Early Recurrence of Cerebrovascular Events After Transient Ischaemic Attack

To the Editor:

We read with great interest the recent article by Lisabeth et al regarding the stroke risk after a transient ischemic attack (TIA). Their results are similar to those reported in the mid- and late-1990s and considerably lower than more recent studies reported in the UK and Canada. We run rapid access TIA clinics for the assessment and investigation of individuals referred by their general practitioner following a suspected cerebrovascular event that has not necessitated in-patient management. During a recent audit of this service we examined the rate of recurrent cerebrovascular events in new referrals over a 6-month period, to 2 hospitals in East Glasgow, Scotland. Information was obtained from the referral letter, clinic letters, health care practices, hospital records and investigating departments.

Of 372 new referrals to the clinics, 37 (10%) did not attend, 130 (35%) had a non-cerebrovascular diagnosis, and 205 (55%) were deemed to have suffered a probable or definite new TIA (121 [32.5%]) or minor stroke (84 [22.5%]). There were 19 documented recurrent cerebrovascular events in this group giving a crude recurrence rate of 9% (95% CI, 5 to 13%), of which 10 cases (5%; 95% CI, 2 to 8%) were known to have occurred within one week, and 15 (7%; 95% CI, 4 to 11%) within one month of the initial episode.

Of the patients who had an initial diagnosis of TIA there were 17 recurrent events (14%; 95% CI 8 to 20%), with 7 cases (6%; 95% CI 1 to 10%) occurring within one week, and 13 (11%; 95% CI 5 to 16%) within one month. Multivariate analysis identified current cigarette smoking as the only independent risk factor for a recurrent event.

Our findings are more similar to those of Coull et al and Johnston et al and raise the concern that very early recurrence is a significant problem that will continue to grow in tandem with an ageing population. Although, it is presently unclear whether secondary preventative measures can reduce these early recurrent events, future research should be directed toward identifying the medical and organizational strategies that would best identify and reduce the risk of such events.

M.A. Whitehead, MRCP
Department of Aging and Health
Stirling Royal Infirmary
Livilands, Stirling, Scotland, UK

J. McManus, MRCP
Falkirk and District Royal Infirmary
Falkirk, Scotland, UK

C. McAlpine, FRCP
Department of Medicine for the Elderly
Stobhill Hospital
Glasgow, Scotland, UK

P. Langhorne, PhD, FRCP
Division of Cardiovascular and Medical Sciences
University of Glasgow
Glasgow, Scotland, UK


Response:

We would like to thank Drs Whitehead, McManus, McAlpine, and Prof Langhorne for their interest in our paper. As their letter indicates, in our paper we found stroke risk after transient ischemic attack to be somewhat lower than recent studies on this topic. We feel it is critically important to examine findings from various studies using different methods and study populations to understand the risk of stroke after TIA. To this end, our findings provide estimates of risk from a prospective, population-based study of stroke and TIA in an ethnically diverse community using rigorous case ascertainment procedures to acquire all strokes and TIAS that present for medical attention.

Lynda D. Lisabeth, PhD
Lewis B. Morgenstern, MD
Stroke Program
University of Michigan Health System
Ann Arbor, Mich

CT Perfusion Imaging in Cerebral Ischemia

To the Editor:

We read with interest the Guidelines and Recommendations for Perfusion Imaging in Cerebral Ischemia by the Writing Group on Perfusion Imaging, from the Council on Cardiovascular Radiology of the American Heart Association. The authors have succeeded admirably in summarizing the important recent developments of perfusion imaging and their relevance to clinical investigations of cerebral ischemia. We have been involved in the development of the First-Pass Bolus Tracking Methodology of CT Perfusion for over a decade and would like to comment on a few issues raised by the authors concerning this particular methodology.

1. Radiation dose.

The Table is a comparison of the effective dose equivalent (Hₑ) of each of the three perfusion imaging methods discussed in the Guidelines that involve the use of ionizing radiation. The effective dose equivalents for the 2 computed tomography (CT) techniques are estimated using the methodology published by Huda et al based on the CT dose index values published for LightSpeed QXi scanners (General Electric Medical Systems). For CT scanners of other models or from other manufacturers, the values in the Table can be scaled proportionally according to the computed tomography dose index value of the scanner relative to the LightSpeed QXi scanner.
The Table shows that CT perfusion (CTP) imaging does not necessarily give a higher radiation dose to the subject than XeCT and SPECT perfusion imaging. In comparison, a screening head CT scan has an effective dose equivalent of 1.5 mSv. With the recent interest in using a saline chaser to shorten the duration of scans for each slice, the scan duration for CTP can be reduced to around 25 to 30 s resulting in an even lower dose of 1.8 to 2.2 mSv.


