Common carotid intima-media thickness measurement is not a pertinent predictor for secondary cardiovascular events after coronary bypass surgery. A prospective study

Victor Aboyans*, Jérôme Guilloux, Philippe Lacroix, Cengiz Yildiz, Annabel Postil, Marc Laskar

Department of Thoracic & Cardiovascular Surgery and Vascular Medicine, Dupuytren University Hospital, 2, Ave. Martin Luther King, Limoges 87042, France

Received 15 April 2005; received in revised form 7 June 2005; accepted 8 June 2005

Abstract

Objective: We aimed to assess the utility of common carotid intima-media thickness (CCA-IMT) to predict secondary cardiovascular events after coronary artery bypass grafting (CABG). In primary prevention, carotid-IMT is known as a valuable cardiovascular risk marker, but its interest in secondary prevention has been less studied. We hypothesized that CCA-IMT could be used for peri-operative and long-term risk stratification in candidates for CABG.

Methods: A total of 609 patients (66.8 ± 9.2 years) were prospectively enrolled for preoperative CCA-IMT measurement and follow-up. The primary end-point combined cardiovascular death, non-fatal acute coronary syndromes, stroke, secondary coronary revascularization and peripheral arterial surgery during follow-up. The secondary end-point was the 1-month post-operative death. Univariate and multivariate analysis were performed by usual methods.

Results: A subgroup of 150 patients (24.6%) was individualized with a CCA-IMT above 90th percentile (≥0.90 mm) or presenting plaques in their CCA. At 1 month, there was no significant difference in the prevalence of elevated CCA-IMT between deceased patients and survivors (16.7 vs. 24.9%, P = ns). During a mean follow-up of 41.8 ± 16 months, 121 patients (19.8%) met the primary end-point. High CCA-IMT was predictive (OR = 1.67, 95% CI 1.14–2.46, P = 0.009) in the univariate analysis. In the multivariate analysis, age (OR = 1.03, 95% CI 1.00–1.05, P = 0.029) concomitant valvular surgery (OR = 2.17, P = 0.003) arrhythmia (OR = 2.20, P = 0.021), and peripheral arterial disease (OR = 2.41, P < 0.001) were significant independent prognostic factors whereas CCA-IMT failed to remain independently significant.

Conclusions: Pre-operative CCA-IMT can provide prognostic information for candidates to CABG. However, clinical data present stronger prognostic values.

Keywords: Coronary surgery; Prognosis; Intima-media thickness; Carotid

1. Introduction

Since its first description by Pignoli et al. [1], the intima-media thickness (IMT), especially in carotid arteries, has been extensively studied as a cardiovascular risk marker [2-7]. An increased cross-sectional carotid IMT is well correlated with age [2] and associated with elevated levels of major cardiovascular risk factors such as dyslipidemia [4,8] or hypertension [3,4,6,9] as well as prevalent cardiovascular disease [10]. In some large-cohort prospective studies, subjects with the highest levels of carotid-IMT were more prone to further cardiovascular events during the follow-up periods [3,7,11].

The interest of carotid-IMT for risk stratification in the field of secondary cardiovascular prevention has been less studied. Some studies suggest its usefulness to predict secondary events in patients with coronary artery disease (CAD) [12-14], and after coronary revascularization [15,16]. Data on the usefulness of carotid IMT as a predictive marker in patients undergoing coronary bypass grafting (CABG) are scarce [15]. In a prospective study, we aimed to determine the ability for carotid IMT to detect candidates for CABG whose further risk of secondary cardiovascular events would be high. We hypothesized that common carotid artery IMT could be used as a prognostic marker, both for postoperative short-term and long-term periods.

2. Materials and methods

2.1. Study population

The cohort was constituted from patients addressed to our department for a CABG during the period 1998-2001. Preoperative data included cardiovascular past history and risk factors as well as those obtained during cardiac catheterization. The presence of major CV risk factors (smoking, diabetes, hypertension, hypercholesterolemia) and past history were determined according to the patient’s report and the presentation letter of the cardiologist referring
the patient, as well as the presence of specific treatment (i.e. anti-diabetic or anti-hypertensive drugs). Renal failure was defined by a pre-operative blood creatinine > 150 μmol/L. Peripheral arterial disease (PAD) was defined according to the presence of an intermittent claudication and/or a history of vascular surgery for PAD. The presence of supra-ventricular arrhythmia was noted on the pre-operative ECG. Per-operative data concerned the total number of bypasses performed and the number of arterial conduits used, whether the revascularization was complete, the requirement of a cardiopulmonary bypass or an off-pump surgery, and the performance of any additive surgery (i.e. concomitant valvular surgery).

