Is Visible Infarction on Computed Tomography Associated With an Adverse Prognosis in Acute Ischemic Stroke?

To the Editor:

In the article by Wardlaw et al in the July issue of Stroke,1 the outcome of stroke patients with an evident lesion on CT scan was compared with the outcome of stroke patients with no evident lesion. The result was that the prognosis for a patient with a “clinical stroke” evident on CT scan also was worse than the prognosis for a patient showing no evidence on CT scan of the lesion causing the clinical stroke.

However, obvious, it may due to a bias. How severe were the patients without the CT lesion? How were the various times of their CT scans distributed? Was it in a manner similar to that shown in the article’s Figure 2, for patients with CT lesions? In fact, patients with total anterior circulation infarcts (TACI) are more frequent (80%–95%) in the group with a positive CT, and vice-versa, lacunar infarcts (LACI) are more frequent in the group without positive CT scan (45%–60%); ie, the results may be due just to this unbalance. In fact, the sentence, “Patients who had a CT scan within a week of the stroke” after all other possible confounding factors had been accounted for including time from symptom onset to CT, clinical stroke syndrome (TACI, LACI, PACI, POCI), severity of the stroke, and so on. We wished to avoid confounding due to problems such as the fact that patients with more severe strokes may reach the hospital more quickly and be scanned more quickly than those with milder strokes, as eluded to by Dr Lenzi in his letter. To that end, we developed a logistic regression model, detailed in the methods and in the tables and appendix, to take account of all these factors. This, therefore, as far as one possibly can, avoids the problem of bias and confounding so that when all these factors are taken into consideration, the bottom line is that a patient with a particular syndrome scanned at a particular time after their stroke with a particular severity of stroke, and so on, has a slightly greater risk of poor functional outcome if the scan shows a recent infarct corresponding with their symptoms than does an identical patient whose CT scan does not show a recent relevant infarct. It is well known that patients with a TACI are much more likely to have a visible infarct on their CT scan than those with a LACI, and so one has to take the stroke syndrome, along with everything else, into consideration to avoid bias.

We obviously had to exclude from the analysis any patients who had not had a CT scan, whatever the reason (some of them had MR instead, some of them died before the scan could be done, some of them were moribund on admission), but we were concerned to see whether exclusion of those patients (and there was nothing else we could do with them) would introduce significant bias to the patient group. The group not CT scanned on average were more likely to have died early on, because they were either moribund on admission or died before the scan was done, which two groups made up the majority. However, apart from acknowledging the slight difference in this patient population, there is not much else we can do about them. Dr Lenzi quite rightly points out a typographical error on page 1317 that should be 19%, not 15%, of those who did not have a CT scan died within 14 days; however this difference of 4% is not statistically or clinically significant.

Finally, the functional outcome for TACI and PACI patients in our cohort was very similar to that described in previous cohorts and is, as we all know, a clear indication of what a devastating condition stroke is and clear justification for urgently finding an effective treatment. We don’t see how anybody could possibly disagree with that, but it was really not anything to do with the content of our paper.

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Response

Our study set out to answer the question “Is visible infarction on CT associated with an adverse prognosis in acute ischemic stroke?” after all other possible confounding factors had been accounted for including time from symptom onset to CT, clinical stroke syndrome (TACI, LACI, PACI, POCI), severity of the stroke, and so on. We wished to avoid confounding due to problems such as the fact that patients with more severe strokes may reach the hospital more quickly and be scanned more quickly than those with milder strokes, as eluded to by Dr Lenzi in his letter. To that end, we developed a logistic regression model, detailed in the methods and in the tables and appendix, to take account of all these factors. This, therefore, as far as one possibly can, avoids the problem of bias and confounding so that when all these factors are taken into consideration, the bottom line is that a patient with a particular syndrome scanned at a particular time after their stroke with a particular severity of stroke, and so on, has a slightly greater risk of poor functional outcome if the scan shows a recent infarct corresponding with their symptoms than does an identical patient whose CT scan does not show a recent relevant infarct. It is well known that patients with a TACI are much more likely to have a visible infarct on their CT scan than those with a LACI, and so one has to take the stroke syndrome, along with everything else, into consideration to avoid bias.

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Finally, the functional outcome for TACI and PACI patients in our cohort was very similar to that described in previous cohorts and is, as we all know, a clear indication of what a devastating condition stroke is and clear justification for urgently finding an effective treatment. We don’t see how anybody could possibly disagree with that, but it was really not anything to do with the content of our paper.