While xenon-enhanced computed tomography (XeCT) and single photon emission computed tomography (SPECT) can only measure cerebral blood flow (CBF), CTP can simultaneously measure CBF, cerebral blood volume (CBV) and mean transit time (MTT). Although the results need to be confirmed in a larger clinical trial, Wintermark et al. have shown that CBV and CBF together can provide a more complete assessment of cerebral ischemia than either XeCT or SPECT in that both the severity and duration of ischemia would be assessed.

3. Arterial input function (AIF).

The authors are correct in their conclusion that measurement of the arterial input function from proximal branches of the middle cerebral artery (MCA) or anterior cerebral artery (ACA) is affected by partial volume averaging (PVA). It is also true that this PVA effect is more prominent when a distal MCA, or ACA branches are used for the determination of the AIF when the slice of interest is higher than the usual one through the basal ganglia. However, methods are available for the correction of the PVA effect. We described a method in a prior publication, which requires an independent calibration of the scanner, and thus may not be convenient to use in clinical departments. A more convenient method is to reference the area under the AIF to that of the time-density curve of a venous sinus in one of the acquired CT slices. The assumption is that the venous sinus used is large relative to the limited spatial resolution of CT scanners (0.67 to 0.71 mm) for the PVA effect to be negligible. If that is the case, the ratio of the two areas should give the fraction by which the AIF has to be divided. A proper comparison of speed between MR and CT should include considerations of spatial resolution and signal-to-noise of the resultant images not just on the raw speed of image acquisition. As discussed earlier good spatial resolution is required for PVA correction of the AIF. If we compare the spatial resolution achieved with CTP with those of echoplanar MR, then the comparison may not be as favorable to CT. For instance, an echoplanar T2* weighted spin-echo imaging sequence can acquire a slab of 11 x 6 mm slices every 1.6 s at an in-plane resolution of 4.8 mm (phase encode [-y] direction) and 1.7 mm (read [x-] direction), whereas a CTP sequence can acquire a slab of 4 x 5 mm slices every 0.5 to 1.0 s at an in-plane resolution of 0.67 to 0.71 mm in both x and y directions. CTP can measure the time-density curve from a venous sinus unaffected by the PVA effect. This critical for the correction of the PVA effect on the AIF. Currently used MR echoplanar imaging sequences, because of its poorer spatial resolution, cannot implement the same correction method for the PVA effect on the AIF as CTP imaging can.

4. Mean transit time.

It is stated that the MTT measured by CTP is not “the transit time through the same volume in which the CBV is determined” instead it is the transit time between MCA and a venous sinus. In CTP imaging, the MTT map is determined by the deconvolution of the AIF and the tissue time-density curve corresponding to each pixel of the map. The deconvolution determines the impulse residue function for the tissue volume in each pixel and the transit time through that tissue volume is calculated as the ratio of the area to the height of the impulse residue function as prescribed by Meier and Zieler. It is important to note that the calculation of MTT in CTP does not involve a deconvolution between the AIF and the venous sinus time-density curve to determine the transit time between MCA and the venous sinus. The venous sinus time-density curve is used just for PVA correction as discussed above in point #3.


There is concern that CTP imaging may return erroneous CBF and CBV values when the blood–brain barrier becomes permeable following ischemia. We have extended the basic CTP tracer kinetics model to account for blood-tissue permeability to contrast agent. Furthermore, 2 of our prior publications have validated the extended CTP imaging method in the measurement of CBF in a brain tumor model as well as the measurement of tumor blood flow in a soft tissue tumor model against a gold standard—microspheres (class I data).

6. Imaging speed.

The characterization by the authors that echoplanar magnetic resonance (MR) is faster than CT is a simplification of a complicated issue. A proper comparison of speed between CT and MR should include considerations of spatial resolution and signal-to-noise of the resultant images not just on the raw speed of image acquisition. As discussed earlier good spatial resolution is required for PVA correction of the AIF. If we compare the spatial resolution achieved with CTP with those of echoplanar MR, then the comparison may not be as favorable to MR. For instance, an echoplanar T2* weighted spin-echo imaging sequence can acquire a slab of 11 x 6 mm slices every 1.6 s at an in-plane resolution of 4.8 mm (phase encode [-y] direction) and 1.7 mm (read [x-] direction), whereas a CTP sequence can acquire a slab of 4 x 5 mm slices every 0.5 to 1.0 s at an in-plane resolution of 0.67 to 0.71 mm in both x and y directions. CTP can measure the time-density curve from a venous sinus unaffected by the PVA effect. This critical for the correction of the PVA effect on the AIF. Currently used MR echoplanar imaging sequences, because of its poorer spatial resolution, cannot implement the same correction method for the PVA effect on the AIF as CTP imaging can.

