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Serum Gamma-Glutamyltransferase as a Risk Factor of Ischemic Stroke Might Be Independent of Alcohol Consumption

Michele Emdin, Claudio Passino, Luigi Donato, Aldo Paolicchi and Alfonso Pompella

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Serum Gamma-Glutamyltransferase as a Risk Factor of Ischemic Stroke Might Be Independent of Alcohol Consumption

To the Editor:

In a recent issue of *Stroke*, Jousilahti et al reported on the association of stroke with serum levels of gamma-glutamyltransferase (GGT) and alcohol consumption in a cohort of more than 14 000 subjects.¹ In particular, the authors observed that the incidence of ischemic stroke had a good correlation with serum GGT—which they interpreted as a surrogate marker of alcohol consumption—in both genders (relative risk in men 1.29, 95% CI 1.04 to 1.60; in women 1.42, 95% CI 1.10 to 1.84). On the other hand, no correlation of ischemic stroke was observed with the self-reported individual alcohol intakes, although “a significant linear increasing trend in the mean levels of self-reported alcohol drinking by quartiles of the serum GGT” was found. The obvious conclusion is that GGT is an independent risk factor for ischemic stroke, irrespective of alcohol drinking, whereas the authors concluded that answers given by patients to questionnaires concerning their lifestyles are unreliable and that serum GGT is a more faithful indicator of alcohol consumption, ie, the actual determinant of stroke occurrence.

We would like to suggest an alternative explanation to the findings of this study, based on previous evidence in the literature in favor of a direct GGT involvement in atherosclerotic plaque complication. GGT, present in serum and on the surface of most cell types, is the enzyme responsible for the extracellular catabolism of glutathione, the main antioxidant in mammalian cells, and its role in cardiovascular diseases may be more complex than currently thought.² While it is certainly true that serum GGT is a well-assessed marker of alcohol abuse, higher GGT levels are also found to be independently correlated with conditions associated with increased atherosclerosis, such as obesity, elevated serum cholesterol, high blood pressure, and myocardial infarction.^{3–5} Epidemiologic studies have reported a positive correlation between GGT levels and cardiovascular mortality, namely from ischemic heart disease, irrespective of alcohol consumption.^{5–7} A recent study by us has shown

that serum GGT level is an independent risk factor for cardiac death and reinfarction in patients with angiographically documented coronary artery disease. Remarkably, its strong predictive value is independent from self-reported alcohol consumption,⁸ which instead has a protective effect on survival, confirming previous observations.⁹

Which mechanisms can underlie the association of serum GGT with atherosclerotic disease and its consequences? Our previous studies documented that GGT, in the presence of iron, can catalyze the oxidation of LDL,¹⁰ a process involved in pathogenesis of atherosclerosis. Moreover, serum GGT is partially adsorbed onto circulating LDL,¹¹ which can carry GGT activity inside atheromatous plaques. Active GGT is colocalized with oxidized LDL¹⁰ (see Figure), and free iron was present at levels sufficient to catalyze LDL oxidation.¹² Also, available evidence is in favor of a pathogenic role of GGT activity in the evolution and instability of atherosclerotic plaques in different vascular districts. It thus seems appropriate to suggest that the significance of serum GGT should not be restricted to that of a mere “biological marker”¹ of alcohol consumption, when evaluated in a context of atherosclerosis and cardiovascular disease.