The short-term post-operative period consists of the first month following CABG. The long-term follow-up period corresponds to the interval between the day of CABG and March 1st, 2004. Follow-up was performed by reviewing hospital charts, as well as telephone contacts with patients’ family physicians. The primary end-point was composite, combining any cardiovascular event during the long-term follow-up period: cardiovascular death, acute coronary syndromes (ACS) with admission to a cardiac care unit, stroke or transient ischemic attack (TIA), secondary coronary revascularization, peripheral arterial surgery. A secondary end-point was defined by the occurrence of death in the first month post-operative period.

2.2. Measurement of carotid IMT

Carotid B-mode echography was performed on the last two centimeters of both common carotid arteries, prior to its bifurcation, by using a 10 MHz linear probe (ATL, HDI 3000, Philips Ultrasound, Bothell, WA, USA). Images were recorded on S-VHS format videotapes for off-line interpretation. Off-line interpretation of the two last centimeters of the common carotid artery (CCA) prior to the carotid bulb consisted first to describe the presence or absence of plaques of atheroma, defined as a focal widening relative to adjacent segments, protruding the lumen of more than 1.5 mm, with our without calcifications. End-diastolic images were frozen, digitized and displayed on a personal computer screen. The far wall IMT was identified as the region between the lumen-intima interface and the media-adventitia interface. In the absence of plaques, the CCA-IMT was measured through a dedicated automated edge-detection software (IoDP 3.4.4, Iotec system, Iodata processing, Paris, France). The measurement was repeated three times each side, and the mean of the six measurements had been used for this study. All the readings and measurements were performed by two of us (J.G., C.Y.) blinded to the subjects case status. In a sub-sample of 50 patients, the intra-class correlation coefficient was at 0.96 for the intra-observer and 0.63 for the inter-observer reproducibility.

2.3. Statistical analysis

Data are reported as mean±SD. In the univariate analysis, risk factors for different end-points were analyzed using Chi-square test for discrete variables and Student’s t-test for continuous variables. For the immediate post-operative period (<30 days), multiple logistic regression analysis was then used to determine the model with independent predictive factors. For this purpose, all factors presenting a P-value <0.25 in the univariate analysis were introduced in the multivariate model. For the long-term follow-up, the Kaplan-Meier survival method was used for the comparison of presence versus absence of each factor, using the log-rank test. The multivariate analysis was performed by a Cox proportional-hazards model. A P-value <0.05 was considered statistically significant. The software for statistical analysis was Statview 5.0 (SAS institute, Cary, NC).

3. Results

We enrolled 609 patients, 500 males (82.1%) and 109 females (17.9%) with a mean age of 66.8±9.2 years. Baseline characteristics are presented in Table 1. The mean carotid IMT was at 0.74±0.13 mm (0.74±0.13 mm in men and 0.72±0.14 in women, P=0.20). The 90th percentile of CCA-IMT in the overall group was at 0.91 mm. Ninety-five patients (15.6%) presented at least one plaque on their CCA. These patients have been added to the group with a CCA-IMT >0.90. In overall, 150 patients (24.6%) presented a high CCA-IMT (>0.90 mm) or presented plaques at echography.

During the 30-day post-operative period, 18 patients died (mortality rate =2.9%). The mean carotid IMT was at 0.79±0.11 mm in the deceased group vs. 0.74±0.12 mm in the alive group (P=0.11). The comparison of different variables between the two groups are displayed in Table 2. An elevated level of CCA-IMT as defined above was not a significant predictive factor between both groups. In the multivariate analysis, an ejection fraction <40%, a concomitant valvular surgery and the presence of a peripheral arterial disease were the significant independent risk factors of death in the 30-day post-operative period.

For the long term follow-up, the mean duration was at 41.8±16 months. No patient had been lost during the follow-up. During this period, following events (including those in the post-operative period) occurred: CV death, 48 patients

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
<th>Mean value or prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.8±9.2 years</td>
</tr>
<tr>
<td>Male sex</td>
<td>500 (82.1%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>189 (31.1%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>359 (59.2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>286 (47.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>157 (25.9%)</td>
</tr>
<tr>
<td>Body mass index (BMI) &gt; 30 kg/m²</td>
<td>95 (15.8%)</td>
</tr>
<tr>
<td>Familial history of cardiovascular disease</td>
<td>307 (50.7%)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>50 (8.2%)</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>38 (6.2%)</td>
</tr>
<tr>
<td>Left main coronary artery stenosis</td>
<td>91 (14.9%)</td>
</tr>
<tr>
<td>(LMCA) &gt;50%</td>
<td>392 (64.3%)</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%</td>
<td>52 (8.5%)</td>
</tr>
<tr>
<td>Peripheral arterial disease (PAD)</td>
<td>88 (14.5%)</td>
</tr>
<tr>
<td>Renal failure (blood creatinine &gt;150 mg/L)</td>
<td>30 (4.9%)</td>
</tr>
</tbody>
</table>
(7.8%); ACS, 24 patients (3.9%); myocardial revascularization, 15 patients (2.4%); stroke or TIA, 36 patients (5.9%); vascular surgery, 27 patients (4.4%). In overall, 121 patients (19.8%) presented at least one of the events included in the primary composite endpoint. The mean CCA-IMT was at 0.75 ± 0.13 mm in the group having experienced any CV event vs. 0.74 ± 0.13 mm for the remaining group (P = 0.36).

