Does a Visible Retinal Embolus Increase the Likelihood of Hemodynamically Significant Carotid Artery Stenosis in Patients With Acute Retinal Arterial Occlusion?

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Objective: To determine the value of visible retinal emboli as a diagnostic “test” for the detection of hemodynamically significant carotid artery stenosis in the setting of acute retinal artery occlusion.

Methods: A cross-sectional diagnostic accuracy study was performed in a tertiary North American center, with the results of the dichotomous diagnostic test (the presence or absence of visible retinal emboli) being placed against the dichotomous outcome of the presence or absence of hemodynamically significant carotid artery stenosis (defined as $\geq 60\%$, or $<60\%$, carotid artery stenosis on either side).

Results: Forty-eight (18.7%) of our 256 patients had hemodynamically significant carotid artery stenosis. The sensitivity and specificity of retinal emboli for the detection of hemodynamically significant carotid artery stenosis were 39% and 68%, respectively. The presence of a visible retinal embolus generated a likelihood ratio of 1.24 (95% confidence interval, 0.84-1.86). This value corresponds to a patient with a pretest probability of 50% having a posttest probability of 55.3%. The absence of a visible retinal embolus generated a likelihood ratio of 0.88 (95% confidence interval, 0.68-1.15).

Conclusions: The presence of a visible retinal embolus is a poor diagnostic test for the detection of hemodynamically significant carotid artery stenosis in the setting of acute retinal artery occlusion. Accordingly, the presence of an embolus should not influence the decision to perform carotid Doppler ultrasonography in patients with acute retinal arterial occlusion.


Acute retinal artery occlusion typically causes profound and irreversible visual loss. This entity is often classified clinically by the presence or absence of visible retinal emboli, with visible retinal emboli being seen in 25% to 40% of cases of acute retinal arterial obstruction. Patients with acute retinal artery occlusion who have visible emboli have a higher overall mortality rate when compared with their non-embolic cohort. Given this fact, in conjunction with the fact that visible retinal emboli are often seen in 25% to 40% of cases of acute retinal arterial obstruction, patients with acute retinal artery occlusion who have visible emboli have a higher overall mortality rate when compared with their non-embolic cohort. 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STUDY DESIGN

Our study was designed as a cross-sectional diagnostic study to determine the accuracy of visible retinal emboli (a physical finding) for the likelihood of HSCAS in the setting of acute retinal artery occlusion. The study was performed through the Retina Vascular Unit of Wills Eye Hospital, Philadelphia, Pa. This center was chosen for 2 principal reasons. The first was that our protocol was written to test the accuracy of visible retinal emboli in a population of patients suffering from acute retinal arterial occlusion, a disorder that is exceedingly rare. Wills Eye Hospital was one of few centers that would have a large enough series to perform the study. The second reason for performing the study specifically at the Retina Vascular Unit of Wills Eye Hospital was that carotid Doppler ultrasonography is performed on all patients with acute retinal artery occlusion, independent of embolic status. This fact is important since it allows for an unbiased calculation of the sensitivity, specificity, and likelihood ratios.

STUDY POPULATION

Our study population was defined as all patients with acute retinal artery occlusion from January 1, 1991, to December 31, 1996. These patients were identified by searching the patient log books of the Vascular Imaging Department. During this period, 303 patients came to the Retina Vascular Unit of Wills Eye Hospital with acute retinal artery occlusion.

Patients were included in our study if they met the following inclusion criteria: (1) acute retinal artery occlusion (central or branch) based on clinical examination findings (documented confluent retinal cloudy swelling) and (2) unequivocal documentation regarding embolic status (noting as to either the presence or absence of visible retinal emboli, or photographic evidence of emboli). Patients were excluded for any of the following criteria: (1) absence of carotid Doppler ultrasonographic documentation, (2) a poor-quality carotid Doppler ultrasonographic study, or (3) previous endarterectomy. A total of 256 patients were included in the study.