Michele Emdin, MD, PhD

Claudio Passino, MD

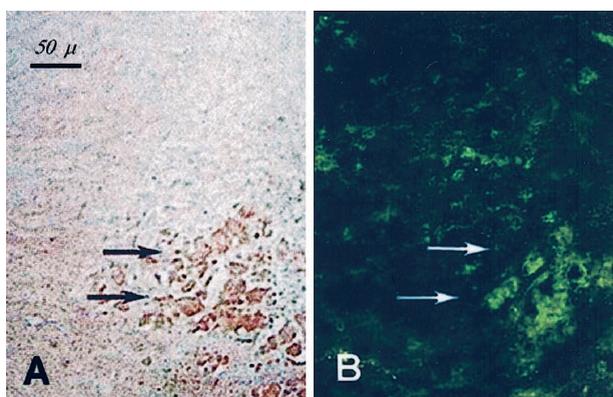
Luigi Donato, MD

*Institute of Clinical Physiology
National Research Council - CNR
Pisa, Italy*

Aldo Paolicchi, MD

Alfonso Pompella, MD

*Department of Experimental Pathology
University of Pisa Medical School
Pisa, Italy*



Colocalization of GGT activity with oxidized LDL in human atherosclerotic plaques. A, GGT activity (histochemical azocoupling reaction). B, colocalization of oxidized LDL (arrows, adjacent section, indirect immunofluorescence with a monoclonal antibody against human oxidized LDL). The sample shown is from a cerebral artery plaque revealed during the autopsy of a 62-year-old patient.

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Re: Slowly Activating Potassium Conductance (I_D): A Potential Target for Stroke Therapy

To the Editor:

We read with great interest the article by Bains et al¹ in which they hypothesize that the blood pressure-independent susceptibility of spontaneous hypertensive rats (SHR) to stroke could be explained by increased angiotensin II levels in the brain nuclei. Indeed, they convincingly documented that resistance to death of magnocellular neurons of paraventricular nucleus (PVN) after injection of an *N*-methyl-D-aspartate receptor agonist (NMDAa) is present in normotensive rats but absent in SHR and that preadministration of saralasin into these nuclei of SHR generated resistance of these cells to NMDAa-induced death, by preventing the angiotensin II-mediated increase of neuronal excitability, which is secondary to inhibition of a D-type specific potassium conductance. Indeed, inhibition of this conductance results in higher frequency of depolarization in the penumbra surrounding a focal brain ischemia and, therefore, results in increased infarct size. However, while the authors stressed the potential pathophysiological significance of their observation by recalling that the AT1 receptor antagonist losartan protects SHR against stroke even at nonantihypertensive dose,² they unfortunately did not examine the effect of specific AT1 receptor blockade in their experimental model, and we wonder why they have chosen saralasin, a nonspecific angiotensin II antagonist.

Preadministration of losartan and candesartan have been shown to be more stroke protective than angiotensin-converting enzyme inhibitor (ACEI) in the gerbil model of acute brain ischemia by unilateral carotid ligation, whereas preadministration of ACEI with these AT1 receptor antagonists resulted in the same mortality as with ACEI alone, suggesting that stimulation of non-AT1 receptors was responsible for the stroke protective effect of AT1 receptor antagonists.^{3,4} Indeed, AT1 receptors blockade blunts the angiotensin II-mediated suppression of renin secretion and stimulates angiotensin II formation and therefore the nonopposed non-AT1 receptors, whereas ACE inhibition prevents angiotensin II formation and therefore non-AT1 receptor stimulation. Furthermore, in the rat stroke model induced by transient middle cerebral artery occlusion, previous intracerebroventricular injection of irbesartan (at low doses leaving the systemic angiotensin II system unaffected) was able to improve the neurological outcome, in parallel with a decrease of the expression of AP-1 transcription factors associated with neuron apoptosis. Because these beneficial effects were canceled by preadministration of an AT2 receptor blocker, the PD123177, this suggests that they were mediated by the AT2 receptors.⁵

Because of the duality of its receptors, angiotensin II seems to act as the two-edge sword, with AT1 and AT2 mediating opposing effects.³ The crucial question as to whether, depending on the balance of the expression of these receptors, angiotensin II is protective during brain ischemia through stimulation of AT2 or deleterious through stimulation of AT1 is still pending. As the important results presented by Bains et al point to the regulation of the D-type potassium channel as to a central effector to neuron protection during ischemic insult, we would be very eager to know if the authors have examined the effects of preadministration of AT1 and AT2 receptor antagonists on the channel inhibition by angiotensin II. An AT1-mediated inhibitory effect but an AT2-mediated stimulatory effect of angiotensin II of the K channel-dependent neuroprotective effect would provide an important new experimen-

tal evidence supporting the idea that AT1 specific blockade is better suited than ACE inhibition for cerebral protection.

