Time Course of $AD_{Cw}$ Changes in Ischemic Stroke

To the Editor:

Our laboratory team was excited to learn of the observation that there is an early increase in apparent diffusion coefficient (ADC) at the edge of ischemic lesions during stroke.1 We have recently completed a study that actually predicts this result and provides a potential explanation.2 Using 1000-µm-thick hippocampal brain slices as a model of the ischemic penumbra and a series of radiotrace molecules, we observed an increase in the rate of extracellular diffusion under ischemic conditions. Even though the extracellular space (ECS) was modestly reduced in volume in these slices, the diffusion coefficient rose with all 4 tracers. We have interpreted our surprising results as indicating that ECS becomes less tortuous during mild-to-moderate ischemia. In the simplest model, this would be explained by postulating that there are large and small fluid channels in the ECS of brain with different rates of diffusion, and that during less severe ischemia, the smaller and more slowly diffusing channels close while the larger, more rapidly diffusing channels remain open. The result is a net increase in the rate of diffusion even though ECS volume declines. Naturally, there are other interpretations. However, based on these results, we have predicted that there should be a measurable increase in the ADC of brain regions exposed to flow rates of 20 to 30 mL/100 g per minute.

It is clear that ischemic injury is a complex and dynamic process. The meticulous measurements involved in this MRI study provide a valuable example of how that complexity can be made in model systems.

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Response

We thank Dr Newman for his gracious comments on our paper1 and for drawing our attention to the recent body of work by his team on the diffusion of radiotracers in ischemic brain slices.2 Their interpretation of an increased ADC resulting from the ECS being less tortuous is provided by comprehensive diffusion-compartment analysis. We believe their work on tracer kinetic analyses in conjunction with histology in thick slices provides important and relevant information for the assessment of ischemic tissue in humans, particularly the penumbral region that is potentially salvageable.

The signal in diffusion-weighted MRI (DW-MRI) is a weighted average of intracellular and extracellular protons (with 75% to 80% of the protons being intracellular). The ADC value of each of the individual compartments cannot be resolved in our MRI studies. Nevertheless, the sensitivity of the quantitative diffusion coefficient to ischemia offers an opportunity to resolve the heterogeneity and temporal evolution of the injury. Based on experimental animal models, an MR tissue signature model using ADC and T2 measures was developed to predict the histopathology of human stroke.3 Results of the study confirmed heterogeneity of tissue damage and differing rates of evolution toward infarction (in different patients). Yet again, stroke in humans is a highly individualized event, due to the complex interaction of numerous biophysical and biochemical processes.

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Decreasing Costs of Stroke Hospitalization in Toronto

To the Editor:

Our previous article on the costs of stroke care in Toronto in 19934 has been cited in numerous other publications,5–6 but these costs are no longer valid and may be misleading. We have recalculated them in the light of recent major changes in stroke management and hospital restructuring that has occurred throughout Canada since the previous publication.

Patients were retrospectively identified from the Stroke Registry at Sunnybrook Health Science Centre (SWCHSC) and via chart reviews for the 1996 fiscal year (April 1, 1996, through March 31, 1997). Only ischemic strokes (identified by clinical and CT criteria) were included. All were first strokes admitted to SWCHSC, a university teaching hospital and tertiary care center with 428 acute care beds.

Demographic, social, and clinical data were located in patient charts and recorded in the Stroke Registry. Social data was defined as family support, whether the patient was living with family before the stroke and discharged home to family after the stroke. The subtype of ischemic stroke was classified according to the TOAST criteria.7 The modified Rankin scale was used to determine the stroke severity: 0–1, mild stroke; 2–3, moderate stroke; and 4–5, severe stroke. Fatal stroke includes both early deaths (0 to 7 days) and late deaths (>7 days).

Treatment and hospitalization costs (direct costs only) were determined from the Transitional System Incorporated costing system at SWCHSC for the 1996 fiscal year. The costs incorporated in the total cost were nursing, medical services (psychology, speech pathology, social services, and pathology), laboratory tests (CT, vascular ultrasound, Holter, electrocardiography, con-
ventitional angiography, biochemistry, hematology, and microbiology), physiotherapy, occupational therapy, physician fees (fees for service for each patient according to the Ontario Health Insurance Plan), and pharmacy (medication costs for each patient). Canadian cost figures were converted into American dollars with use of the exchange rate from June 1998 (US $1 = Can $1.45).