Fig. 1 represents the occurrence of the primary end-point in both groups according to their carotid IMT value (< 0.9 mm or presence of plaques). The difference between the actuarial survival curves is significant (P < 0.009).

We secondarily modified the threshold of definition of high mean CCA-IMT up to 1.0 mm as well as we changed the mode of CCA-IMT measurement by replacing the mean value of the six measurements by the maximal one. All of these modifications led to similar results.

4. Discussion

Despite different technical aspects reported in the literature [17], the IMT, especially of the carotid arteries, is presently considered as a marker of the cardiovascular risk. In populations without known cardiovascular diseases, a high carotid-IMT is associated with an elevated risk level risk of further CV events [3,7,11]. According to the AHA prevention conference [18], carotid-IMT, as other vascular markers, would be of great interest in primary prevention for risk stratification in subjects at an intermediate level of risk according their CV risk factors.

Studies on the value of carotid-IMT in patients with CAD are scarce. The carotid-IMT is well correlated with the angiographic presence and extent of CAD [19,20]. Regarding to the prognostic aspect, Fathi et al. [13] failed to demonstrate a significant predictive value of CCA-IMT during the follow-up of a subgroup of 150 patients with a history of CAD. Conversely, in the Angina Prognosis Study in Stockholm [12], carotid IMT and plaques were correlated with the risk of subsequent cardiac events in 558 patients with stable angina pectoris. However, this relationship failed to predict cardiovascular events after adjustment with age and cardiovascular risk factors, whereas the presence of plaques tended to remain predictive (P = 0.056). Papamichael et al. [14] followed 165 consecutive patients referred for elective coronary angiography during 14.5 months. In the univariate analysis, CCA-IMT was predictive for coronary revascularization procedures, but not for fatal or non-fatal coronary events.
To our knowledge, two studies assessed the interest of CCA-IMT measurement for the risk stratification after coronary revascularization. In a consecutive series of 113 patients having a PTCA [16], a CCA-IMT > 0.7 mm was a significant marker of cardiac events during a short follow-up of 10.2 ± 4 months. In the multivariate analysis, this marker did not remain independently predictive. In an ancillary study of the Cholesterol Lowering Atherosclerosis Study, Hodis et al. [15] studied 146 men who had previously had CABG during an average of 8.8 years. Patients had a CCA-IMT measurement every 6 months during the first 2 years. The baseline CCA-IMT was not different between those with and without any coronary event during the follow-up period. Conversely, the CCA-IMT change rate during the first 2 years was a significant predictive marker. Consequently, the absolute value of CCA-IMT at the end of the first 2 years was also a significant marker of subsequent coronary events. We did not sequentially study our patients. In our study, the mean value of CCA-IMT was also similar in both groups with or without cardiovascular events. However, by selecting a high level threshold and considering the presence of atherosclerotic plaques in the terminal CCA segment, we have been able to evidence CCA-IMT as a predictive marker of CV events in a less than 3 years period. Nevertheless, other clinical factors (age, arrhythmia, PAD and concomitant valvular surgery) presented stronger predictive value for this risk stratification, and the addition of CCA-IMT in the predictive model did not add any significant incremental value. In the Hodis et al. study [15], the prognostic value of CCA-IMT was not confronted to other clinical factors generally assessed in surgical series.

Hence, conversely to other studies in patients with coronary revascularization, the major interest of this study is to assess the predictive value of CCA-IMT, not only in an univariate analysis but also in a multivariate analysis, where other well-evidenced prognostic markers were included. In the univariate analysis, our findings on other significant factors (i.e. PAD or concomitant valvular surgery) for short-term and long-term prognosis are in line with findings issued from other series, and their persistence in the multivariate model highlight their superior predictive value to those of CCA-IMT.

The relatively short duration of the follow-up period can be considered as one limitation of this study. However, in that period, about 24% of patients had experienced a CV event. Hence, we consider the rate of events elevated enough to assess the predictive value CCA-IMT. Even though CCA-IMT would be a statistically significant independent predictor of CV events in a larger cohort and/or longer follow-up period, its additive informative prognostic value would be weak and then its usefulness in the daily management of those patients would be limited. Another drawback is the lack of information on the patients drug therapy, which could affect the outcome. However, with the aim of determination of pre- and per-operative predictive factors, this information would not affect our analysis.

5. Conclusion

According to our findings in this prospective study, a pre-operative measurement of CCA-IMT cannot be used for the surgical risk stratification. For the long-term post-operative period, CCA-IMT can be considered as a marker of further cardiovascular events, but its interest compared to the simple assessment of other predictive markers is of poor clinical relevance.

References


