Prediction of Cardiovascular Morbidity and Mortality
Comparison of the Internal Carotid Artery Resistive Index With the Common Carotid Artery Intima-Media Thickness

Daniel Staub, MD; Alessandro Meyerhans, MD; Beat Bundi, MD; Hans Peter Schmid, MD; Beat Frauchiger, MD

Background and Purpose—The intima-media thickness (IMT) of the common carotid artery (CCA) is well correlated with the degree of arteriosclerosis and is a predictor of cardiovascular morbidity and mortality. The (hemodynamic) resistive index (RI) of the internal carotid artery (ICA) correlates with the degree of arteriosclerosis just as well as IMT. The aim of the study was to compare the predictive values of RI and IMT with regard to cardiovascular morbidity and mortality.

Methods—A total of 146 patients with cardiovascular risk factors or established arteriosclerosis were included. Duplex sonography of the CCA and ICA was performed, and the IMT and RI were measured in both vessels. During follow-up for a median of 36 months, the occurrence of cardiovascular events (myocardial infarction, stroke, or cardiovascular death) was assessed.

Results—Thirty-nine cardiovascular events occurred in 28 patients (19.2%). The relative risk for a cardiovascular event per increase of the IMT by 1 SD (0.16 mm) was 1.53 (95% CI, 1.07 to 2.18) and 1.91 (95% CI, 1.34 to 2.73) for RI ICA (0.08). The event rate in patients with IMT >0.79 mm (mean) and RI ICA >0.66 (mean) was 11.8% and 12.7% compared with 25.6% (P = 0.03) and 25.0% (P = 0.06) in patients with IMT ≥0.79 mm and RI ICA ≥0.66, respectively. Log rank analysis showed a continuous increase in the risk of cardiovascular event with increasing range of the IMT (P = 0.029) and RI ICA (P < 0.001).

Conclusion—The RI ICA is a predictor of cardiovascular mortality and morbidity, at least comparable to the well-established IMT. (Stroke. 2006;37:800-805.)

Key Words: carotid arteries ■ cardiovascular diseases ■ prognosis ■ ultrasonography

The intima-media thickness (IMT) of the common carotid artery (CCA) has proved to be a good marker for both the presence of early arteriosclerosis and the degree of arteriosclerosis of an individual.1–5 Prospective studies have shown a positive correlation between increased carotid artery IMT and the risk for myocardial infarction, stroke, and cardiovascular mortality.6–9 The assessment of the IMT requires a high-resolution ultrasound unit. The intraobserver and interobserver coefficient of variability of IMT measurement is reported as being between 3% and 12%.1,10,11 Whereas IMT measurement is an established surrogate parameter in epidemiologic studies,6–9 its role in clinical practice has to be determined.

The resistive index (RI) according to Pourcelot is not a morphological but a hemodynamic parameter that can be easily determined by Doppler sonography. It reflects local wall extensibility and the related vascular resistance.1,12,13 There is a clear correlation between increasing RI values and arteriosclerosis risk factors and manifestations.14–16 In the renal arteries, RI has also been shown to have prognostic value for revascularization in renovascular hypertension.17,18

In our previous study, we showed that the RI of the internal carotid artery (ICA) correlates as well as IMT with the degree of arteriosclerosis as measured by a clinical arteriosclerosis score (SMART score).1 The measurement of RI is simple, with interobserver and intraobserver coefficients of variability between 3.5% and 7.8% for the ICA.1 Thus, RI could be a prognostic parameter that is easily, accurately, and reproducibly applied in everyday practice. The aim of this study was to compare the predictive value of RI with that of IMT with regard to cardiovascular morbidity and mortality.

Methods

Patients
As described previously,1 157 consecutive patients with ≥1 cardiovascular risk factor as current or former smoker of ≥10 cigarettes per day for ≥12 months, diabetes mellitus, hypertension or hyperlipidemia, or with established arteriosclerosis as coronary heart disease (CAD), transient ischemic attack (TIA), or ischemic stroke, periph-
eral arterial occlusive disease, or renovascular disease were included in this cohort study. Definitions of risk factors and vascular diseases were described previously. Patients were treated in our hospital between December 1, 1999, and February 28, 2000. Cancer patients with a life expectancy <2 years and patients aged <16 years or >80 years were excluded. The study was approved by the local ethics committee, and all patients gave written informed consent.

Study Design

On enrollment in the study, the degree of arteriosclerosis was determined clinically by means of the SMART risk score. All patients underwent duplex sonography of the carotid flow bed. At the time of the examination, the examiner did not know the subjects’ arteriosclerosis risk score. All patients were informed that follow-up interviews and examinations are scheduled within the next years.