Microsoft Excel (version 7.0) was used to determine descriptive statistics (ie, mean and SD) and Pearson’s correlation coefficient the relationship between cost, length of stay (LOS), and stroke severity. The t test was used to determine significant differences between means (P < 0.05), and the χ² test was used to determine significant differences between proportions.19

A total of 73 patients were identified with a mean ± SD age of 77 ± 13 years and a mean ± SD LOS of 20 ± 21 days. There were 35 men (mean age, 72 ± 15 years) and 38 women (81 ± 9 years), with a significant difference in age (P < 0.05). The mean LOS for the male patients was 18 ± 20 days versus 22 ± 23 days for the female patients (P < 0.05).

The mean cost of all ischemic strokes was Can $9763 ± 11 053 (US $6738 ± 7628). The cost and LOS associated with large-artery disease (n = 14) were Can $11 183 ± 12 248 (US $8153 ± 8453) and 17 ± 18 days, respectively; for cardioembolic stroke (n = 31), Can $10 756 ± 11 485 (US $7424 ± 7927) and 22 ± 24 days; for lacunar strokes (n = 10), Can $10 437 ± 14 054 (US $7424 ± 7297) and 20 ± 23 days; and for undetermined strokes (n = 18), Can $8740 ± 8789 (US $6032 ± 6066) and 19 ± 20 days, respectively. There was no significant difference in cost for the stroke subtypes (P > 0.05).

Stroke costs related to LOS (r = 0.94) and severity (r = 0.41), with severe strokes being the most expensive and having the greatest LOS (see the Table). Fatal cases were also costly because of the extended LOS before death.

Our new data, compared with the 1993 data, show that a greater proportion of patients were discharged home (41% versus 28%, P < 0.05) and fewer went to rehabilitation (23% versus 35%, P < 0.05) or nursing home/long-term care facilities (8% versus 22%, P < 0.05). However, there were more deaths in the current group of patients than in our 1993 study (27% versus 15%, P < 0.05), probably a function of the small sample size.

Patients discharged home to their family (n = 41) had a shorter LOS (16 ± 16 days) than those living alone (n = 32; 24 ± 26 days) (P < 0.05). There was no difference (P > 0.05) in the number of patients with family support in comparison with our 1993 study. Therefore, the cost of treating a stroke patient discharged home to family was Can $8236 ± 9078 (US $5684 ± 6265) compared with Can $11 721 ± 13 053 (US $8090 ± 9009) for a patient living alone (P < 0.05).

There are some limitations to this study. First, our data were captured from one center in Canada, and the costs may represent only the province of Ontario. Second, we did not include indirect costs, which remains a difficult and complex parameter to measure,11 so the overall economic impact of stroke is underestimated. Third, our sample size was small and there may be changes in the demographic information (eg, number of stroke fatalities), as evident in a larger study that we are currently undertaking to examine hospitalization and posthospitalization stroke costs. This future study will also address the issue of whether cost shifting from the acute care hospital to rehabilitation centers, long-term care institutions, or home care has occurred. Last, thrombolytic therapy is not yet available as “open label” in Canada and thus has not been factored into these costs.

We feel that in view of the striking decrease in costs of stroke management in hospitals between 1993 and the present, a brief communication is warranted before completion of our new evaluation.
wine, high wine consumption, blond [light?] cigarettes, diabetes, and body mass index of ≈30), wine and high wine consumption had a partial correlation coefficient of −0.12; (P=0.43) and 0.14 (P=0.37), respectively. When the analysis was repeated after exclusion of illiteracy because there was correlation with body mass index and blond cigarettes, the partial correlation coefficient for wine and high wine consumption was −0.32 (P=0.034) and 0.28 (P=0.065), respectively. The authors claimed in the beginning of the “Discussion” that lower wine consumption might explain the higher CVD mortality in the southern and eastern parts of the country. In the last paragraph of the same article they stated that IHD mortality showed the same pattern, ie, wine consumption was associated with a “higher” mortality. Actually, the article about IHD mortality showed that wine consumption had a partial correlation coefficient of −0.31 (P=0.038), while high wine consumption had a partial correlation coefficient of 0.35 (P=0.037). However, in neither of these 2 articles did the authors clearly define “high wine consumption.” The crude correlation coefficients seemed to express a straightforward beneficial effect of increasing intake of wine. Was “high wine consumption” defined according to criteria before initiation of the study, or was it chosen after seeing a scatterplot of wine intake and SMR, a plot that would have been very valuable to the readers?

