Arterial Stiffness From Monitoring of Timing of Korotkoff Sounds Predicts the Occurrence of Cardiovascular Events Independently of Left Ventricular Mass in Hypertensive Patients

Philippe Gosse, Antoine Cremer, Georgios Papaioannou, Sunthareth Yeim

Abstract—Several studies have established that the increase in arterial stiffness (AS) is a cardiovascular risk factor but to date no studies have evaluated in hypertensive patients its prognostic value in comparison with another powerful risk factor, left ventricular mass (LVM) as measured by echocardiography. We prospectively evaluated the prognostic value of AS and LVM in patients with essential hypertension. The population studied comprised 793 patients (56% men) aged 54±14 years. For 519 patients, baseline measurements were made before any antihypertensive treatment, for 274 patients, the measurement were obtained during the follow-up period under antihypertensive treatment. AS was assessed from ambulatory monitoring of blood pressure and timing of Korotkoff sounds. Left ventricular mass was measured in 523 patients. After a mean follow-up of 97 months, 122 cardiovascular events were recorded in the whole population and 74 in the group with LVM determination. AS as continuous or discontinuous variable was independently related to cardiovascular events. The existence or not of antihypertensive treatment at the time of its measurement did not affect its prognostic value. When LVM was forced in the model, AS remained significantly related to cardiovascular events. Thus, AS has an independent prognostic value in the hypertensive, whether measured before or after the administration of antihypertensive treatment. This prognostic value persists after taking LVM into account. (Hypertension. 2013;62:161-167.)

Key Words: arterial stiffness ■ ambulatory BP monitoring ■ cardiovascular events ■ left ventricular mass ■ QKD

Markers of subclinical target organ damage increase cardiovascular risk prediction beyond traditional risk factors. Arterial stiffness (AS) is one of these markers. The predictive value for future cardiovascular events (CVEs) has been demonstrated for the carotid-femoral pulse wave velocity (PWV) in patients with renal failure, in hypertensives, and in the general population, as well as from ambulatory measurement of the timing of Korotkoff sounds (QKD) in hypertensives. The predictive value of AS is independent of traditional risk factors: sex, age, diabetes mellitus, smoking, cholesterol, and blood pressure (BP), even when monitored during 24 hours with the QKD method. However, very few studies have compared the respective predictive values of different markers of target organ damage. This is a major issue because the question whether all parameters should be measured, or only some of them, in routine condition is opened. To date there are no studies that have evaluated the prognostic value of AS in comparison with another powerful risk factor, left ventricular mass (LVM) as measured by echocardiography in hypertensive patients. We evaluated the prognostic value of these 2 parameters in the same population of patients with essential hypertension using the QKD method, which offers the advantages to combine 24-hour BP monitoring and an estimation of AS independent of BP.

Methods

Population

The patients included in this study belong to the Bordeaux cohort of hypertensive. This registry was started in 1984 and includes all patients consecutively referred to our center before administration of antihypertensive treatment and fulfilling the following criteria:

Office BP>140/90 on ≥2 occasions; Essential hypertension. Absence of cardiovascular complications or pathology likely to affect the prognosis, absence of type 1 diabetes mellitus.

For the validity of the ambulatory measurement of AS, 2 other selection criteria were used.

Absence of bundle-branch block on ECG (QRS duration <120 ms).
Absence of known thyroid pathology.

All the patients gave their consent to participation in this registry, which was approved by our local committee of ethics and protection.
of the individual (Committee for Protection of Persons in the South-West and overseas III).

After the initial evaluation, the patients were given antihypertensive treatment and followed up by their family physicians who were not informed of AS results. These patients were not systematically convened, but could be sent again by their doctors during the follow-up period. We included in this study the patients of the cohort who had benefited from a good quality ambulatory measurement of BP and QKD either on inclusion in the cohort before treatment or during the follow-up under treatment for the patients for whom this measurement was not initially available, as this monitoring became available only in late 1992. Baseline for this study was defined as the time of the first QKD monitoring, at entry in the cohort (untreated patients) or later on treatment for patients for whom QKD could not be monitored before treatment, at entry in the cohort.

