risk factors to analyze better the determinants of discrepancies between aortic and CS. The 3 patient populations were healthy normotensives (NTs), nondiabetic hypertensives (HTs), and patients with hypertension and type 2 diabetes (T2D). Thus, we aimed to: (1) determine the univariate relationship between aortic and CCA stiffness in these 3 populations; (2) identify and compare the determinants of aortic and CCA stiffness in each population; and (3) identify the determinants of discrepancies between aortic and CCA stiffness.

Methods

Subjects and Study Design
The study cohort included 463 patients who attended the outpatient hypertension clinic at the Broussais and Pompidou Hospitals. The patients were divided into three groups: healthy subjects (NT, \( n = 94 \)), patients with essential hypertension and no diabetes (HT, \( n = 243 \)) and patients with hypertension and type 2 diabetes mellitus (T2D, \( n = 126 \)). At the time of arterial investigation, 43% of HT patients and 62% of T2D patients were treated with antihypertensive
The noninvasive investigation was carried out in a controlled environment at 22°C after subjects had reclined at rest for 15 minutes. Arterial and BP measurements were taken by a senior technician (B.L.) and physician (P.B.), who were trained and certified in vascular echography. BP was monitored with an oscillometric method (Dinamap 845; CRITIKON). The mean BP (MBP) was calculated from DBP and SBP as MBP = (SBP + 2 DBP)/3, allowing us to compare parameters. Thus, both aortic stiffness and CS were measured as m/s^2.

### Data Analysis

Data are expressed as mean±SD. Comparison of categorical variables were performed using χ^2 test. We used ANOVA to detect differences between groups for baseline quantitative variables, completed with Bonferroni all-pair post hoc comparison. Because age is unbalanced between groups, age was included as a covariate in ANOVA. We used simple regression to evaluate linear associations between aortic PWV and CS. Mean BP (oscillometric) was used for CS and SBP for cortical PWV. All of the independent parameters were performed using Bonferroni all-pair post hoc comparison. Because age is unbalanced between groups, age was included as a covariate in ANOVA. We used simple regression to evaluate linear associations between aortic PWV and CS. Mean BP (oscillometric) was used for CS and SBP for cortical PWV.

### Table 1. Demographic and Hemodynamic Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NT Patients (n=94)</th>
<th>HT Patients (n=243)</th>
<th>T2D Patients (n=126)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±21</td>
<td>53±12</td>
<td>63±8†</td>
<td>¶</td>
</tr>
<tr>
<td>Sex (M/F) n, %</td>
<td>70 (74/44) (46)</td>
<td>151/92</td>
<td>73/53</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68±12</td>
<td>76±13</td>
<td>80±12</td>
<td>¶</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170±9</td>
<td>169±9</td>
<td>166±10†</td>
<td>¶</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.4±3.1</td>
<td>26.4±3.8*</td>
<td>29.1±3.7†</td>
<td>¶</td>
</tr>
<tr>
<td>Smokers (never/past/current), n</td>
<td>67/27/0</td>
<td>179/37/27</td>
<td>84/20/22</td>
<td></td>
</tr>
<tr>
<td>Smokers (never/past/current), %</td>
<td>71±29/0</td>
<td>74/15/11</td>
<td>66/16/18</td>
<td>¶</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>1 (1)</td>
<td>49 (20)*</td>
<td>49 (39)*</td>
<td>¶</td>
</tr>
<tr>
<td>BP lowering drugs, n (%)</td>
<td>0 (0)</td>
<td>104 (43)*</td>
<td>78 (62)*</td>
<td>¶</td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>119±15</td>
<td>150±21*</td>
<td>151±19*</td>
<td>¶</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>69±9</td>
<td>89±12*</td>
<td>82±10†</td>
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<tr>
<td>Brachial MBP, mm Hg</td>
<td>86±10</td>
<td>110±15*</td>
<td>105±12†</td>
<td>¶</td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>50±12</td>
<td>52±15*</td>
<td>68±15†</td>
<td>¶</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>66±10</td>
<td>67±11</td>
<td>68±12</td>
<td>¶</td>
</tr>
</tbody>
</table>

*P<0.01 vs NT; †P<0.01 vs HT; ‡ANOVA significant (P<0.05).