In an article published in Stroke in August 1998, Artalejo et al reported that an increase in fruit and a decrease in wine consumption from 1964 to 1980 may have contributed to the decline in CVD mortality in Spain during 1975–1993, using the same material. They based this on the findings of a partial correlation coefficient for percentage change in wine consumption of 0.30 (P=0.04) in a multiple linear regression analysis, including fruit, fish, vegetables, tobacco, and illiteracy. The authors stated that the data were consistent with those in a previous study, in which they found that excess wine consumption was associated with higher CVD mortality across regions in Spain.

The conclusion that the percentage change in wine consumption is responsible for the decline in CVD mortality does not seem to be warranted. Changes in percentage of consumption will depend on the existing intake, and a 10% decrease in a high-intake region is very different from a 10% decrease in a region with low intake, in terms of absolute values. This becomes even more interesting, as the authors have found that at least some wine intake was associated with a reduced risk of CVD mortality. While the authors in their previous 2 articles estimated the effect of an undefined “high wine intake” group, it did not appear in the latest article. It would have been interesting to see whether CVD changes followed the changes in percentage wine consumption equally for regions with high, medium, and low wine intakes.

Response

We thank Drs Truelsen and Gronbaek for their interest in our work on the determinants of the geographic distribution of ischaemic heart disease and cerebrovascular disease (CVD) mortality in Spain. They raise three main issues. The first is whether the model regressing CVD mortality on wine consumption was specified before or after examining the data. The second issue concerns the form of measuring changes in CVD and its determinants, and the third refers to the consistency between the cross-sectional and the longitudinal analysis of the data.

Regarding the first issue, model specification was theory driven and was carried out before watching the data. Most information on the relationship between alcohol consumption and cerebrovascular disease suggest that the relationship is U- or J-shaped. Therefore, the model should initially include a “wine” term to describe the left part of the relationship, and a “wine2” term to describe the right part. Once the model was fitted, we checked its appropriateness against the data by examining scatterplots and by residual analysis. Finally, we also checked that a polynomial model was a better description of the data than a model without a quadratic term. The correct interpretation of the wine and wine2 terms is not low and high wine consumption, but rather lower and higher consumption across the provincial distribution of wine consumption in Spain. The limit between lower and higher wine consumption in our data is approximately 2 dL/person per day (approximately 24 g/person per day of alcohol, assuming that alcohol volume in wine is 12%). However, this figure should be valued with caution because of the limited number of observations involved (Figure).

Regarding the second issue, we have used relative measures of change to correct for baseline values of the study variables. This is common practice in etiologic studies, in the same way as exposure effects are measured by relative as opposed to absolute measures. Obviously, we agree that a fixed relative change can correspond to different absolute changes, depending on the baseline values. However, the existence of only 50 provinces (observations) precludes any meaningful analysis stratified by categories of baseline wine consumption.

Regarding the third issue, there is not a quadratic term in the model of the longitudinal analysis. It was removed from an initial model after we verified that in this case the quadratic term did not contribute to the description of the data.

There is no inconsistency in the results of the cross-sectional and longitudinal analyses. In the period 1964–1980, there has been a decline in wine consumption in Spain. This decline affected to a greater extent those provinces with higher consumption in 1964. Therefore, the decline has been more important in
the provinces situated in the right part of the wine distribution, having a favorable effect on the CVD mortality of those provinces and therefore contributing to the decline in CVD mortality in Spain overall.