Ambulatory Measurement of BP and QKD Interval
All the patients benefited from an ambulatory measurement of BP coupled with the measurement of QKD interval. 3 The equipment (Diasys 200RK then Diasys Integra, Novacor, France) is a device based on the auscultatory measurement of BP, which also determined for each measurement the duration of the QKD interval as the time between the QRS wave on the ECG and the detection of the last Korotkoff sound on deflation of the cuff. So Q is for the ECG QRS, K for Korotkoff sound, and D for diastolic BP. This interval is measured every 15 min along with BP and heart rate (HR) during 24 hours (Figure 1). This time has 2 components: the pre-ejection time and the time of transmission of the pulse wave from the aortic valves to the brachial artery, which for a cuff usually placed on the left arm, includes the aortic arch, the left subclavian artery, and part of the brachial artery. This time is related to the PWV 9–10 and the length of the arterial route. The ambulatory measurement of BP, QKD, and HR enables evaluation of the variations in QKD with the spontaneous variations in BP and HR. The variations with HR depend primarily on variations in the pre-ejection time, and the variations with systolic BP (SBP) in those of PWV. From the 96 measurements obtained, the software automatically calculates the bivariate linear regression equation of QKD according to SBP and HR and the theoretical value of QKD for a 100 mmHg SBP and a 60 bpm HR. The interest of this index, the QKD 100-60, is 2-fold. First, it effectively reduces the influence of the pre-ejection time. The QKD 100-60 is no longer correlated with mean 24 hours HR >24 hours or with systolic function evaluated by echocardiography.11 Second, it provides an isobaric index of AS, making it possible to compare patients at equal BP, a clear advantage over PWV, which is highly dependent on BP and HR at the time of the measurement. The QKD 100-60 also depends on the length of the arterial segment considered. We defined its correlation to height in a population of adult young subjects (<30) without risk factors12 and proposed an equation for calculating QKD 100-60 referred to height: theoretical QKD 100-60 = 0.73×height (cm)+91. The measured value of the QKD 100-60 is thus presented with reference to the value predicted by height in normal subjects. We only included patients who had ≥80 valid measurements during 24 hours. Results of 24-hour BP recordings were sent to the family physician but the results of QKD were not.

Measurement of LVM
LVM was measured at the same time as QKD, the day ABPM (ambulatory blood pressure monitoring) was fitted in most cases and within a 3-month interval in few cases. LVM was measured from M mode tracings of the left ventricle obtained from the left parasternal view. The tracings were read blind to clinical and QKD data, according to the PENN convention. LVM was calculated from Devereux formula13 and indexed to height to the power 2.7 (LVM index [LVMI]). Other modes of indexation (height and body surface area) and relative wall thickness were also tested.

Estimation of Risk SCORE
An estimation of 10-year risk of fatal CVE was calculated from the SCORE (Systematic COronary Risk Evaluation) project14 charts for low-risk populations using office SBP and total cholesterol levels. For patients with diabetes mellitus, results were multiplied by 2 in men and 4 in women.

Follow-Up
Information from these patients is obtained regularly (every 2 years on average) either directly from the patients or from their physicians. A detailed report was requested in the event of CVE. The CVEs retained for analysis were myocardial infarction, coronary revascularization, stroke documented by computed tomography.

Figure 1. Twenty-four-hour ambulatory recording of blood pressure (BP), heart rate (HR), and timing of Korotkoff sound (QKD) in a 64-year-old hypertensive patient. A, Results of monitoring. B, Univariate linear regression of QKD vs systolic BP (SBP). C, Univariate linear regression of QKD vs HR. QKD0.60, value of QKD for 100 mm Hg SBP and 60 bpm HR; QKDh, measured QKD100-60/height predicted value in normal subjects. Results in this patient: bivariate regression analysis: QKD=215–0.369×SBP–0.146×HR; QKD100-60=169 ms; height predicted QKD100-60=182 cm×0.73+91=209 ms; QKDh=0.81.
scan or NMRI (nuclear magnetic resonance imaging), sudden death, terminal renal failure, cardiac failure, arteriopathy of the lower limbs requiring revascularization, aneurism of the abdominal aorta operated or ruptured, carotid stenosis requiring angioplasty. We regarded as major events coronary events (infarction or coronary revascularization), stroke, and deaths from all causes.