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Electrocardiographic Diagnosis of Patent Foramen Ovale Associated With Ischemic Stroke

To the Editor:

The report of Ay et al1 showed the value of an electrocardiographic finding called “crochetage” to identify stroke patients with patent foramen ovale (PFO). In this series of 60 patients with cryptogenic stroke, the sensitivity and specificity of the crochetage pattern for diagnosis of PFO were 36% and 91%, respectively. Nevertheless, as the authors admitted, this study was limited by the very restrictive selection criteria and the low sensitivity of the color transthoracic echocardiography (TTE) used to detect PFO in more than 20% of patients. Additionally, the investigators were not blinded to the crochetage pattern when they selected the study population from those patients with cryptogenic stroke.

Our purpose was to duplicate their results in a nonselected population of patients in whom PFO was evaluated prospectively with a more sensitive technique. Moreover, we analyzed the relationship between the degree of the right-to-left shunt (RLS) and the presence of crochetage.

Between February 1996 and May 1997, we performed a contrast transthoracic Doppler (TCD) study in 208 patients admitted consecutively within the first 48 hours of an acute ischemic stroke or transient ischemic attack. The procedure to diagnose and quantify PFO as well as the main results have been published recently. Briefly, patients were divided into three different groups based on the number of microbubbles detected in MCA in any single frame after intravenous air-saline contrast injection during Valsalva maneuver: “normal” TCD study (if 0 signals were detected), “small” RLS (<10 signals) and “large” degree of shunt (>10 signals). In this last group, “shower” (>50 microbubbles) and “curtain” (uncountable microbubbles) patterns were considered. Patients with cryptogenic stroke were classified according to predefined criteria that did not include ECG findings other than the absence of flutter or atrial fibrillation.

We studied all the 68 patients with cardiac RLS and 68 controls randomly selected from the 135 patients without RLS, matched by sex and age. Mean age was 64.40±13.4 years for the case patients and 64.45±12.19 years for the control subjects. There were 48 men and 20 women in both the case and control groups. In all patients we evaluated the ECG performed at admission. Two different physicians blinded to diagnosis independently reviewed the ECG of every patient looking for the crochetage pattern in one or more limb leads (II, III or aVF), defined as a notch in R wave with a rapid up-and-down in the ascending branch or near the zenith which produce a M-shaped or bifid form and always involving the initial 80 ms of the QRS complex.

The crochetage pattern was identified in 7 patients by the first physician and in 12 patients by the second (κ=0.718). It is remarkable that no patient classified as having crochetage by the first examiner was classified in the second in a different way. After interobserver agreement still blind to the study groups, crochetage was noted in 10 patients, 2 with cardiac RLS and 8 without (P=0.049). When patients were classified according to the presence of a massive RLS (ie, cases with shower or curtain pattern in TCD), crochetage was not present in patients with massive RLS and was detected in 10 without a high degree of shunting (P=0.16) (see the Table). We obtained similar results in the subgroup of 44 patients with cryptogenic stroke (crochetage was not present in patients with RLS; P=0.027). These results indicate not only that crochetage is not related to the presence of PFO but suggest a trend to a negative relationship.

In our series, crochetage could be easily recognized in ECG with small interobserver differences; however, it was not related to RLS nor to its magnitude. Therefore, in our opinion, crochetage is not a useful sign to identify stroke patients with PFO. Several reasons may be argued to explain the opposing results in the article of Ay et al and in our study: first, the conservative selection scheme in the former could lead to a selection bias; second, our study was more sensitive in detecting PFO and used the same diagnostic tool in all the patients, in contrast to the investigation of Ay et al; third, the time between stroke onset and ECG, which was more prolonged in the first study, could modify the ECG tracing. In fact, we can speculate that in some cases crochetage might be due to hemodynamic disturbances or cardiac conduction defects seen particularly in the early acute phase of stroke. We can ruled out a misdiagnosis of patients with PFO because we proved in our series the accuracy of contrast TCD for the diagnosis of PFO in comparison with transesophageal echocardiography.

In conclusion, the crochetage pattern is not an accurate sign for the diagnosis of cardiac RLS in the acute clinical setting. We think contrast TCD is the ideal method to perform a simple and safe bedside diagnosis of PFO in patients with acute stroke.