Duplex Sonographic Measurements

The duplex sonographic examination was performed with an Acuson Sequoia unit (Siemens AG, Medical Technology Division, Henkelstrasse 127, 91052, Erlangen, Germany). A linear 10-MHz ultrasound probe (minimal axial and lateral resolution of 0.1 mm) was used for the IMT measurement and a linear 5-MHz ultrasound probe was used for the RI measurement. The examination procedure and documentation have been described previously in detail. The RI was calculated according to Pourcelot as follows: 1/min [minimum diastolic velocity/maximum systolic velocity]. Figure 1 illustrate the principles of measurement of RI and IMT.

Follow-Up for Cardiovascular Events

The patients were contacted again between January 2003 and March 2003. Of the 157 patients originally examined, 11 (7%) could no longer be found. For the remaining 146 patients (93%), it was possible to determine outcomes by direct questioning of the patients through medical reports and files for any hospitalizations, outpatient examinations, or autopsy, and by interviewing the family doctor. Eighty-eight patients (60.3%) could be questioned personally during outpatient follow-up. In 25 patients (17.1%), apart from a study of any inpatient or outpatient medical files and contacts with the family doctor, only telephone questioning was possible. Thirty-three patients (22.6%) had died in the meantime.

The end point assessed in this study was the occurrence of cardiac events including myocardial infarction (positive troponin T/I and/or at least 2-fold increase of creatine kinase-MB with ST-elevation or with other typical ECG alterations without ST-elevation or typical history with persistent ECG alterations without documented enzyme responses) or unstable angina pectoris (hospitalization attributable to angina pectoris of Braunwald classification IIB or IIIB) and cerebrovascular events including TIA (short-term focal neurological deficit regressing completely within 24 hours as confirmed by hospital discharge report or neurological or angiographical evaluation, or typical TIA history according to the medical information) or stroke (ischemic or ischemic, secondary hemorrhagic stroke confirmed by hospital discharge report or neurological or angiographical evaluation, or typical stroke history according to the medical information, or cardiovascular death (autopsy with unequivocal cardiovascular cause of death, or based on the final hospital report together with the clinical course or autopsy, indicating probable cardiovascular cause of death) during the observation period.

Statistical Analysis

All calculations were performed with SPSS for Windows (version 12.0; SPSS Inc.). Continuous variables with normal distribution were expressed as means (±SD), discrete variables as percentage. The clinical characteristics for patients with and without cardiovascular events during the observation period were compared using the unpaired t test, χ² test, or Fisher’s exact test. The event-free survival rates to the occurrence of the first end point were presented as Kaplan–Meier survival curves and compared by the log-rank test.

Figure 1. A, Principle of RI measurement. The lower part of the illustration shows a normal Doppler flow curve with RI=0.60, the upper part the position of the sample volume in the ICA. B, Principle of the measurement of IMT.
Cox regression analysis was used to determine the relative risk for a cardiovascular event. Apart from univariate analysis of IMT and RI ICA, a multivariate Cox regression analysis model was used to investigate the additional effects of age and sex in relation to the cardiovascular prognosis. A 2-sided value of $P<0.05$ was defined as significant.

**Results**

Table 1 gives a summary of the general patient characteristics at the start of the study. Mean age on enrollment was $64.6\pm12.8$ years (range 19 to 80 years); 58.2% of patients were men. The mean IMT in the CCA was $0.79\pm0.16$ mm, and the mean RI in the ICA was $0.66\pm0.08$.

**End Points**

The median duration of observation of the 146 patients who were followed up was 36 months (range 1 to 39). During this time, 39 cardiovascular events were observed in 28 patients (19.2%). Of these, 15 (10.3%) were cardiovascular death (6 attributable to myocardial infarction, 8 attributable to heart failure in the context of CAD, and 1 attributable to a primary ischemic secondary hemorrhagic stroke), 9 were cardiac events (6 myocardial infarctions and 3 unstable angina pectoris) in 7 patients (4.8%), and 15 were cerebrovascular events (8 ischemic strokes; 7 TIA) in 10 patients (6.8%). When determining the clinical end point, the first event to occur was evaluated. The cumulative event-free survival after 12, 24, and 36 months was 89%, 85%, and 77%, respectively.

**Correlation Between Risk Score, IMT, or RI ICA and the Cardiovascular End Points**

In the univariate analysis, IMT, RI ICA, age, hypertension, and the SMART score were significantly associated with the occurrence of a cardiovascular event during follow-up (Table 1). It should be particularly noted that IMT and RI ICA were higher in patients with an event during follow-up than in patients without an event ($0.86\pm0.13$ mm versus $0.78\pm0.16$ mm; $P=0.017$ and $0.71\pm0.08$ versus $0.65\pm0.07$; $P=0.001$).