DATA COLLECTION

Patients were classified as having an “embolic” occlusion if there was evidence of embolic material on either the clinical examination or the clinical photographs. Emboli were classified as present or absent rather than qualitatively. This decision was made because our observer variability studies have demonstrated that the presence of retinal emboli is a reproducible finding and, while observers can agree on the presence or absence of visible retinal emboli, they cannot agree on their qualitative assessment.11,12 The patients’ clinical charts were also searched for demographic data regarding sex and age, as well as history of carotid endarterectomy. The patients’ ultrasonographic files were searched for the presence or absence of HSCAS. The ultrasonographic results were classified in a dichotomous fashion as being either at least 60% or less than 60% carotid stenosis on either side. The dichotomous classification of carotid artery stenosis is associated with high degree of reproducibility (κ = 0.73 to 0.97).13 The decision to classify carotid artery stenosis as at least 60% or less than 60% was made because carotid endarterectomy has been demonstrated to be of benefit when performed in patients with 60% or greater stenosis.14

All data were abstracted by masked observers (ophthalmology residents or retinal fellows) onto precoded forms. To ensure masking, the study variables were encoded on separate sheets (page 1 contained a sample patient’s clinical data, including embolic status, and page 2 was solely dedicated to our outcome variable of HSCAS).

DATA ANALYSIS

The traditional indexes of a diagnostic test’s accuracy, including sensitivity, specificity, predictive values, and likelihood ratios, were calculated in the usual fashion15 (Table 1). In addition to an overall calculation of the likelihood ratio, the likelihood ratios were calculated among various strata to ensure that other variables (such as sex or the level of arterial obstruction) were not acting as possible confounders.

Because a diagnostic study of visible retinal emboli for the detection of HSCAS had not been previously attempted, an initial feasibility pilot series of patients was analyzed to determine estimates of sensitivity and specificity for sample size calculations. The results of our initial feasibility pilot series showed that the sensitivity and specificity of visible retinal emboli were 46% and 69%, respectively.16 The prevalence of HSCAS in that sample approximated 20%.16

A positive likelihood ratio of 1 would indicate that the odds of a positive test result (ie, emboli) in patients with HSCAS are the same as the odds of a positive test result in patients without HSCAS. Our study was designed to detect a positive likelihood ratio of 4. This value for the likelihood ratio was chosen because it was deemed clinically significant, as it is the value where a patient with a pretest probability of 50% (50:50 chance) would have an 80% probability of HSCAS, given the presence of a retinal embolus. Given these facts, a sample of 42 patients was necessary to detect a positive likelihood ratio of 4 (assuming a prevalence of HSCAS of 20%, an α of 0.05, and a β of 0.2). Ninety-five percent confidence intervals (CIs) were calculated around our likelihood ratios to assess their statistical significance.17

RESULTS

Three hundred three consecutive patients with unilateral acute retinal artery occlusion came to the Wills Eye Hospital Retina Vascular Unit during the designated study period. The mean age of our patient population was 68.3 years, with a range of 24 to 90 years. Two hundred twenty-
eight patients (75.2%) had evidence of central retinal arterial occlusion, and the remaining 75 (24.8%) had branch retinal arterial occlusions. Our patient population consisted of 175 men (57.8%) and 128 women (42.2%).

Of the 303 patients, 47 were deemed ineligible for calculation of accuracy measures; 6 had no documentation of carotid Doppler ultrasonography, 12 had poor-quality ultrasonograms, 3 had a history of previous carotid endarterectomy surgery, and 26 had equivocal embolic documentation. Thus, of the 303 patients with acute retinal arterial occlusion, 256 (84.5%) were eligible for our study.

Our overall results are summarized in Table 2. The prevalence of HSCAS in the setting of acute retinal artery occlusion was 18.8% (48/256). Of the 48 patients who had evidence of 60% or greater carotid artery stenosis, 19 had evidence of visible retinal emboli. Thus, visible retinal emboli had a sensitivity of 39.6% (19/48) for the detection of HSCAS. Two-hundred eight patients had less than 60% carotid artery stenosis measured by carotid Doppler ultrasonography. Of these patients, 142 had no evidence of visible retinal emboli. Thus, the specificity of visible retinal emboli for the likelihood of HSCAS was 68.3% (142/208). Nineteen of our 85 embolic patients had evidence of at least 60% carotid artery stenosis. Thus, the positive predictive value of a visible retinal embolus was 22.4% (19/85). One hundred forty-two of our nonembolic patients had less than 60% carotid artery stenosis. Accordingly, the predictive value of the absence of visible retinal emboli (negative predictive value) was 83.0% (142/171).