### Table 2. Arterial Parameters

<table>
<thead>
<tr>
<th>Arterial Parameters</th>
<th>NT Patients</th>
<th>HT Patients</th>
<th>T2D Patients</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid PP, mm Hg</td>
<td>54±20</td>
<td>67±24*</td>
<td>77±26†</td>
<td>¶</td>
</tr>
<tr>
<td>Carotid diastolic diameter, mm</td>
<td>6.70±0.91</td>
<td>7.55±1.19*</td>
<td>7.85±1.16*</td>
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</tr>
<tr>
<td>Stroke change in diameter, μm</td>
<td>407±262</td>
<td>351±113*</td>
<td>371±131</td>
<td>¶</td>
</tr>
<tr>
<td>Cdist, kPa 10⁻³</td>
<td>24.33±18.85</td>
<td>12.69±7.03*</td>
<td>10.63±4.58*</td>
<td>¶</td>
</tr>
<tr>
<td>CS, m/s</td>
<td>7.79±2.66</td>
<td>9.65±2.28*</td>
<td>10.45±2.48*</td>
<td>¶</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>12.81±4.43</td>
<td>14.18±3.52*</td>
<td>18.32±6.04†</td>
<td>¶</td>
</tr>
</tbody>
</table>

*P<0.01 vs NT; †P<0.01 vs HT; ‡ANOVA significant (P<0.05).
analysis in the entire population and in the 3 groups. We identified factors differentially affecting aortic and CS from correlation studies in each population using the residual of the PWV-CS correlation.\textsuperscript{22} A value of $P < 0.05$ was considered significant. Statistical analysis was carried out using NCSS 2004 package software (Hintze JL).

**Results**

The characteristics of the 3 groups (94 NTs, 243 HTs, and 126 T2Ds) are described in Table 1. T2D patients were older and shorter than NT and HT patients. The 3 groups were comparable for weight, heart rate (HR), sex, and cigarette smoking. NT patients were leaner than HT patients, who themselves were leaner than T2D patients. Hypercholesterolemia was more common in HT and T2D patients than in NT patients (respectively, 17.7%, 17.5%, and 0.3%). By definition, hypertensive patients (either HT or T2D) had significantly higher BP values than NT patients, either central or peripheral, and for all components [mean, systolic, diastolic, and pulse pressures (PPs); Table 1].

The CCA diastolic diameter was larger in T2D patients than in HT and NT patients ($P < 0.05$ for trend; Table 2). Carotid distensibility was significantly lower and CS was significantly higher in hypertensive patients (HT and T2D) than in NT patients. Aortic PWV was significantly higher in T2D patients than in HT patients and was higher in HT patients than in NT patients (Table 2).

We observed a significant positive correlation between aortic PWV and CS when we considered the entire population ($r^2 = 0.34; P < 0.001$). Aortic PWV and CS were significantly correlated within each group. The correlation was stronger for NT patients ($r^2 = 0.41; P < 0.001$) than for HT ($r^2 = 0.16; P < 0.001$) and T2D patients ($r^2 = 0.108; P < 0.001$; Figure 1).

**Determinants of Aortic and CS**

In the univariate analysis, we found that the following parameters were significant ($P < 0.01$) determinants of aortic PWV and CS: in NT patients: age, SBP, DBP, MBP, brachial PP, body mass index (BMI), weight, and sex; in HT patients: age, SBP, DBP, MBP, brachial PP, BMI, height, and hypercholesterolemia; and in T2D patients: age, SBP, MBP, BMI, smoking, and sex.

Using a multivariate model of stepwise regression analysis (Table 3), we found that age and BP were the major independent determinants of aortic PWV and CS in NT patients, explaining 41% and 66% of aortic and CS variance, respectively. Age had a major independent influence on CS, whereas MBP had a marginal influence. In HT patients, age and BP explained 45% and 60% of aortic and CS variance, respectively. In HT patients, hypercholesterolemia had a marginal influence on CS (explaining 1% of the variance).

We observed a similar pattern in T2D patients. Age had a strong independent influence on aortic PWV and CS, whereas BMI and smoking had only a marginal influence. In T2D patients, the total explained variance for CS was 49% and was only 33% for aortic stiffness, leaving a large part of the aortic PWV variance unexplained (Table 3).