**Prognostic Subgroups of RI ICA and IMT**

In the survival curve analysis of Figure 2, the patient population is divided into 3 groups. Group 1 includes patients in the lowest third of RI or IMT values, group 2 patients in the medium, and group 3 those in the highest third of RI or IMT values, respectively. There is a continuous increase in the risk for a cardiovascular event with each third for both IMT and RI ICA (Figure 2).

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**TABLE 1. Patient Data at Study Entry**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients With Cardiovascular Event (n=28)</th>
<th>Patients Without Cardiovascular Event (n=118)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>70.2±8.8</td>
<td>63.3±13.2</td>
<td>0.010</td>
</tr>
<tr>
<td>Range</td>
<td>48–80</td>
<td>19–79</td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>15 (53.6)</td>
<td>70 (59.3)</td>
<td>0.579</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>11 (39.3)</td>
<td>67 (56.8)</td>
<td>0.095</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 (32.1)</td>
<td>42 (35.6)</td>
<td>0.731</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>11 (39.3)</td>
<td>46 (39.0)</td>
<td>0.976</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>24 (85.7)</td>
<td>68 (57.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m², n (%)</td>
<td>7 (25.0)</td>
<td>24 (20.3)</td>
<td>0.588</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>8 (28.6)</td>
<td>22 (18.6)</td>
<td>0.242</td>
</tr>
<tr>
<td>TIA/stroke, n (%)</td>
<td>9 (32.1)</td>
<td>19 (16.1)</td>
<td>0.053</td>
</tr>
<tr>
<td>Peripheral occlusive arterial disease, n (%)</td>
<td>7 (25.0)</td>
<td>28 (23.7)</td>
<td>0.887</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm, n (%)</td>
<td>2 (7.1)</td>
<td>4 (3.4)</td>
<td>0.368</td>
</tr>
<tr>
<td>Renovascular disease, n (%)</td>
<td>7 (25.0)</td>
<td>16 (13.6)</td>
<td>0.135</td>
</tr>
<tr>
<td>Body mass index, mean±SD, kg/m²</td>
<td>27.0±5.2</td>
<td>27.1±5.8</td>
<td>0.920</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>126.1±26.4</td>
<td>129.5±21.6</td>
<td>0.473</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.7±14.0</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td>Pulse, bpm</td>
<td>72.2±15.7</td>
<td>73.7±11.7</td>
<td>0.572</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.5±1.6</td>
<td>5.6±1.4</td>
<td>0.730</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.9±1.7</td>
<td>1.9±0.9</td>
<td>0.947</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>3.5±1.3</td>
<td>3.6±1.4</td>
<td>0.892</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>6.2±1.5</td>
<td>5.9±1.6</td>
<td>0.326</td>
</tr>
<tr>
<td>SMART score, median (range)</td>
<td>11 (5–15)</td>
<td>8 (5–17)</td>
<td>0.004</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.86±0.13</td>
<td>0.78±0.16</td>
<td>0.017</td>
</tr>
<tr>
<td>RI CCA</td>
<td>0.79±0.06</td>
<td>0.78±0.07</td>
<td>0.288</td>
</tr>
<tr>
<td>RI ICA</td>
<td>0.71±0.08</td>
<td>0.65±0.07</td>
<td>0.001</td>
</tr>
</tbody>
</table>
ICA are strongly associated with the occurrence of a cardiovascular event during follow-up. The relative risk for a cardiovascular event per increase by 1 SD was 1.53 (95% CI, 1.07 to 2.18) for IMT (0.16 mm) and 1.91 (95% CI, 1.34 to 2.73) for RI ICA (0.08). After adjustment for age and sex, the difference in relative risk was still present for RI ICA but not for IMT.

The calculated cumulative event rate for an end point after 3 years in patients with IMT <0.79 mm and RI ICA <0.66 (mean in each instance) was 11.8% and 12.7% (P=0.03; log-rank test) in patients with IMT ≥0.79 mm and ≥0.66 (P=0.06; log-rank test) in patients with RI ICA ≥0.66.

Sensitivity, specificity, and positive and negative predictive values for IMT and RI ICA (mean) are shown in Table 3. Sensitivity and specificity for IMT ≥0.79 mm and RI ICA ≥0.66 are similar (71% versus 71%; P=1.00 and 51% versus 48%; P=0.64, respectively).