The accuracy measures of visible retinal emboli for the prediction of HSCAS are summarized in Table 3.

Overall, the presence of a visible retinal embolus generated a likelihood ratio (positive likelihood ratio) of 1.24 (95% CI, 0.84-1.86). The likelihood ratio given the absence of a visible retinal embolus (negative likelihood ratio) was 0.88 (95% CI, 0.70-1.15). The diagnostic test accuracy measures by subgroups stratified by sex and level of arterial occlusion are also summarized in Table 3.

**Table 2. Carotid Doppler Ultrasonographic Results of All Study Patients, Given Embolic Status**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>&lt;60% Stenosis</th>
<th>&gt;60% Stenosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emboli</td>
<td>19</td>
<td>66</td>
<td>85</td>
</tr>
<tr>
<td>No embolus</td>
<td>29</td>
<td>142</td>
<td>171</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>208</td>
<td>256</td>
</tr>
</tbody>
</table>

**Table 3. Calculation of Various Accuracy Measures Regarding Diagnostic Tests**

<table>
<thead>
<tr>
<th>Disease Present</th>
<th>Disease Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test</td>
<td>a (true positives)</td>
<td>b (false positives)</td>
</tr>
<tr>
<td>Negative test</td>
<td>c (false negatives)</td>
<td>d (true positives)</td>
</tr>
<tr>
<td>Total</td>
<td>a + c</td>
<td>b + d</td>
</tr>
</tbody>
</table>

*Sensitivity (proportion of patients with the disease who test positive) = a/(a + c). Specificity (proportion of patients without the disease who test negative) = d/(b + d). Positive predictive value (proportion of patients who test positive who actually have the disease) = a/(a + b). Negative predictive value (proportion of patients who test negative who do not have the disease) = d/(c + d). Positive likelihood ratio (odds that a positive test result would be expected in a patient with the target disorder, as compared with one without the disorder)\(^2\) = sensitivity/(1 – specificity). Negative likelihood ratio (odds that a negative test result would be expected in a patient with the target disorder, as compared with one without the disorder)\(^2\) = (1 – sensitivity)/specificity.

**COMMENT**

Acute retinal artery occlusion is known to be associated with carotid artery stenosis.\(^1\)\(^3\) However, previous studies\(^1\)\(^3\)\(^8\) regarding the association of this entity with carotid artery stenosis were based on small numbers and frequently did not consider carotid stenosis in terms of hemodynamic significance. Given that carotid endarterectomy has been proved to be beneficial for patients with HSCAS,\(^14\)\(^19\)\(^20\) we conducted our study to consider the prevalence of HSCAS.

Our data show that the prevalence of HSCAS in the setting of acute retinal arterial occlusion was 18.8%. Previous studies have reported that the prevalence for carotid atherosclerotic disease is in the range of 11% to 43% in the setting of acute retinal artery occlusion.\(^1\)\(^15\) Unfortunately, these previous reports were performed before the benefit of endarterectomy had been clearly demonstrated. Accordingly, many of these studies considered carotid atherosclerotic disease in terms of presence or absence, and not in terms of hemodynamic significance. It should also be noted that with 303 patients, our study is the largest to be performed involving the patient population of acute retinal artery occlusion.

In a classic diagnostic accuracy study, the results of a diagnostic test are analyzed with respect to the “truth.”\(^10\) Our study was designed to test the accuracy of our diagnostic “test” (presence or absence of visible retinal emboli) for the detection of our dichotomous truth: HSCAS.