Statistics
The data were analyzed with SPSS 18 IBM software. Survival was analyzed according to the Cox model for the whole study population and then in the group whose LVM was measured. The analysis was carried out for all the CVE, then for the major events and deaths. QKDh was used as both continuous and discontinuous variable (normal or abnormal values). Abnormal QKDh was defined as value <100% of the normal height predicted value. The risk factors included for analyses were discontinuous variables: sex, diabetes mellitus, smoking, hypercholesterolemia, recording performed on treatment; continuous variables: average 24-hour pulse pressure (PP) and mean BP (MBP), mean 24-hour HR, body mass index, LVMI. In another model, 24-hour MBP and PP were replaced by 24-hour SBP and diastolic BP. The adjusted hazard ratio was calculated as the antilogarithm of the \( \beta \) coefficient of the Cox model.

Results
The population studied comprised 793 patients whose main characteristics are summarized in Table 1. For 519 patients, baseline measurements were made before any antihypertensive treatment; for 274 patients, the measurement of the QKD could only be obtained during the follow-up period under

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**Table 1. Main Characteristics of Population Studied at Baseline**

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>442/351</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers (Y/N)</td>
<td>153/460</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia (Y/N)</td>
<td>154/639</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (Y/N)</td>
<td>67/726</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous treatment (Y/N)</td>
<td>274/519</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>793</td>
<td>18</td>
<td>80</td>
<td>54</td>
<td>14</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>793</td>
<td>17</td>
<td>39</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Office SBP, mmHg</td>
<td>793</td>
<td>110</td>
<td>240</td>
<td>154</td>
<td>18</td>
</tr>
<tr>
<td>Office DBP, mmHg</td>
<td>793</td>
<td>60</td>
<td>140</td>
<td>93</td>
<td>11</td>
</tr>
<tr>
<td>24-h SBP, mmHg</td>
<td>793</td>
<td>95</td>
<td>198</td>
<td>131</td>
<td>16</td>
</tr>
<tr>
<td>24-h DBP, mmHg</td>
<td>793</td>
<td>54</td>
<td>135</td>
<td>84</td>
<td>11</td>
</tr>
<tr>
<td>24-h HR, bpm</td>
<td>793</td>
<td>41</td>
<td>105</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>24-h PP, mm Hg</td>
<td>793</td>
<td>20</td>
<td>102</td>
<td>46</td>
<td>13</td>
</tr>
<tr>
<td>24-h MBP, mm Hg</td>
<td>793</td>
<td>72</td>
<td>154</td>
<td>101</td>
<td>11</td>
</tr>
<tr>
<td>QKD100-60, ms</td>
<td>793</td>
<td>66</td>
<td>226</td>
<td>206</td>
<td>19</td>
</tr>
<tr>
<td>QKDh, %</td>
<td>793</td>
<td>123</td>
<td>97</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>SOKOLOFF, mm</td>
<td>605</td>
<td>3</td>
<td>58</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td>Plasma fasting blood glucose, mmol/L</td>
<td>601</td>
<td>3.4</td>
<td>15.1</td>
<td>5.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Plasma creatinin, μmol/L</td>
<td>560</td>
<td>40</td>
<td>221</td>
<td>86</td>
<td>23</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>497</td>
<td>2</td>
<td>10.0</td>
<td>5.6</td>
<td>1.2</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>523</td>
<td>18</td>
<td>149</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>523</td>
<td>49</td>
<td>319</td>
<td>115</td>
<td>37</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; LVMI, left ventricular mass indexed for height to the power 2.7 (g/m².7) or for body surface area (g/m²); MBP, mean blood pressure; PP, pulse pressure; QKD, timing of Korotkoff sound; QKDh, measured QKD100-60/height predicted value in normal subjects; and SBP, systolic blood pressure.

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**Table 2. Cardiovascular Complications Observed as a Function of Normal or Reduced QKDh at Baseline**

<table>
<thead>
<tr>
<th>Events</th>
<th>Normal QKDh</th>
<th>Reduced QKDh</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>16</td>
<td>106</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>9</td>
<td>52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths</td>
<td>3</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>2</td>
<td>20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Major events</td>
<td>16</td>
<td>95</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

QKD indicates timing of Korotkoff sound; and QKDh, measured QKD100-60/height predicted value in normal subjects.
antihypertensive treatment. Only 15 patients were lost to follow-up. For the patients followed up, a measurement of LVM was obtained in 523 patients. The group for which LVM was available was on average younger (51±13 versus 58±14 years; \( P < 0.01 \)), had a lower mean 24-hour PP (46±12 versus 48±14 mm Hg; \( P < 0.05 \)) and longer QKDh (98±8 versus 95±9%; \( P < 0.01 \)). The average follow-up period for the population was 97±61 months.