Ting-Yim Lee, PhD
Imaging Program
Lawson Health Research Institute and Imaging Research Laboratories
Robarts Research Institute
London, Ontario, Canada

Vadim Belesky, MD
Clinical Neurosciences
London Health Sciences Centre
London, Ontario, Canada

Paul Kalapos, MD
Donald Lee, MD
Department of Radiology
London Health Sciences Centre
London, Ontario, Canada

Vladimir Hachinski, MD
Clinical Neurosciences
London Health Sciences Centre
London, Ontario, Canada

David Spence, MD
Clinical Neurosciences and Stroke Prevention and Atherosclerosis Research Centre
Robarts Research Institute
London, Ontario, Canada

Effective Dose Equivalent, mSv Axial Coverage, cm

<table>
<thead>
<tr>
<th>XeCT*</th>
<th>4.4–6.6</th>
<th>4–6</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT†</td>
<td>8.84</td>
<td>Whole head</td>
</tr>
<tr>
<td>CTP‡</td>
<td>3.3</td>
<td>2</td>
</tr>
</tbody>
</table>

*80 kVp, 200 mA, 2s per scan, 1 baseline scan plus 6 post-enhancement scans for each slice.
†Assume 740 MBq of 99m Tc-HMPAO injected.
‡80 kVp, 200 mA, 2s per scan, 1 baseline scan plus 6 post-enhancement scans for each slice.
Response:

Speaking for my colleagues in the Writing Group on Perfusion Imaging from the Council on Cardiovascular Radiology of the American Heart Association, I would like to make a few points in response to the excellent, informative letter of Dr. Lee and his colleagues.

1. In point 2, they state that the combination of computed tomography perfusion (CTP)-derived cerebral blood volume (CBV) and cerebral blood flow (CBF) can differentiate reversible from non-reversible ischemia. All neuroscientists would applaud if that statement were proven to be true. I would suggest the word, "might". Animal studies with comparative techniques acting as gold standards, and much larger controlled clinical studies will be necessary to ascertain the truth. "Reversibility" can be either spontaneous or through interventions such as the administration, intravenously or intraarterially, of a thrombolytic agent, among many possibilities. Such treatments can be either spontaneous or through interventions such as the administration, intravenously or intra-arterially, of a thrombolytic agent, among many possibilities. Such treatments may or may not be helpful in making difficult clinical decisions. As discussed in our article, there has been an extensive experience using CBF as determined with XeCT, a single quantified value, to predict not only the potential reversibility of the ischemic process, but also the propensity for edema formation and hemorrhage. SPECT has also demonstrated an ability to predict hemorrhage with thrombolytic treatment. Thus, we should insist on "efficacy" of a technique for clinical utilization, whether that is with one or more parameters, rather than on the number of variables that can be calculated.

2. In point 5, the authors cite their excellent work on calculating correction factors to account for a permeable blood-brain barrier in tumor models. However, a well-defined tumor is not the same as a heterogeneous region of ischemia/infarction. The use of CBV plus CBF is similar to the magnetic resonance (MR) paradigm of using diffusion and perfusion, with CBV paralleling diffusion, and CBF the perfusion parameter. Similarity problems regarding "reversibility" may confront CTP as they do with MR perfusion/diffusion imaging. Recent articles suggest that diffusion as measured with MR is not as simple as initially thought. Physiologically, a focus of ischemia is heterogeneous. Within this focus there is a mixture of diffusion values, dependent on a variety of factors, including local collateral flow. This collateral allows CBV to increase initially as an attempt to maintain tissue oxygenation, but then the average CBV value drops as this autoregulatory mechanism fails. While a low CBV value probably indicates that some infarction is present, how much? Is any of this process reversible? Is there a population of cells that can be rescued? Over what time period?

It is said that CBV might be a surrogate marker for "time since ischemia". Given the physiological discussion above, it is difficult to understand that statement. CBV depends on, to a greater degree, the status of the collateral circulation, not the time since the insult. It is a reflection of severity—the failure of an autoregulatory mechanism.

It is also said that CTP can provide a "more complete assessment" of ischemia than either XeCT or SPECT. By more complete, the authors mean the multiple calculated parameters. That may or may not be helpful in making difficult clinical decisions.

3. In point 6, mixing speed of image acquisition with other parameters such as spatial resolution makes for a very difficult comparison of perfusion techniques. Contrast resolution, with MR leading the other methodologies reviewed, could be added to the equation, too. The message we attempted to convey is that MR permits imaging of the whole brain, whereas current quantitative CT methodologies are limited to a relatively small field of view within the defined region of interest.