Jean Michel Achard, MD, PhD

Physiology Department

CHU

Limoges, France

Oliver Godefroy, MD

Michel Andrejak, MD

Hakim Mazouz, MD

Albert Fournier, MD

Departments of Neurology, Pharmacology, and Nephrology

Internal Medicine

CHU

Amiens, France

Leonardo Fernandez, MD

Pathology Department

Yale Medical School

New Haven, Connecticut

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Response

We are not surprised by the very sensible question from Achard et al as to why selective AT1 receptor antagonists were not used in our experiments reported in *Stroke*.¹ The reason for this decision is academically somewhat disappointing while unfortunately very relevant in the current era, with an increased awareness of the real value of intellectual property. Our request for losartan to be used in these experiments was accompanied by the very familiar standard agreement to assign at minimum a portion of patent rights from any work coming from the use of this compound to the pharmaceutical supplier. Working with the technology transfer office at Queen's University, PARTEQ, we decided not to give up our intellectual property rights at this time, as we felt that the primary question could be answered using the nonselective peptide antagonist saralasin. The data from these experiments are reported in our article and, as pointed out by Achard et al, do not allow us to differentiate between potential AT1 and AT2 receptor-mediated effects.

We agree that the issue is indeed an intriguing one, and our recent study unfortunately fails to provide a definitive answer. The literature does, however, provide some hints. While we have not assessed the effects of AT1 receptor blockade on the delay current directly, previous work from this laboratory has shown AT1-mediated inhibition of transient potassium currents at that time identified as I_A , which in all probability included a component of I_D .² In addition, in cultured hypothalamic neurons, Kang et al³ have reported both AT1-mediated inhibition of net potassium currents (blocked by losartan), and AT2-mediated enhancement (blocked by PD123177 and PD123319) of these same net potassium currents. Again, caution is necessary in interpreting these data as they do not assess specific effects on isolated currents. It should be stressed, however, that even though these effects are in accordance with the hypothesis of Achard et al with regard to potential effects on I_D , direct

assessment of AT receptor subtypes responsible for effects on this current has not to our knowledge been carried out.

Finally, we would agree that the available data do suggest AT1 receptor antagonists to be more effective in achieving cerebral protection than ACE inhibition. The novelty of our data, we believe, rests in the suggestion of a potential mechanism underlying such protection, namely inhibition of transient potassium conductances. We believe that the strength of our study is that we have provided both *in vivo* and *in vitro* validation of this hypothesis using 2 separate pharmacological agents that both inhibit these currents and endow neuroprotection. Obviously, as Achard et al point out, future studies will be necessary to more completely test this hypothesis in a variety of stroke models.

Alastair V. Ferguson, PhD

*Department of Physiology
Queen's University
Kingston, Ontario, Canada*

Jaideep S. Bains, PhD

*Neuroscience Research Group
Department of Physiology and Biophysics
University of Calgary
Calgary, Alberta, Canada*

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Re: Safety of Intraventricular Sodium Nitroprusside and Thiosulfate for the Treatment of Cerebral Vasospasm in the Intensive Care Unit Setting

To the Editor:

I read with interest the report by Thomas and McGinnis on safety of intraventricular sodium nitroprusside for the treatment of cerebral vasospasm.¹ As Director of Cerebrovascular Surgery and Surgical Director of the Neurosurgical Intensive Care Service at Thomas Jefferson University, I had firsthand interaction with and care of every patient listed in this study. Virtually all of these patients were treated with prophylactic volume expansion and HHH (hypertensive, hypervolemic, hemodilutional) therapy, and, as reported in Table 1 of the article, several were treated with angioplasty. The conclusion that the beneficial effects were from sodium nitroprusside and thiosulfate is entirely misleading. That conclusion cannot be drawn. Many of these patients had intractable intracranial pressure, necessitating interruption of the therapy, and in patients who were awake, therapy often had to be interrupted due to intractable nausea and vomiting, even when they were premedicated with doses of Zofran, administered even in the chemotherapeutic range.

