**Time Course of ADC\textsubscript{W} 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 radiotracer 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 unraveled when there is sufficient attention to detail. The more finely we analyze our clinical and imaging observations, the more likely we are to find useful correlations with measurements made in model systems.

George C. Newman, MD, PhD  
Department of Neurology  
School of Medicine  
SUNY at Stony Brook  
Stony Brook, New York

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**Response**

We thank Dr Newman for his gracious comments on our paper\(^1\) 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.

V. Nagesh, PhD  
Department of Neurology  
Nuclear Magnetic Resonance and Stroke Research Center  
Henry Ford Health Sciences Center  
Detroit, Michigan

K.M.A. Welch, MD  
University of Kansas Medical Center  
Kansas City, Kansas


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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 1993\(^4\) 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\(^7\) 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.\(^8\) The modified Rankin scale\(^9\) 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.10

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.

Chau Tran, BSc
Department of Clinical Pharmacology
Zurab Nadareishvili, MD, PhD
Liliana Smurawska, MD
Stoke Research Unit
Paul I.T. Oh, MD
Department of Clinical Pharmacology and Department of Epidemiology and Internal Medicine
John W. Norris, MD
Stoke Research Unit
Sunnybrook Health Science Centre
University of Toronto, Toronto, Canada


Wine Consumption and Cerebrovascular Disease Mortality in Spain

To the Editor:

Artalejo et al1–3 have studied the association between various diet and lifestyle habits and the risk of cerebrovascular disease (CVD) and ischemic heart disease (IHD) mortality in Spain. The CVD mortality showed considerable variation within the 50 Spanish provinces, and high wine intake was observed in regions with low CVD mortality rates.

In one article,1 it was shown that the correlation coefficient between wine intake and standardized mortality rate (SMR) from CVD was −0.26 (P=0.061). In subsequent multiple correlation analyses (including illiteracy, hypertension, sedentary lifestyle,
Letters to the Editor

Morten Grønbæk, PhD, MD
Institute of Preventive Medicine
Kommunehospitalet
Copenhagen, Denmark

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.1-3 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-sectional2 and the longitudinal3 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.4 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.5 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-sectional2 and longitudinal3 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

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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.

Fernando Rodríguez Artalejo, MD, PhD1,2
Pilar Guallar-Castillón, MD, PhD2,3
José Ramón Banegas Banegas, MD, PhD2
Belen de Andrés Manzano, MD, PhD2,3
Juan del Rey Calero, MD, PhD1
1Department of Preventive Medicine and Public Health Universidad del País Vasco
2Department of Preventive Medicine and Public Health Universidad Autónoma de Madrid
3Centro Universitario de Salud Pública Consejería de Sanidad y Servicios Sociales Universidad Autónoma de Madrid
Madrid, Spain


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 of a logician, but that he should be mad.”

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 \( r_1 r_2 r_3 \) (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) represents another, and these are the same for both the inner and outer ellipsoids. The width (w) of the 2 ellipsoids differs, so the formula can then be approximated as \( LTW_1 - LTW_2 \)/2. Since the difference between the widths is represented by W, the entire formula simplifies to \( LTW \), or ABC/2.

Thus, “Though this be madness, yet there is method in ’t.”3 Was this the method of Gebel et al?

Response

We wish to thank Dr Kasner for his most eloquent and convincing mathematical explanation of our serendipitous madness.

Scott E. Kasner, MD
Comprehensive Stroke Center
Department of Neurology
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania


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
Letters to the Editor

William D. Leslie, MD, FRCP, MSc
Section of Nuclear Medicine
St Boniface General Hospital
Winnipeg, Canada

Siraj Wali, MD, FRCP
Meir Kryger, MD, FRCP
Sleep Disorders Laboratory
St Boniface Research Center
Winnipeg, Canada

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-
Chronic Atrial Fibrillation and Low Cognitive Function

To the Editor:

We read with great interest the article by Kilander et al 1 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 (Policlinico 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) those with 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.

<table>
<thead>
<tr>
<th>Cognitive Impairment</th>
<th>Crude Analysis</th>
<th>Adjusted Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>Yes: 43</td>
<td>OR: 1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>No: 171</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation†</td>
<td>3</td>
<td>0.3–4.5</td>
</tr>
<tr>
<td>Chronic atrial fibrillation‡</td>
<td>19</td>
<td>3.2</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.

Nikolaus C. Netzer, MD
Kingman P. Strohl, MD
Department of Medicine
Division of Pulmonary and Critical Care Medicine
Case Western Reserve University
Cleveland, Ohio

Renzo Rozzini, MD
Tony Sabatini, MD
Medical Unit for the Acute Care of the Elderly
Policlinico Hospital
Marco Trabucchi, MD
Geriatric Research Group
Brescia, Italy

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.

Lena Kilander, MD  
Merike Boberg, MD  
Department of Public Health and Caring Sciences/Geriatrics  
Uppsala University  
Uppsala, Sweden  