Richard E. Latchaw, MD
Department of Radiology, Section of Neuroradiology, University of California at Davis
Davis, California


Cellular Fibroblast and Matrix Metalloproteinase-9 in Patients With Stroke

To the Editor:
The article by Castellanos et al on the plasma cellular-fibronectin (c-Fn) and matrix metalloproteinase-9 (MMP-9) concentrations in patients with acute ischemic stroke needs some clarification.

In the Materials and Methods section it is stated that plasma MMP-9 levels were measured by a commercially available ELISA assay. The Amersham Biosciences, from which the assay was purchased, provides different types of assay for determination of MMP-9. One of them is for human MMP-9 and measures both free pro-MMP-9 and pro-MMP-9 complexed to TIMP-1. The other method, called MMP-9 activity assay, is used for determination of the active form of the compound.

It is not clear which form of MMP-9 was determined in the study. The MMP-9 human assay’s range of detection in plasma is 4 to 128 ng/mL, whereas the median values obtained in the study were within the range of 54 to 225 ng/mL. We therefore guess that the authors did not measure the active form of the enzyme because the assay range is much lower, 0.5 to 16 ng/mL.
This could have given different results as to the changes in proteolytic activity, in agreement with findings in a study by our group. In our study the total (pro-, active and complexed) concentrations of MMP-9 were significantly higher in peritoneal fluid of women with endometriosis (reproductive-age inflammation-associated disease of women) than of healthy controls. No differences between the 2 groups were found in the concentrations of the active form of the compound. We suggested it was due to the presence of a pro-MMP-9 form and possibly attenuation of the pro-MMP-9 activation processes in peritoneal fluid. Castellanos et al found that c-Fn was a more specific marker of high risk for cellular hemorrhage and thrombosis. We are in agreement with the authors that increased c-Fn synthesis could be an attempt to decrease endothelial destruction by MMPs. However, we doubt that this explains the positive correlation found between c-Fn and MMP-9. We believe this conclusion would be better founded if activity of the enzyme was measured with the appropriate method.

P. Laudanski, MD, PhD
Department of Pathophysiology of Pregnancy

J. Szamatowicz, MD, PhD
Department of Gynecology

H. Laudanska, MD, PhD
Department of Dermatology
Medical University of Białystok
Białystok, Poland


Response:

We thank Drs Laudanski, Szamatowicz, and Laudanska for their comments on our article.

In our study we determined both free pro-metalloproteinase-9 (MMP-9) and pro-MMP-9 complexed to TIMP-1 using the appropriate Amersham Biosciences ELISA assay kit and so Laudanski and colleagues are right that we have not independently analyzed the MMP-9 active form.

In Laudanski’s study into the pathogenesis of endometriosis they analyzed both the complexed and the active form of MMP-9 separately, obtaining different levels of the molecule, which allowed them to conclude that there was a disturbed equilibrium between MMP-9 and TIMP-1 in the peritoneal fluid of women with endometriosis. In our study we aimed to investigate whether high plasma levels of cellular-fibronectin (c-Fn) and MMP-9 were related to hemorrhagic transformation (HT) in patients with ischemic stroke who had received thrombolytic treatment. As we analyzed the active form together with the complexed MMP-9 levels, we are not able to determine whether a possible imbalance between MMP-9 and its inhibitor might be related to HT in our patients. However, it has recently been demonstrated that only the active MMP-9 form participates in the degradation of the components of the extracellular matrix in an experimental model of cerebral ischemia, and so we can hypothesize that the difference in the levels of MMP-9 between patients with and without HT are due to higher levels of the active form. As Laudanski et al suggest, further analysis of both molecules would give us a better understanding of the mechanisms participating in the development of bleeding after cerebral ischemia, and until such a study is performed we can only speculate as to how the c-Fn/MMP-9 positive correlation is to be explained.

Independently of what the precise mechanism may be, our findings demonstrate that high levels of both molecules predict subsequent bleeding in our stroke patients and so has the potential to be of great practical value.

Mar Castellanos, MD, PhD
Department of Neurology
Hospital Universitari Doctor Josep Trueta
Girona, Spain

José Castillo, MD, PhD
Hospital Clínico Universitario Santiago de Compostela
Santiago de Compostela, Spain

Antoni Dávalos, MD, PhD
Department of Neurology
Hospital Universitari Doctor Josep Trueta
Girona, Spain


Early Recurrence of Cerebrovascular Events After Transient Ischaemic Attack
M.A. Whitehead, J. McManus, C. McAlpine and P. Langhorne

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/36/1/1.1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/