Carotid intima-media thickness measurement as a risk predictor of transient ischemic attack

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Resumen
Objetivos. Determinar si el riesgo de accidente isquémico transitorio (AIT) es mayor en pacientes con valores anormales de espesor miointimal carotídeo (EMIC).

Materiales y Métodos. Evaluación de 168 pacientes con y sin AIT estudiados con ecografías de vasos de cuello, midiendo EMIC. Diseño de casos y controles apareados por distintas variables. Análisis estadístico: variables continuas (media ± DS), comparadas mediante prueba “t de Student” para muestras relacionadas. Variables categóricas (porcentajes) comparadas mediante pruebas de McNemar. Para evaluar EMIC como predictor de AIT, se ajustaron dos modelos de regresión logística condicional, considerando EMIC como variable continua y como variable binaria EMIC normal (≤1 mm) vs. patológico (>1 mm). Se construyó una curva ROC para evaluar la capacidad discriminativa de EMIC, calculando la sensibilidad y especificidad para diferentes puntos de corte.

Resultados. Valor de ROC para evaluar la capacidad discriminativa de EMIC: casos 1,03 ± 0,31 mm (IC 95%: 0,97-1,10); controles 0,77 ± 0,27 mm (IC 95%: 0,71-0,83); p<0,001. El riesgo de AIT fue casi 9 veces mayor en pacientes con EMIC patológico (OR=8,8; p<0,001). Con un 95% de confianza pudo afirmarse que por cada 0,05 mm de incremento en el EMIC, el riesgo de AIT aumentó entre 16 y 44%. Área bajo la curva ROC: 0,75 (IC 95%: 0,67-0,82).

Conclusiones. Los valores anormales de EMIC están significativamente asociados a una mayor probabilidad de presentar AIT. En nuestra experiencia, el estudio de las paredes carotídeas con ecografía permitiría predecir enfermedad preclínica cerebrovascular.


INTRODUCCIÓN

Atherosclerosis is a chronic, diffuse and systemic disease that causes focal complications in different vascular beds and disorders that may lead to cerebrovascular, peripheral and coronary artery disease. The hypothesis that the interface and interaction between the vascular wall and the circulation is the primary site of the mechanism underlying cardiovascular events is based on the fact that all stages of atherosclerosis may be at distant and at multiple locations simultaneously (1,3).

According to Furchgott and Zawadzki (3), for many years the endothelium has been considered as an inert layer of cells lining the inner surface of blood vessels. However, current evidence has shown that it is a structure that senses and responds to a large number of internal and external stimuli, through membrane receptor complexes and signal-transduction mechanisms, leading to the synthesis and release of vasoactive, thromboregulatory and growth factor substances. It is known to play an essential role in vascular
tissue regulation, thrombogenicity, muscle cell proliferation and platelet adhesion and aggregation. For this reason, the endothelial dysfunction is one of the initial steps in the development of atherosclerosis and it is directly associated with an increase in cardiac, cerebrovascular and peripheral artery disease. Risk factors such as hypertension, diabetes, smoking, dyslipidemia, sedentary lifestyle, among others, contribute to endothelial dysfunction, favoring the release of vasoconstrictors, pro-aggregant substances, pro-inflammatory factors, atherosclerosis due to increased oxidation of LDL, procoagulant factors and antiplatelet factors.

The transient ischemic attack (TIA)—defined as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction—occurs in 200,000 to 500,000 patients per year in the United States. After a TIA, the recurrence risk is 8% in the first month, 5% yearly and there is also a 5% annual risk for acute myocardial infarction. The risk of stroke after a TIA ranges from 24% to 29% in 5 years, 4% to 8% in the first month and 12% to 13% in the first year.

Carotid intima-media thickness measurement by high-definition ultrasound is a useful tool for the early diagnosis of subclinical atherosclerosis, cerebral vascular disease and coronary artery disease. This marker provides a safe, noninvasive and reproducible method for assessing the extent and progression of the disease and response to treatment.

The aim of our study was to determine if the risk of TIA is higher in patients with abnormal values of carotid intima-media thickness (CIMT) using high-resolution carotid ultrasound.