In this population, 122 CVE were recorded (Table 2), 111 major events including 45 deaths (22 of proved cardiovascular origin). QKDh was significantly correlated with 24-hour PP (\( r = -0.50; \ P < 0.0001 \)) and with age (\( r = -0.38; \ P < 0.001 \)).

In this population (Table 3), 6 variables remained significantly and independently linked to the occurrence of CVE in multivariate Cox model: age, QKDh as a continuous or discontinuous variable (Figure 2A), smoking, recording performed on treatment, 24-hour PP, and 24-hour MBP. The QKDh as continuous or discontinuous variable was also independently related to the major events together with age, smoking, recording on treatment, and 24-hour MBP but in this case 24-hour PP was no more significant independent predictor. It was also independently related to all-cause deaths with age and 24-hour MBP. Figure 3 presents the receiver operating characteristic curve plots of the relations of QKDh with the occurrence of CVE (left) or major events (right). The 100% threshold had a sensitivity of 86% and a specificity of 43% for the prediction of CVE and a sensitivity of 95% with a specificity of 40% for the prediction of major events. The best total sensitivity (83%) plus specificity (47%) for prediction of CVE was obtained for a QKDh of 99%. When the analysis was performed with 24-hour SBP and diastolic BP instead of 24-hour PP and MBP, only SBP was significantly related to event-free survival. The results for the other variables and specially QKD are almost the same. In our cohort, 24-hour SBP was the best predictor of events as compared with daytime or nighttime BP. However, the differences among the 3 are small and whatever BP level is entered in the COX model the results for QKD stay unchanged. The population was split into 3 groups according to the risk SCORE: low (\( \leq 1\% \)), moderate (\( >1\% \) to \( <5\% \)), and high (\( \geq 5\% \)). Table 4 shows the number of patients with reduced QKDh and the number of events recorded in each subgroup. In all SCORE groups, reduced QKDh was associated with a significant increase in CVE and all-cause deaths. QKDh was reduced in 42% of patients in the low-risk score with a 10-fold increased incidence of all-cause deaths. In the Cox analysis, QKDh remained a significant predictor of all CVEs, major events, and all-cause deaths when the risk SCORE was entered in the model.

In the subgroup, where LVM was measured, 74 CVEs were recorded, 65 major events, and 23 deaths. LVMi was correlated significantly with QKDh (\( r = -0.18; \ P < 0.001 \)). LVMi was related to the risk of CVE (n=74) or major events (n=65) in the monovariate analysis (\( P < 0.001 \)). The

![Figure 2. Event-free survival curves (all events) according to baseline values of QKDh adjusted for all significant risk factors (A) plus left ventricular mass (LVM) index in the population with baseline LVM assessment (B). QKDh, measured QKD_{100-60/height} predicted value in normal subjects.](http://hyper.ahajournals.org/)
results of multivariate Cox analysis are shown in Table 5. QKDh (continuous or discontinuous) remained significantly predictive of outcome independently of LVMI which was significant only in the study of major events. Figure 2B shows the adjusted event-free survival curves according to normal or reduced QKDh. The use of other modes of indexation of LVM (height, body surface area, or relative wall thickness) did not change the results.

### Discussion

The ambulatory measurement of QKD interval enables determination of an index of AS coupled with a measurement of BP. The index obtained, measured QKD$_{100-60}$/height-predicted theoretical value, QKDh, is inversely related to AS. It is significantly reduced in the hypertensive and in other populations where AS is increased (renal failure and systemic sclerosis). A criticism of this technique is the evaluation of the transmission of the pulse wave over a territory, including muscular arteries (subclavian and brachial). In fact, the stiffness of these arteries is little influenced by age or hypertension, and so has little influence on the overall QKD. One of the interests of this method is that it mainly depends on the transmission of the pulse wave along the aortic arch whose physiological role is paramount and which is more subjected to the consequences of physiological or premature aging than is the rest of the aorta. This portion of the aorta is not taken into account by the carotid-femoral PWV considered as the gold standard. We have also shown with an invasive study that the QKD interval was significantly correlated to aortic SBP and could be used for a assessment of central BP by a noninvasive method. Finally, the QKD$_{100-60}$ is a reproducible technique with a SD of the differences between 2 examinations ranging from 9 to 12 ms for a normal value of 200 to 210 ms.