To the Editor:

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Geometry and Subdural Hematoma Volume

To the Editor:

Gebel and colleagues1 reported a seemingly simple and accurate method for estimating the volume of a subdural hematoma. However, as 17th century philosopher and mathematician Thomas Hobbes wrote about a similarly bewildering calculation, “To understand this for sense it is not required that a man should be a geometer or a logician, but that he should be mad.”2

The ABC/2 method for an intraparenchymal hematoma is based on the formula for the volume of a ellipsoid which is given by 4/3 \( \pi r_1 r_2 r_3 \) (where the \( r \) represents each radius). With an approximation of 3 for \( \pi \), and substitution of each of the radii with each diameter (d) divided by 2, the formula becomes \( d_1 d_2 d_3 / 2 \), or ABC/2.

At first, it seems quite unlikely that this formula should be useful in the estimation of the volume of a crescent-shaped subdural hematoma. Nevertheless, the method has proven accuracy, and its derivation must be explained. Consider the 3-dimensional crescent as the difference between 1 large outer ellipsoid and 1 small inner ellipsoid, which is then cut in half (ie, the crescent is akin to a solid semicircle). The volume of the crescent is then given by (4/3 \( \pi r_1 r_2 r_3 \) – 4/3 \( \pi r_4 r_5 r_6 \))/2. Using the measurements as defined by Gebel et al1 (Figure), the length (L) represents 1 diameter, the thickness (T) which is perpendicular to the plane shown. The third radius is designated as the width (w), and the difference between the widths of the 2 ellipsoids is marked by W.

The entire formula simplifies to \( L T W / 2 \), or ABC/2.

Thus, “Though this be madness, yet there is method in ‘t.”3 Was this the method of Gebel et al?


Blood Flow of the Middle Cerebral Artery With Sleep-Disordered Breathing: Correlation With Obstructive Hypopneas

To the Editor:

Netzer et al1 recently reported that obstructive sleep hypopnea and apnea are associated with reductions in middle cerebral...
artery (MCA) blood flow compared with central sleep apnea. This study may explain the increased incidence of ischemic stroke in obstructive sleep disorders, although it is important to remember that other mechanisms independent of cerebral hemodynamics have also been proposed.

Transcranial Doppler blood flow measurements of the MCA are assumed to reflect total brain flow, but it should be noted that this technique does not evaluate regional cerebral blood flow (CBF). Several lines of evidence suggest that localized disturbances in CBF may be important in patients who sustain cerebrovascular events in association with sleep disorders. NonREM sleep in normal subjects is associated with a global reduction in brain blood flow (measured by stable xenon computed tomography) and global glucose hypometabolism (measured by positron emission tomography). Against this global fall in CBF are important regional variations, with some brain regions (frontal cortex, basal ganglia, thalamus, pons, cerebellum) affected to a greater degree while others (temporal cortex) are relatively unaffected. During REM sleep there is increased CBF to the associated visual area, presumably reflecting the activation involved in processing visual dream experiences, with a reduction in inferior frontal cortical flow. Preliminary observations in sleep apnea syndromes indicate the presence of focal cortical perfusion abnormalities in the awake or apneic state that are reversed with therapeutic transnasal continuous positive airway pressure (CPAP).

We recently assessed regional CBF in 7 patients with severe obstructive sleep apnea (OSA) using single-photon emission computed tomography (SPECT) imaging and the cerebral flow tracer \(^{99m}\text{Tc}\)ethyl cysteinate dimer (ECD; Neurolite, DuPont Pharma). The diagnosis of OSA was made from overnight polysomnography (apnea-hypopnea index of >40). Subjects had no other sleep disorders, no past history of cerebral vascular or cardiovascular disease, and normal findings on neurological examination, and they were not taking any medications. All patients underwent 2 morning sleep studies of 3 hours’ duration. For the first examination, \(^{99m}\text{Tc}\)ECD was injected intravenously at the onset of an apneic episode, and the patient was scanned 1 hour later. The exact time of injection, sleep stage, subsequent arousal, oxygen saturation, and total and postinjection duration of the desaturation episode (oxygen saturation of <85%) were carefully noted. The same procedure was repeated with the second sleep study, except that nasal CPAP (mean, 14 cm water; range, 10–20 cm) was applied throughout the study. \(^{99m}\text{Tc}\)ECD was injected in the sleep study at the same time as with the apneic scan. Patients underwent awake brain scanning on a third occasion. Six normal control subjects were recruited from among hospital employees, and polysomnography confirmed a normal sleep pattern. \(^{99m}\text{Tc}\)ECD injection was performed after 2 hours of normal sleep, with SPECT scanning 1 hour later. An awake SPECT scan was performed on a second occasion.