**MATERIALS AND METHODS**

We present an epidemiological matched case-control study. All patients with a clinical diagnosis of TIA as per the definition provided by Albers et al., who had been hospitalized at our institution from February 2009 to May 2010 (n = 84) were included in the analysis. In addition, we selected eighty-four patients without TIA who were hospitalized during the same period, and who were matched to case subjects according to the following variables: age (± 5 years), gender, hypertension (HTN), type I and type II diabetes (DBT), dyslipidemia and smoking.

All cases and controls were subjected to carotid ultrasound with intima-media thickness measurement. Scans were performed with a Philips HDI11® scanner with automated software for measurement of CIMT. With the patients in the dorsal decubitus position and in the same position as in a standard carotid ultrasound, twelve CIMT measurements were obtained:

- The CIMT on the common carotid artery was measured 1 cm below the carotid bifurcation.
- The CIMT at the bifurcation was measured from the origin of the bifurcation to the flow divider (carotid bulb).
- The internal carotid artery CIMT was measured from the flow divider, at the proximal 1 cm of the carotid.

Measurements were performed from the intima-media interface to the adventitia-media interphase, over a 1-cm segment, with an automated system.

For confounding variables considered, HTN was defined at systolic pressure values ≥ 130 mmHg, diastolic pressure values ≥ 85 mmHg and dyslipidemia as plasma triglycerides ≥ 1.7 mmol/l or HDL cholesterol < 1 mmol/l in males and <1.29 mmol/l in females. For diabetes, one of the following three criteria had to be met (and where confirmed on more than one occa-
sion): 1. Blood glucose (at any time) \( \geq 200 \text{ mg/dL} \), associated with classic symptoms (polyuria, polydipsia and weight loss); 2. Blood glucose \( \geq 126 \text{ mg/dl} \) on two or more testing occasions; 3. Abnormal response to glucose overloads with two-hour post-overload glucose \( \geq 200 \text{ mg/dl} \).

**Statistical Analysis**

Continuous variables were expressed as mean ± standard deviation and compared between the groups of analysis using the Student’s t test for paired samples and Wilcoxon signed-rank test. Categorical variables were expressed as absolute and relative frequencies. The McNemar test was used to compare if the probability of pathologic CIMT is the same for cases and controls. Tests with p values < 0.05 were considered as significant.

In order to assess CIMT as a predictor of TIA, two models of conditional logistic regression were adjusted: one of them considering CIMT as a continuous variable and the other as a binary variable (normal CIMT <1mm or abnormal CIMT >1 mm) (Figs. 1, 2). The odds ratio (OR) and their 95% confidence intervals were calculated. Using the coefficients obtained by logistic regression, the odds of disease were estimated for each individual. Proposing different cut-off points for such disease and considering individuals with odds above such cut-off values as individuals with the disease, the status assigned by the model was compared to the real status, estimating the sensitivity and specificity for each cut-off value, and the ROC (Receiver Operating Characteristic) plot was performed. The sensitivity and specificity for each cut-off value of the odds estimated by the logistic model was calculated by standard formulas.

Finally, an important aspect to evaluate the validity of the logistic regression model is its discriminative capacity (the extent to which the logistic model differentiates individuals in whom the event occurs from those in whom it does not occur). The area under the ROC curve is used as a discriminative measure, which can be considered as a predictive value measure.

All statistical analyses were performed with the statistical software STATA version 8.

**RESULTS**

Table 1 shows case-control matching results according to the potential confounding variables analyzed.

Table 2 shows the frequency distribution of normal vs. abnormal CIMT in case and control subjects. In 29 matched pairs (case-control), CIMT was normal both in case and control subjects; in 16 matched pairs, it was abnormal both in case and control subjects; in 35 matched pairs CIMT was abnormal in case and normal in control subjects; and in 4 matched pairs CIMT was normal in case and abnormal in control subjects. The proportion of matched pairs in which CIMT was abnormal in case and normal in control subjects was significantly higher (McNemar Test: p < 0.001) than the proportion of matched pairs in which CIMT was normal in case and abnormal in control subjects. This result indicates that the odd of abnormal CIMT is significantly higher in cases than in controls.

Table 3 shows mean CIMT values in cases and controls, with their respective 95% confidence intervals (95% CI). The mean CIMT value for cases was significantly higher than that for controls (t test for paired samples: p<0.001). Graph 1 (box plot) shows the different distribution of CIMT values in cases and

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**Graph 1:** Box plot showing median, 25th and 75th percentiles, and minimum and maximum values of CIMT for case and control subjects.