We have already shown in our cohort that QKDh is significantly related to the occurrence of cardiovascular complications independently of age, mean 24-hour BP, and other traditional risk factors. This index also has a prognostic value for worsening of systemic sclerosis. This new analysis of our cohort is based on a larger number of CVE (122 versus 62). It confirms our previous results showing a relation between QKDh and CVE independently of age, mean 24-hour BP (SBP, PP, or MBP), sex, diabetes mellitus, smoking, and hypercholesterolemia. The present analysis affords new data. The QKDh is an independent predictor of all-cause deaths. The predictive value of QKDh does not seem to be influenced by the existence or not of antihypertensive treatment at the time of measurement. Above all, it remains significantly correlated with the prognosis when LVMI is also introduced into the model. An increasing number of intermediate markers of cardiovascular risk are now proposed: LVM, intima-media thickness, and AS. LVM is the intermediate marker that seems to be the best documented and it may be proposed as a surrogate end point in hypertension. Its reduction with antihypertensive treatment is related to an improved prognosis. LVM and AS are linked. We noted a significant but weak correlation between the 2 parameters in our population. It was thus important to check whether the link between AS and cardiovascular risk was independent of LVM. This seemed to be the case. The lack of predictive value of LVMI in multivariate analysis when both 24-hour BP and QKD are entered in the model is probably linked to the fact that these 2 parameters are important determinants of increased LVM. Our study raises the question of whether LVM remains an independent risk factor when AS is known. Unfortunately, our study was not powerful enough.

### Table 4. Risk Classification According to Risk SCORE and Value of QKD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low-Risk Score, ≤1%</th>
<th>Medium Risk, &gt;1%, &lt;5%</th>
<th>High-Risk Score, ≥5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>191</td>
<td>138</td>
<td>73</td>
</tr>
<tr>
<td>Average FU, y</td>
<td>8.7±5</td>
<td>9.6±5</td>
<td>7.4±5</td>
</tr>
<tr>
<td>All CVE</td>
<td>7 (3.7%)</td>
<td>15 (10.9%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Major events</td>
<td>7 (3.7%)</td>
<td>15 (10.9%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (0.5%)</td>
<td>7 (5%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

CVE indicates cardiovascular event; FU, follow-up; QKD, timing of Korotkoff sound; and QKDh, measured QKD$_{100-60}$/height predicted value in normal subjects.
to demonstrate this. As far as we know, only 1 other study tested the predictive value of PWV as compared with LVM in a population of 1968 healthy patients. In a Cox multivariate model, LVM was not significantly associated with cardiovascular deaths when PWV and SCORE were entered in the model but remained significantly associated with a composite of fatal and nonfatal CVEs.

Some important limitations stem from the structure of this study. It is a prospective registry. Only 67% of patients benefited from an echocardiographic examination at the time of QKD measurement. Initially, the antihypertensive treatments were proposed by our team, but later choices and modifications were carried out by the family doctors and were based only on the office BP. It was impossible to study the influence of the different classes of antihypertensive agent in this cohort. The number of recorded CVE is still modest. Finally, this population was mostly composed of white individuals, although it should be noted that race information is not available for this population.

Perspectives

AS evaluated by the ambulatory measurement of QKD interval has an independent prognostic value in the hypertensive, whether measured before or after the administration of antihypertensive treatment. The prognostic value of QKD-assessed AS persists after taking 24-hour BP and LVM into account, 2 important risk factors. This emphasizes the idea that AS may allow a better assessment of risk in hypertensive patients and could be a target for future intervention studies.

Disclosures

None.

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What Is New?

• Arterial stiffness measured with the QKD method is a strong predictor of cardiovascular event and all-cause deaths in hypertensive patients.
• It remains significantly correlated with future events when left ventricular mass, another powerful and independent risk factor, is taken into account.
• Current antihypertensive treatment does not interfere with the prognostic value of the QKD method.

What Is Relevant?

• The QKD method allows to measure 24-hour blood pressure and arterial stiffness in a single examination.

What Is New?

• This method may help to better assess cardiovascular risk in hypertensive patients.

Summary

Measurement of arterial stiffness with QKD method is predictive of future cardiovascular event and all-cause deaths independently of 24-hour blood pressure and left ventricular mass in hypertensive patients.
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