Patient 4 (seen in Figure 3A of the article), who was directly under my care, is listed as a satisfactory result. Although he walks and smiles, he is in fact neurologically and cognitively devastated and cannot even remember where the bathroom is in his own house.

Although the data are interesting, I think the conclusions drawn are very similar to a conclusion that $2+2=8$. The results of the initial reports were certainly very encouraging; however, at this point I do not think any conclusions can be drawn and I would certainly not advocate a prospectively randomized trial at this point.

Robert H. Rosenwasser, MD

*Division of Cerebrovascular Surgery
and Interventional Neuroradiology*

*Department of Neurosurgery
Thomas Jefferson University
Philadelphia, Pennsylvania*

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Response

Thank you for the opportunity to respond to the letter written by Dr Rosenwasser. I do question the reasoning behind Dr Rosenwasser's letter, as he seems to simply reiterate the points of the article, the emphasis of which is safety and not efficacy. It is clearly stated in the article, for example, that patient received HHH therapy and, in some cases, cerebral angioplasty. It is also stated that the administration of the medication was limited by intracranial hypertension so that in almost all cases therapy could not be initiated until vasospasm was already established. It is also clearly stated that nausea and vomiting were common side effects of the therapy. The reason for reiterating these points from the article in a letter to the Editor as though they were new information is obscure.

With regard to the patient to whom Dr Rosenwasser alluded (1 of 2 treated by him in this study), the facts of the case are stated quite clearly:

1. Vasospasm sufficiently severe to produce paraplegia and diagnostic confusion (the patient was misdiagnosed with a spinal cord lesion for several days) was present for a prolonged period of time.
2. The patient's vasospasm was refractory to HHH therapy, which was the reason and justification for commencing intraventricular (intrathecal) sodium nitroprusside and thiosulfate (ITSNP/T) therapy. Most importantly, US Food and Drug Administration approval of this protocol under Investigational New Drug Protocol 52-307 (Jeffrey E. Thomas, MD) was the basis for initial Institutional Review Board approval at Thomas Jefferson University (#97.9035), which initially required that the protocol be instituted only for medically refractory vasospasm. Therefore, Dr Rosenwasser's assertion that neurological improvement resulted from volume expansion and HHH therapy is illogical. Had this been the case, ITSNP/T therapy would not have been indicated and Dr Rosenwasser presumably would not have suggested it for his own patient.
3. The patient began to move his legs, for the first time in several days, within 1 hour of receiving medication and recovered to full ambulatory status.
4. The patient's neurological improvement coincided exactly with a profound drop in transcranial Doppler ultrasonography velocities (mean 200 to 60 cm/sec within 60 minutes) as demonstrated in the accompanying table (Figure 3). Although it is possible that the patient's abrupt neurological improvement occurred coincidentally with the administration of medication, it does not seem likely.
5. A short-term memory deficit in a patient with severe prolonged vasospasm in the anterior cerebral artery distribution following rupture of an aneurysm of the anterior communicating artery is certainly not inconsistent with the aftermath of perihypothalamic subarachnoid hemorrhage and cerebral vasospasm. Because the patient presented with paraplegia and severe mental status abnormality, it is not reasonable to assume that this residual memory deficit was somehow caused by the medication when all other clinical responses demonstrated a beneficial effect. This is especially true in view of the clinical responses of other patients, both in this study and in others.^{1–5} Since this patient's vasospasm was clearly refractory to aggressive HHH therapy, it is more reasonable to assume that his outcome might have been worse without this intervention, although this is most certainly not a conclusion of the article. Finally the patient's memory deficit is specifically and accurately noted in the text, Figure 3, and Table 2, and therefore Dr Rosenwasser's statement that this patient is 'listed as a satisfactory result' is also grossly erroneous.