### Table 1. Crochetage Pattern by the Magnitude of the RLS in Contrast TCD

<table>
<thead>
<tr>
<th>Crochetage Pattern in ECG at Admission</th>
<th>Yes (n=10)</th>
<th>No (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RLS</td>
<td>8 (80)</td>
<td>60 (47.6)</td>
</tr>
<tr>
<td>&lt;10 signals</td>
<td>2 (20)</td>
<td>27 (21.4)</td>
</tr>
<tr>
<td>&gt;10 signals</td>
<td>0</td>
<td>17 (13.5)</td>
</tr>
<tr>
<td>Shower</td>
<td>0</td>
<td>13 (10.3)</td>
</tr>
<tr>
<td>Curtain</td>
<td>0</td>
<td>9 (7.1)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

“right-to-left shunting” on transcranial Doppler ultrasonography, clouding the issue regarding the underlying pathology. Eventually, we learn that transesophageal echocardiography was performed in 44 patients with cryptogenic stroke, of whom only 22 had patent foramen ovale.

Despite the methodological discrepancies between the study of Tembl et al and our study, it is still difficult to explain the differences between the studies in observed crochetage. We showed a 36% prevalence rate of crochetage in our patients with patent foramen ovale. Heller et al\(^2\) reported crochetage in 66% to 97% of 532 patients with various types of ostium secundum atrial septal defects. The high variability in the prevalence necessitates a clear reassessment of the definition criteria for crochetage. We have frequently observed hump-like, subtle excursions on the ascending limb of the R wave; although the pattern on the R wave still appeared M-shaped, the intersections between the arms of the M had a rounded appearance. In our patients, this pattern was not persistent but changed from one R wave to another. The interexaminer concordance rate for these subtle excursions was very low. We did not count them as crochetage. On the other hand, M-shaped patterns with spiky arms were invariably observed on all R waves in a given ECG, with excellent interexaminer concordance. We would also like to point that when the arms of M-shaped patterns are very close to each other, a crochetage may easily be missed, especially if it is situated at the top of R wave; unless special attention is given, the two arms of the M may be perceived as a single upstroke.

Both the sensitivity and positive predictive value increased in our study when patients were excluded who had undergone low-yield echocardiography (color transesophageal echocardiography, used in 16% of all patients, 1 in the patent foramen ovale and 9 in the control groups).

It is unlikely that crochetage is due to the effect of stroke as suggested by Tembl et al, because both the control and patent foramen ovale groups comprised patients with stroke.

The possible relationship between crochetage and degree of right-to-left shunt awaits study in a larger prospective series, in which there are careful definitions of the ECG patterns, the underlying cardiac anatomy, and the degree of interatrial shunting.

Finally, we would like to state that the ECG finding of crochetage does not replace transcranial Doppler ultrasonography or echocardiography for diagnosis of patent foramen ovale. Management of patients with patent foramen ovale is a multistep procedure. First, an initial suspicion may be raised in the emergency setting; ECG can be helpful at this step. Second, demonstration of cardiac right-to-left shunting is necessary to determine the stroke mechanism and to guide acute treatment; contrast transcranial Doppler ultrasonography has proved its value at this level. Third, the morphological characteristics underlying the intracardiac right-to-left shunt (eg, the type of defect, size of the defect, associated atrial septal aneurysm) should be determined before long-term decisions are made regarding platelet antiaggregation, anticoagulation, or possible surgery; a transesophageal echocardiography study remains essential at this step.

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Timing of Carotid Endarterectomy After Stroke

To the Editor:

We read the review article\(^1\) on the timing of carotid endarterectomy after stroke with interest. We would like to emphasize several observations from the NASCET database. Although the article\(^2\) on timing of endarterectomy may influence surgeons to perform early endarterectomy, it is important to recognize that all patients in the early-surgery group were operated on at least 3 days (misprinted as 2 days in the review article) after the initial stroke, with a median interval time of 16 days. Furthermore, the study did not enroll any patient with disabling stroke. In regard to delaying surgery in patients with high-grade stenosis, this practice may result in an increase in stroke recurrence (4.9% and 1.9% for nondisabling and disabling, respectively) during the first 30 days after the initial stroke, which may further postpone surgery. Thus, the combined risk associated with delaying surgery may be as high as 10.1% (4.9% recurrence in the first 30 days plus 5.2% delayed surgery perioperative risk) versus 4.8% perioperative risk related to the early endarterectomy. Given comparable perioperative complication rates between early (≤30 days) and delayed (>30 days) endarterectomy (4.8% versus 5.2%, respectively), the risk of recurrence during the first 30 days (4.9% in NASCET) adds a considerable risk and should be counted against delaying surgery. We suggest that future studies should compare the risk of early surgery with a combined estimate of risk during the waiting period and the perioperative risk of delayed surgery.