**Graph 2:** ROC plot: CIMT’s capacity to predict TIA.
The application of the conditional logistic regression model showed that CIMT is significantly associated with the risk of TIA (OR = 8.8; p < 0.01 - 95% CI: 3.11 – 4.62), as the risk is about 9 fold higher in patients with abnormal CIMT (>1mm).

In addition, for each 0.05 mm increase in CIMT, there was a 29% increase in the risk of TIA (OR = 1.29; 95% CI = 1.16 – 1.44; p<0.001). With 95% confidence interval we can affirm that for each 0.05 mm increase in CIMT, the risk of TIA increases between 16 and 44%. Based on this result and with the aim of assessing the usefulness of CIMT as predictor of TIA occurrence, the area under the curve was calculated (Graph 1, ROC plot), and it was 0.746 (95% CI: 0.671-0.821) with a good discriminative capacity (p<0.001).

For CIMT values above 0.75 mm, the specificity was 63% and the sensibility was 75%, while for values above 1.05 mm, the specificity was 76% and the sensitivity was 61%.

**DISCUSSION**

As shown by a great number of studies and reviews (14-23), intima-media thickening of carotid and peripheral arteries is a powerful predictor and indicator of subclinical cardiovascular and cerebrovascular disease.

Endothelial dysfunction starts when morphologically and functionally intact endothelium is exposed to a variety of potentially damaging risk factors. If the risk factor persists, the vessel wall is damaged and the atheromatous plaques develop generating vulnerable plaques with a risk of rupture and occurrence of cardiovascular or cerebrovascular events (10, 11, 24).

Carotid ultrasound, with CIMT measurement, makes it possible to infer in a simple and non-invasive manner the state of the patient's vascular system, and to assume the diffuse presentation of atherosclerotic disease (25, 26).

B-mode ultrasound has become the imaging method of choice for the assessment of CIMT and the atheromatous plaque, when present. This method not only allows us to measure the intima-media interphase, but also to characterize the plaque by permitting visualization of plaque echogenicity, which is influenced by its composition: heterogeneous hypoechoic plaque is associated with the presence of lipids, whereas homogeneous hyperechoic plaque is mostly fibrous. This differentiation may help predict plaque behaviour (27), since softer, more echolucent plaques (poorly reflecting ultrasound waves) are the most prone to rupture and cause embolic events. In our study, the independent variable of interest was the CIMT value obtained and no assessment of atheromatous plaques was performed because, if present, they were an exclusion criterion for our analysis. We considered that their mere presence eliminated any opportunity for an early detection of early endothelial changes.

In epidemiological and observational studies,

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**Table 1:** Characteristics of cases and controls matched by the confounding variables considered.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 84)</th>
<th>Matched controls (n = 84)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean ± Standard Deviation</td>
<td>66.1 ± 10.5</td>
<td>66.2 ± 9.9</td>
<td>0.636</td>
</tr>
<tr>
<td>Male gender: % (n)</td>
<td>46.4 (39)</td>
<td>46.4 (39)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension: % (n)</td>
<td>51.2 (43)</td>
<td>51.2 (43)</td>
<td>1.000</td>
</tr>
<tr>
<td>Type I diabetes: % (n)</td>
<td>4.8 (4)</td>
<td>4.8 (4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Type II diabetes: % (n)</td>
<td>13.1 (11)</td>
<td>13.1 (11)</td>
<td>1.000</td>
</tr>
<tr>
<td>Abnormal lipids: % (n)</td>
<td>66.8 (56)</td>
<td>66.8 (56)</td>
<td>1.000</td>
</tr>
<tr>
<td>Smoker: % (n)</td>
<td>46.4 (39)</td>
<td>46.4 (39)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**Table 2:** Normal and abnormal CIMT values in the 84 case-control matched pairs.