Subjects were imaged on a dual-head camera (Helix, Elscint Ltd) fitted with high-resolution, low-energy parallel-hole collimators and a custom-built SPECT headholder. This imaging system has a reconstructed resolution of 9 mm in air of the center of a 15-cm radius of rotation. The scans were reconstructed and reoriented parallel to the orbitomeatal plane with use of external fiduciary markers. A set of region-of-interest (ROI) templates defined from cross-sectional neuroanatomical atlas were superimposed on the patients’ scans with a technique that requires minimal operator intervention. Six transaxial slices (slice thickness interpolated to 1 cm) were used to extract average ROI activity for temporal cortex, parietal cortex, frontal cortex, occipital cortex, anterior cingulate, striatal nuclei, thalamus, and cerebellum. Regional flow measures were normalized to cerebellar activity and to whole cortex activity at the midstriatal level.

The following preplanned comparisons were performed: sleep (control) versus sleep-apneic (OSA), sleep-apneic (OSA) versus sleep-nonapneic (OSA with CPAP), and awake (control) versus awake (OSA). After Bonferroni adjustment for multiple comparisons, no significant differences were identified for any of the brain ROIs studied. Visual assessment of the scans confirmed a normal symmetrical pattern of cortical, subcortical, and cerebellar perfusion.

Although our findings are based on a small number of subjects, we failed to find any significant regional disturbance in CBF during apnea or in the awake state in patients with OSA. Our observations complement the recent study by Netzer et al and suggest that global rather than regional changes in brain hemodynamics are likely to be more important in patients with obstructive sleep disorders.

This work was supported in part through clinical grant 95031 from DuPont Pharma.

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Response

Dr. Leslie, Wali, and Kryger identify key elements and critical issues about our study and its relevance to understanding the relationships between sleep apnea and stroke. First, we agree that the technique of transcranial Doppler flow measurements of the MCA provides no information on regional blood flow, nor can its use in our study predict brain dysfunction or stroke in sleep apnea. We were careful to state that the method provided information concerning dynamic changes in vascular pressures and flows occurring in the MCA with repetitive obstructive apneas and obstructive hypopneas (heavy snoring). Our conclusions were limited to differences in the physiological events among apnea types.

Second, the relevance of studies of cerebral function in sleep apnea are to the cerebrovascular and, possibly, neurocognitive sequelae of sleep apnea. Here data are scant. There are epide-
miological studies showing association, and studies like ours and that reported by Leslie et al that perform physiological studies in patients. There is a need for outcome and observational epidemiological studies of cerebrovascular control that might permit insight into the pathophysiology of stroke in the setting of sleep apnea. Of interest, animal studies suggest that exposure to hypoxia will increase brain microvasculature, and as a result, reduce the neuroanatomical consequences of experimental ischemic stroke.3

Third, the instruments to assess the brain and its function are currently focused on anatomic regions or large vascular structures, and interpretation of results is made without much regard for microvascular events, such as the coordination of localized blood flow to neuronal activity. The clinical vectors to produce cerebral dysfunction in sleep apnea are complex, given the state-related nature of the illness, the attendant intermittent and often profound hypoxemia and alterations in cardiovascular function, and the global consequences of repetitive arousal on daytime performance. Neurocognitive testing in sleep-apnea patients reveals deficits that correlate only moderately well with nighttime events.2 The study reported by Leslie et al nicely illustrates a similar phenomenon, namely, the SPECT imaging shows no regional or global differences between patients with severe degrees of apnea (>40 per hour of sleep) and healthy control subjects or in the same patients before and with definitive treatment, after controlling for state. Other factors to consider that potentially confound measures of brain function and affect the power of any study of sleep apnea are markers of age, comorbidity, and length of illness. As our study suggests, the equivalent effects of heavy snoring and obstructive apnea on MCA flow profiles and the observation that central apneas show less dynamic impact may be important factors to consider in determining the effect size of sleep-disordered breathing on cerebrovascular function and illness.