**Determinants of the Discrepancies Between Aortic and Carotid Stiffness**

We identified the factors differentially affecting aortic and CS from correlation studies in each population using the residual of the correlation between aortic and CS. A high residual indicates a disproportionately stiff aorta compared with the carotid artery and vice versa. In NT patients, BMI was the only parameter independently correlated with a residual (positive correlation). That is, the higher the BMI, the stiffer the aorta compared with the carotid artery (Table
BMI explained only a small part of the correlation residual between aortic and CS (11%). In HT patients, age and MBP were significantly and positively correlated with a residual, explaining 22% of the variance. In T2D patients, age and HR and BMI were significantly and positively correlated with a residual, explaining up to 45% of total variance.

To summarize these data, Figure 2 shows that the correlation (r² of the relationship) between aortic and CS becomes weaker as the number of CV risk factors increased (none; hypertension; and hypertension diabetes), whereas we observed the opposite for the discrepancies (residuals) between aortic and CS (Table 4).

In each group, the slope of the relationship between aortic stiffness and age was higher than the slope of the relationship between CS and age (Table 5). In T2D patients, the slope of the relationship between aortic stiffness and age was higher than the slope of the relationship between CS and age (Table 5). In HT patients, we observed an intermediate relationship.

**Discussion**

Our principal finding is that the correlation between aortic stiffness and CS becomes weaker as the number of CV risk factors increase (none; hypertension; and hypertension + diabetes), whereas we observed the opposite for the discrepancies (residuals) between aortic and CS, an increasing part of which was explained (Figure 2). We believe that this study is the first one to quantify the discrepancies between aortic and CS.

We first aimed to evaluate the correlation between aortic and CS. Because arterial stiffening is thought to be a general phenomenon in large central elastic arteries, we hypothesized that aortic stiffness and CS measurements should agree and be significantly correlated. Indeed, we observed strong and positive correlations between aortic and CS in NT patients (r² = 0.41; P < 0.001) and the entire population (r² = 0.34; P < 0.001). However, the correlation was weaker in HT and T2D patients, indicating a significant level of discrepancies.

Discrepancies between aortic and CS could result from inaccurate measurements. Carotid-femoral PWV is generally considered the gold standard for the direct measurement of aortic stiffness. However, it may not reflect the exact pathophysiological condition, because the distance between the carotid and femoral sites is measured manually and may differ from the true length of the arterial pathway because of anatomic particularities. An identical method would be diffi-
In the present study, we used 2 reproducible and validated techniques: a high-resolution echocardiography system for measuring stroke changes in diameter and applanation tonometry for locally determining PP.

We also use the reverse of the Moens–Korteweg equation to transform into a CS index to allow comparison with PWV. This has the advantages that we can linearly relate CS to aortic PWV. Also, all of the correlations between CS and CV risk factors were linear, whereas we were markedly curvilinear when using carotid distensibility instead of CS.

It is more likely that the discrepancies between aortic and CS result from different influences of CV risk factors on both parameters. As mentioned previously and illustrated by Figure 2, our principal finding is that the correlation between aortic stiffness and CS becomes weaker as the number of CV risk factors increases (none, hypertension, and hyperglycemia), whereas we observed the opposite for the discrepancies (residuals) between aortic and CS, of which an increasing part was explained (Table 4). For example, in NT patients, CS was strongly correlated with aortic stiffness. This is likely because of age and BP (either SBP or MBP), which are the 2 major determinants (Table 3), exerting a parallel influence on the carotid artery and the aorta. Indeed, age and BP were not significant determinants of the residual of the aortic-carotid relationship in the multivariate analysis (Table 4). By contrast, in T2D patients, CS was weakly correlated to aortic stiffness ($r^2=0.11$). This is likely because of age, a major determinant of both carotid and aortic stiffness in this population (Table 3), but exerting a different influence on the carotid artery and the aorta. Indeed, age explained a large part of the residual of the aortic-carotid relationship (Table 4).

Therefore, as these patients get older, their aorta becomes disproportionately stiff compared with the carotid artery. Indeed, age and BP were not significant determinants of the residual of the aortic-carotid relationship in the multivariate analysis (Table 4). By contrast, in T2D patients, CS was weakly correlated to aortic stiffness ($r^2=0.11$). This is likely because of age, a major determinant of both carotid and aortic stiffness in this population (Table 3), but exerting a different influence on the carotid artery and the aorta. Indeed, age explained a large part of the residual of the aortic-carotid relationship (Table 4).