<table>
<thead>
<tr>
<th>CIMT (case/control matched pair)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/Normal</td>
<td>29</td>
<td>34.5</td>
</tr>
<tr>
<td>Normal/Abnormal</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Abnormal/Normal</td>
<td>35</td>
<td>41.7</td>
</tr>
<tr>
<td>Abnormal/Abnormal</td>
<td>16</td>
<td>19.0</td>
</tr>
</tbody>
</table>

Mc Nemar Test: p < 0.001

**Table 3:** Mean CIMT values (mm) with their 95% CI.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± Standard Deviation (mm)</th>
<th>95% CI</th>
<th>t test for paired samples: p &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>1.03 ± 0.31</td>
<td>0.97 – 1.10</td>
<td>95% CI: 95% Confidence Interval</td>
</tr>
<tr>
<td>Controls</td>
<td>0.77 ± 0.27</td>
<td>0.71 – 0.83</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.90 ± 0.32</td>
<td>0.85 – 0.95</td>
<td></td>
</tr>
</tbody>
</table>
CIMT thickening and the occurrence of TIA have been positively associated with classical cerebrovascular and cardiovascular risk factors such as age, gender, HTN, dyslipidemia, smoking and DBT. There is also an association between CIMT and the summation of risk factors, as observed in Framingham risk score (3, 28-30). In our analysis, these variables, which have shown to be associated with CIMT thickening, were considered to match cases to controls, as shown in Table 1. Thus, we prevented these factors from behaving as confounding variables when studying the association between abnormal CIMT and risk of TIA.

The association of risk factors (HTN, DBT, dyslipidemia, etc) with TIA or CIMT thickening was not explored.

A controversial aspect in the evaluation of CIMT is the variety of protocols used for CIMT measurement, since it makes results interpretation and comparison difficult (5). The various protocols reported include the common carotid artery, carotid bulb or bifurcation and the internal carotid artery. Some authors prefer to measure the diffuse increase in intima-media thickness excluding areas with atheromatous plaques and others prefer to incorporate plaque thickness as part of the intima-media complex. Some authors measure the posterior wall of the common carotid artery only or of the three carotid segments, or the anterior and posterior walls of the three segments, and then calculate an average value (5, 35). Some studies (the earliest) report CIMT measurement only in the right carotid artery (34, 36). As most authors, in our study we measured the CIMT in both carotid arteries, in the anterior and posterior walls of the three segments (12 measurements).

Normal intima-media thickness (IMT) values depend on gender and age. The cut-off point to define a normal IMT value is usually arbitrary and is generally set above the 75th percentile of the studied population (5).

The range of normal CIMT values in adults, both for measurements at the common carotid artery or combined measurements in all carotid artery segments, ranges from 0.4 to 1 mm with an annual progression of 0.01 to 0.02 mm (5, 37). In agreement with Salonen et al (38), we consider abnormal a CIMT value above 1 mm thick. However, Bots et al (39), reported a higher risk of cerebrovascular events in adults with intima-media thickness values in the common carotid artery above 0.82 mm.

In consistency with our hypothesis and using the conditional logistic regression model, we observed that the risk of TIA is about nine-fold higher in patients with CIMT >1 mm (p<0.001 – 95% CI: 3.11 – 24.62). If we considered the CIMT cut-off point of 0.82 mm reported by Bots et al (39) in our series of patients, the risk of TIA would be even higher.

In our experience, for each 0.05 mm increase in CIMT, the risk of TIA increases between 16 and 44%.

It should be noted that although the confidence interval obtained when estimating the risk of TIA by comparing patients with abnormal CIMT values vs. patients with normal CIMT values was wide, and that this could be due to the scarce number of patients included in the analysis, the result obtained was statistically significant.

The ROC curve obtained showed, for each potential cut-off value for CIMT, the true positive rate on the ordinate (Sensitivity) and the false positive rate on the abscissa (1- Specificity). Furthermore, it indicated that CIMT measurement is a test that allows distinguishing normal from abnormal CIMT cases. The area under the curve showed 75% diagnostic accuracy of CIMT to predict TIA (considering 100% as the maximum diagnostic accuracy).

CONCLUSIONS

CIMT measurement is a tool with a very good diagnostic accuracy to detect TIA.

Abnormal CIMT values are highly associated with a higher risk of TIA. For each 0.05 mm increase in CIMT, the risk of TIA increases between 16 and 44%.

In our experience, high-resolution ultrasound assessment of the carotid artery would allow to predict cerebrovascular preclinical disease.

References

Carotid intima-media thickness measurement as a risk


12. Barth JD. Which tools are in your cardiac workshop? Carotid ultrasound, endothelial function, and magnetic resonance imaging. Am J Cardiol 2001; 87(4A):8A–14A.