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### Chronic Atrial Fibrillation and Low Cognitive Function

To the Editor:

We write with great interest the article by Kilander et al recently published in Stroke. We would like to support their conclusions by presenting data obtained from our clinical experience. We analyzed the relationship between atrial fibrillation and cognitive function in the elderly patients admitted to our Medical Unit for the Acute Care of the Elderly (Poliambulanza Hospital, Brescia, Italy). During the period from November 1997 through July 1998, 600 patients were consecutively admitted. For the aim of the study we excluded 331 patients: those aged <70 years with previous cerebrovascular events (TIA and minor or major stroke); with terminal, wasting diseases or severe metabolic disorders (chronic renal or liver failure, malignant neoplasm, chronic inflammatory or infectious diseases of a severe degree); and those who were demented or with a score of <20 on Folstein’s Mini Mental Status Examination (MMSE).

The remaining 269 patients (mean age, 80.4±5.8 years; 69% W) were stratified according to ECG features into 3 groups:

1. Sinus rhythm (n=214; 79.5%),
2. those with paroxysmal atrial fibrillation (ie, ≥1 episodes of arrhythmia lasting ≤48 hours) (n=13; 4.8%), and
3. those with chronic atrial fibrillation (ie, arrhythmia lasting >6 months) (n=42; 15.7%).

Cognitive status as assessed by MMSE was found to be significantly different in the 3 groups: group 1, 26.3±2.9; group 2, 25.2±2.5; and group 3, 24.3±2.9 (by ANOVA, F2,266=8.15, P=0.0004). The Table shows the association of atrial fibrillation with cognitive impairment: patients with sinus rhythm were considered the reference group; patients with an MMSE score of ≤24 were considered to have cognitive impairment. In analogy to the study of Kilander and colleagues,1 we found a significant association between chronic atrial fibrillation and cognitive impairment (ie, elderly patients with chronic atrial fibrillation had a 3.3-fold higher risk of cognitive impairment than those with sinus rhythm); the association held after controlling for all the confounders associated with cognitive impairment in a crude analysis (age, education, and depression) and for hypertension and diabetes.

In conclusion, chronic atrial fibrillation is an independent correlate of low cognitive function. Although the pathogenetic link between chronic atrial fibrillation and cognitive impairment is still unclear, the results obtained by Kilander and colleagues1 and our own observations might support the use of anticoagulant therapy whenever indicated. This might prevent not only major cerebrovascular accidents but also the less obvious clinical outcome of cognitive function loss.

### Crude and Adjusted Associations of Chronic Atrial Fibrillation With Cognitive Impairment (MMSE of ≤24) in a Population of 269 Consecutively Admitted Non-demented Elderly Patients

<table>
<thead>
<tr>
<th>Cognitive Impairment</th>
<th>Crude Analysis</th>
<th>Adjusted Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>43</td>
<td>171</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation†</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Chronic atrial fibrillation‡</td>
<td>19</td>
<td>23</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, education, depression, hypertension, and diabetes.
†≥1 episode lasting ≤48 hours.
‡Stable arrhythmia lasting >6 months.

Response

We thank Drs Rozzini, Sabatini, and Trabucchi for their response to our article. Interestingly, our finding of a relationship between atrial fibrillation and low cognitive function was replicated in an older population with acute somatic disorders.

### References


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However, it remains to be established whether a causal relation exists between atrial fibrillation and cognitive impairment, and if so, by which mechanisms. They may be separate phenomena—both indicating general atherosclerosis—or atrial fibrillation may contribute to cognitive impairment by atherothrombotic or hemodynamic mechanisms. Richards and colleagues\(^1\) have reported that men at risk of cardiovascular disease who received primary preventive treatment with low-dose aspirin and/or warfarin performed better in cognitive tests than the placebo group. It is of great importance to further examine this hypothesis in larger, randomized trials.

Time Course of ADC<sub>W</sub> Changes in Ischemic Stroke
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Stroke. 1999;30:185
doi: 10.1161/01.STR.30.1.185
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
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