### Table 2. Relative Risk for Cardiovascular Events in Relation to IMT and RI ICA Expressed as Continuous Variables Based on Cox Regression Analysis

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>Not Adjusted</th>
<th>Adjusted for Age and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 SD (0.16 mm) increase</td>
<td>1.53 (1.07–2.18)</td>
<td>1.24 (0.81–1.90)</td>
</tr>
<tr>
<td>P value</td>
<td>0.021</td>
<td>0.327</td>
</tr>
<tr>
<td>RI ICA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 SD (0.08) increase</td>
<td>1.91 (1.34–2.73)</td>
<td>1.68 (1.07–2.61)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.023</td>
</tr>
</tbody>
</table>

### Discussion

In a previous study, we demonstrated that the RI in the ICA is comparable to the IMT in the CCA as a surrogate marker for the degree of arteriosclerosis in an individual patient. The present study now shows that RI ICA is comparable to IMT CCA with regard to the prognosis of cardiovascular complications. Whereas IMT is slightly superior concerning the event rate above or below the mean value, events are stronger correlated to stepwise increase of the RI than of IMT as well as RI values in the subgroup analysis of the lowest, medium, and highest third seem to be stronger correlated to events than IMT. To our knowledge, this prognostic relevance of the RI has never been reported previously.

At first sight, this comparability between the 2 sonographic parameters with regard both to the determination of the degree of arteriosclerosis and to prognosis is surprising. IMT, measured by B-image technology, is a morphological parameter and represents the histologically verified intima-media segment of the vascular wall. The RI is instead based on Doppler technology. Using Pourcelot’s formula, the minimum end-diastolic and systolic peak flow velocities are linked so that the RI increases with decreasing diastolic flow fraction. Like IMT, the RI is clearly correlated with age and with cardiovascular risk factors. The RI relates to the elasticity or extensibility of the vessel and its related vascular resistance. The extensibility or elasticity of the vessel decreases with age and with any associated cardiovascular risk factors, whereas the related peripheral resistance increases as an expression of the arteriosclerosis. Before the appearance of morphological alterations that are detectable from the thickening of the intima-media complex, the early form of arteriosclerosis leads to endothelial dysfunction as an exclusively functional disorder. Even at this stage, it is already associated with increased cardiovascular mortality. Similarly, before the appearance of sonographically detectable wall thickening, qualitative alterations of the vascular wall lead to reduced elasticity and to the aforementioned increase in peripheral resistance. A low or normal RI may represent a still healthy vessel not damaged by arteriosclerosis. In contrast, with a still normal IMT, there may already be ultrastructural and functional alterations not detectable by the sonographic measurement. The fact that the increase in relative risk is correlated more strongly with RI than with IMT supports the assumption that RI detects the arterioscle-
rotic process at least as early as IMT. The precision of the measurement could also explain the tendency for RI ICA to provide a better cardiovascular prognosis. The reproducibility of RI measurements shows interobserver and intraobserver coefficients of variability between 3.5% and 7.8% equal or even better than those for IMT, which are between 3% and 12%.1,10,11 For everyday clinical practice, it should also be noted that a 5- to 7-MHz probe is normally used for B-imaging in routine examinations of the carotid region. This provides poorer axial resolution than the 10-MHz probe used, especially for scientific purposes in our study. On the other hand, the Doppler frequency of 5 MHz used in this study for the carotid RI measurements is also the standard frequency for clinical examinations. Consequently, it should be possible to determine RI ICA in everyday clinical practice at least as reliably as IMT.

Previous prognostic studies of the clinical relevance of RI have focused exclusively on the renal flow bed of patients with advanced arteriosclerosis.17,18 It is thus not surprising that these individuals with high RI values not only have a poor prognosis with regard to revascularization of renal artery stenoses but are also at high risk for cardiovascular events. The negative prognostic significance of high IMT values was reported in several previous studies and could be confirmed by our results.3,4,6

Our study has also its limits. Thus, the patient population is much smaller and the observation time shorter than in other prospective works.6,9,26 Nevertheless, evaluative follow-up after 3 years was achieved in 93% of the 157 patients originally enrolled. In addition, the proportion of patients with peripheral arterial occlusive disease was comparatively high at 24%.1,8,26

Despite these limitations, the equally or even better predictive value for cardiovascular complications obtained with RI ICA compared with IMT is intriguing because 2 parameters based on different measurement methods show the same potential. However, RI measurements are easier to assess and will therefore have a higher acceptance for clinical practice than the more complex IMT measurements. Furthermore, the rather poorer correlation of IMT with clinical end points compared with RI ICA is another argument for introducing RI ICA as a screening parameter.

In clinical practice, this means that patients with risk constellations or mild first complications of arteriosclerosis can in future be identified as low-risk patients by means of a simple RI measurement. The finding of a favorable RI value could potentially contribute to improvement of risk behavior.

On the other hand, the finding of high RI ICA or IMT values has important implications. In these patients at high risk, who also show clinical signs in most cases, not only secondary prevention must be intensified, but any interventions have to be assessed in the light of the dubious prognosis. Additional larger studies are needed to confirm this initial demonstration of the prospective significance of the RI ICA and to further clarify its relevance to the management and prevention of arteriosclerotic complications.

References


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