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Response

I thank Drs Gasecki and Eliasziw for their interest in my recent review.\(^1\) I look forward to their publication on this subject analyzing the data of the NASCET study for patients with 50% to 99% carotid stenosis. I agree that the risk of stroke recurrence while awaiting endarterectomy needs to be considered and factored into the delayed-surgery group. However, data from others\(^2\)-\(^5\) indicate a risk of recurrent stroke that ranges from 2% to 21%. Furthermore, patients whose carotid artery has become occluded are no longer candidates for endarterectomy.

In addition, while awaiting surgery it is likely, as suggested in this review,\(^1\) that patients with a fixed neurological deficit who are considered for carotid endarterectomy are not a homogeneous
group. This review stratified stroke patients on the basis of the presence or absence of computed tomographic hypodensity, brain shift, level of consciousness, and vascular territory of the infarct. These parameters, as well as others, may better define the risk of early carotid endarterectomy after recent stroke in patients with a fixed neurological deficit.

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Hemocephalus and Not Hydrocephalus as a Predictor of Poor Outcome From Supratentorial Intracerebral Hemorrhage

To the Editor:
I was interested to see the study by Diringer et al on supratentorial intracerebral hemorrhage, which indicated that the poor prognosis conferred by hydrocephalus had not been previously recognized. As a one-time staff member of the Washington University School of Medicine, I felt impelled to correct some pathological misconceptions.

Internal hydrocephalus implies increased ventricular volume associated with accumulation of cerebrospinal fluid. Preexisting hydrocephalus was not excluded. It is unfortunate that this was not a clinico-pathological study. The authors seemingly allude to acute hydrocephalus, since ventricular enlargement in their patients with supratentorial intracerebral hemorrhage correlated with intraventricular hemorrhage and complementary evidence of raised intracranial pressure due to a localized space-occupying effect. The more vigorous the hemorrhage into the ventricles, irrespective of source, the more likely it is that blood clot will form and obstruct the ventricular system, particularly with compression and displacement of the brain parenchyma and rapidly rising intracranial pressure. The more severe the bleeding the greater the tamponade effect, sometimes even with tearing of the ventricular wall. However, acute hydrocephalus, as a poor prognostic sign, is certainly not a novel finding in such patients. Intraventricular hemorrhage has long been recognized in pathology to be a terminal event accompanied by deep coma and high mortality as a consequence of the hemocephalus and tamponade effect. It is incorrect to regard the ventricular volumetric expansion as hydrocephalus.

The submission exemplifies a major problem in modern clinical medicine, whereby the importance of pathological detail in medical education and the relevance of autopsy confirmation have been significantly downgraded.

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Response
We thank Dr Stehbens for his thoughtful comments regarding our recent publication. In his letter he suggests that there were pathological misconceptions that might limit the interpretation of our study and points out that the term “hydrocephalus” implies ventricular enlargement with accumulation of CSF. We, however, applied a clinical definition that describes ventricular enlargement regardless of mechanism.

Preexisting hydrocephalus was not excluded in our study. While establishing the absence of preexisting hydrocephalus would have absolutely confirmed that our patients suffered from acute hydrocephalus, the natural history of intracerebral hemorrhage and the demands of the management of these patients make obtaining such information impossible and probably irrelevant.

In his letter, Dr Stehbens describes how intraventricular hemorrhage (hydrocephalus) leads to the development of hydrocephalus and how acute hydrocephalus is a well-known poor prognostic sign. The focus of our study, however, was hydrocephalus (clinically defined), not hydrocephalus. This is an important distinction, since 25% of our patients with hydrocephalus did not have intraventricular hemorrhage. Finally, while we agree that there has been decreased emphasis on autopsy confirmation in medical education, the purpose of our study was to define prognosis rather than pathology.

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Stroke. 1998;29:2665a-2666
doi: 10.1161/01.STR.29.12.2665.a
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/29/12/2665a

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