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Although both the carotid artery and the aorta are classified as elastic vessels, the ultrastructure of the carotid artery is more like the abdominal aorta than the ascending aorta. Alterations of vascular wall through aging are attributed to structural modifications, such as an increase in collagen content and calcification of the media, elastic lamellae creasing and breakage, and accumulation and migration of vascular smooth cells in the arterial walls. In the presence of additional CV risk factors, such as hypertension, these modifications occur earlier in the aorta than in other arterial territories. We have shown previously that the radial, brachial, and femoral arteries, which have a muscular structure, are resistant to age-induced stiffening compared with the carotid artery.

Other factors may explain the higher sensitivity of the aorta to aging. First, in hypertensive or diabetic patients, there is a marked increase in cross-linked collagen peptides in the aortic media, because of nonenzymatic glycation, which contributes to reduced arterial wall compliance. Second, in the thoracic aorta in humans, the media exceeds a critical thickness, and, thus, the nutrition of the aortic wall is supplemented by blood flow through small vessels, the vasa vasorum, that form a perivascular network and penetrate into the media layers. The decrease in blood flow through the vasa vasorum that occurs with aging and atherosclerosis can increase aortic stiffness. Finally, hypertension and diabetes are characterized by activation of the renin–angiotensin–system. Angiotensin II is an important humoral factor involved in regulating the turnover of extracellular matrix proteins, such as transforming growth factor $\beta$, and a strong regulator of matrix metalloproteinase and tissue inhibitor of metalloproteinases. In hypertension and diabetes, angiotensin II is increased, especially in the aortic wall of nonhuman primates.

These mechanisms may explain the “accelerated aging” of the aortic wall compared with the carotid wall in patients with diabetes and hypertension.

BMI explained a significant part of the discrepancies between aortic and CS in NT patients (Table 4). The influence of metabolic syndrome on arterial stiffness has been reported previously and was attributed to various mechanisms, including glycation of matrix proteins and an adverse effect on the structure and function of large arteries of several peptides produced by the adipose tissue, such as angiotensin, interleukin 6, and tumor necrosis factor $\alpha$. Our results suggest that metabolic syndrome influences aortic stiffness more than CS.

HR explained a significant part of the discrepancies between aortic and CS in T2D patients (Table 4). The influence of HR on aortic PWV has been reported previously showing that the higher the HR, the higher the PWV. However, its influence on CS was only shown under acute conditions during pacing studies.

The main clinical implication of our study is that aortic stiffness and CS cannot be used as interchangeable predictors in high-risk patients. The independent predictive value of CS remains to be determined in populations having different CV risk profiles. Measurement of aortic PWV during these epidemiological studies would allow the independent predictive values of aortic and CS to be compared and the most appropriate parameter to be selected.

Our study has several limitations. The HTs were younger than T2Ds, themselves older than NTs. The age was typical of the patients seen in our institution. We preferred to adjust statistically on age, instead of selecting patients by matching process, in order to keep groups representative of the bulk of patients. In addition, to rule out a confounding effect of age mismatch on our results, we performed the same analysis on a subset of data, after strict matching on age (78 NTs, 62.5±15.8 years; 120 HTs, 62.7±7.0 years; and 126 T2Ds, 62.5±15.8 years; 120 HTs, 62.7±7.0 years; and 126 T2Ds,
62.8±7.7 years). Results were almost identical. Arterial length is estimated, not measured, when PWV is measured. Because arteries lengthen and become tortuous with age and risk factor, the true stiffness of the aorta could be underestimated. We did not study inflammation markers, such as CRP, which may influence arterial stiffness. Most HT and T2D patients were taking antihypertensive drugs at the time of the arterial measurements, which could have influenced both aortic and CS. However, we chose to include these patients in the present study to keep the same conditions as other population studies that have demonstrated the independent predictive value of aortic and CS on CV events. In addition, antihypertensive drug treatment had no significant influence in the univariate and multivariate analyses.

In conclusion, although carotid-femoral PWV and CS provided similar information on the impact of aging on large artery stiffness in normal subjects, this was not the case for high BP and/or diabetes. In these cases, the aorta stiffened more than the carotid artery with age and other CV risk factors.

References