Our results show that the presence of a visible retinal embolus is not a sensitive diagnostic test for the detection of HSCAS (sensitivity, 39.6%) in the setting of acute retinal artery occlusion. Therefore, if one’s practice were to order carotid Doppler ultrasonography only in the setting of a visible retinal embolus, 60.4% of hemodynamically significant lesions would be missed. Furthermore, the presence of a visible retinal embolus is not a physical finding that can be considered pathognomonic of HSCAS, as its predictive value is very low (positive predictive value, 22.4%). Thus, its presence cannot be used to rule in the presence of HSCAS. Furthermore, given the low sensitivity of a visible retinal embolus, its absence cannot be used to rule out HSCAS.

The likelihood ratio, given the presence of a visible retinal embolus, is 1.24. This means that patients who had HSCAS were only marginally more likely to have an embolus than those without HSCAS. This value for the likelihood ratio was not statistically significant, as our 95% CI includes 1 (positive likelihood ratio, 1.24; 95% CI, 0.84-1.86). Our result is also not a clinically relevant value, as our study was designed to detect a positive likelihood ratio of 4.

Our results show that the value for the likelihood ratio obtained in the absence of an embolus (negative like-
The likelihood ratio (95% CI) was also not statistically significant (negative likelihood ratio, 0.88; 95% CI, 0.67-1.15). This value was also not clinically relevant, as a negative likelihood ratio of 0.25 was deemed clinically significant.

To consider the clinical relevance of our likelihood ratios, let us consider a hypothetical patient with a pretest probability of HSCAS of 25%. Let us assume that a visible retinal embolus is present. This patient would have a posttest probability of 29.2%. (Information on calculating the posttest probability is available from the authors.) Thus, the presence of a visible retinal embolus increased the estimate of probability of HSCAS by only 4.2%. In the absence of a visible retinal embolus, this patient would have a posttest probability of 22.7%. (Information on calculating the posttest probability is available from the authors.) Thus, the absence of a visible retinal embolus decreases the estimate of the probability of HSCAS by only 2.3%. Overall, our diagnostic test has the ability to alter the estimate of probability of disease by a mere 6.5% (when applied to a patient with a 25:75 chance of having HSCAS). This is a poor diagnostic test. The posttest probabilities of other hypothetical patients are tabulated in Table 4.

The likelihood ratios obtained by the presence of visible retinal emboli were not clinically relevant or statistically significant when stratified for sex and level of occlusion. However, in 2 strata (branch retinal occlusion and female patients) it is possible that a clinically relevant likelihood ratio may have been missed because of small numbers in each subgroup.

As with any study that is performed on a historical database, there is potential for misclassification of variables. It is unlikely that the various demographic data were misclassified, as the patients’ sex and age were obtained from the typed hospital admission sheets originating from patient records. One of the primary limitations of this study is the potential for misclassification of our diagnostic test. Specifically, it is possible that an acute retinal artery occlusion may have been embolic, but by the time the patient was examined, the embolus may have disintegrated. This situation may arise because the retinal arterial supply is a dynamic biological system. Although misclassification is a possibility, the type of misclassification would be differential, as patients without emboli would not have been misclassified as having emboli. Given that differential misclassification results in a statistical result that is biased away from the null value, the risk for misclassification was likely minimal, as our likelihood ratios approximated 1. Another limitation of our study is that observer agreement of the dichotomous classification of carotid artery stenosis was not examined. However, recent studies have demonstrated that the dichotomous classification of carotid artery stenosis is both highly reproducible and very accurate.

Visible retinal emboli are a poor diagnostic test for the detection of HSCAS in the setting of acute retinal arterial occlusion. Given that the prevalence of HSCAS is close to 20%, all patients with acute retinal artery occlusion, including those without visible retinal emboli, should undergo carotid Doppler ultrasonography to rule out HSCAS.

Accepted for publication August 11, 1998.

This work was supported in part by the Vitreoretinal Research and Educational Fund, Philadelphia, Pa, the Patience Research Foundation, Kingston, Ontario, and the E. A. Baker Foundation, Toronto, Ontario.

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REFERENCES