A most important point of this study that seems to also have been misinterpreted by Dr Rosenwasser is that this is a safety study. This should be clear to anyone reading the title of the article. Although clinical outcomes of patients treated in this manner with ITSNP/T have generally been good and some angiographic,³ laboratory,⁶ and neurological¹⁻⁴ results have been dramatic, no claim to efficacy of this treatment for cerebral ischemia due to vasospasm has ever been made in this or in other articles. Studies by other investigators have been similarly viewed with caution^{5,7} (see reviews). Because preliminary investigations by other investigators^{2,5} have indeed demonstrated beneficial effects pertaining to enhanced cerebral oxygenation and cerebral blood flow, and because we and others have indeed observed good clinical results with this treatment, we believe that a prospective randomized multi-institutional trial of ITSNP/T is justified and advisable. Since the only way to find out whether this new treatment has true therapeutic value is to perform such a study, the suggestion that it should not be performed, in the absence of evidence of unacceptable risk, is both illogical and contradictory.³

Jeffrey E. Thomas, MD

*Neurovascular and Neurointerventional Surgery
Division of Neurosurgery
University of New Mexico Health Sciences Center
Albuquerque, New Mexico*

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Use of Hypertonic Saline in Ischemic Stroke

To the Editor:

We read with interest the article recently published by Schwarz et al.¹ In a small prospective study (n=8 patients), the authors report that an intravenous bolus injection of 10% hypertonic saline lowered intracranial pressure (ICP) (with or without clinical herniation) in patients with stroke for a duration of 4 hours after failure to observe such a response to intravenous administration of 20% mannitol. The conclusions reached by the authors are difficult to reconcile for 2 reasons: (1) the criterion for ICP reduction to <10% of pretreatment values is arbitrary; and (2) patients received different combinations of ICP-lowering therapies (2 patients with decompressive hemi-

craniectomy, 4 patients with hypothermia, and 2 patients with cerebrospinal fluid drainage via intraventricular catheter), and timing of these interventions remains unclear.

Various concentrations of hypertonic saline solutions have been used for the treatment of cerebral edema and elevated ICP from diverse etiologies.² We^{3,4} and others have previously reported a similar beneficial effect of hypertonic saline in patients with elevated ICP, although the patient populations in our reports were more heterogeneous, including patients with traumatic brain injury, brain tumors, intracerebral hemorrhage, and ischemic stroke. Thus, the reported efficacy of hypertonic saline in ameliorating elevated ICP over a short period of observation is not unique, and some fundamental questions regarding its utility, especially in ischemic and hemorrhagic strokes, remain unanswered.

First, is hypertonic saline more efficacious than the widely used and accepted osmotic agent mannitol as a first-line therapy for treatment of elevated ICP and brain resuscitation? The answer to this question would require a well-executed prospective, randomized, blinded trial comparing equiosmolar concentrations as well as equal volumes of hypertonic saline and mannitol in patients with elevated ICP. Such a study is long overdue. Carefully defined end points, including timing, duration, and the osmolar load required to ameliorate elevated ICP (degree, duration of decrement, "rebound" increases in ICP), are key elements that are presently being examined by such an ongoing study at our institution. Second, what is the long-term outcome in patients with ischemic stroke when treated with hypertonic saline? Differential effects of hypertonic saline on accompanying edema during cerebral ischemia (cytotoxic and vasogenic) are not well studied. We point out that midline shift on CT scans performed within 72 hours of admission in our case series was worsened with induction and maintenance of systemic hyponatremia with hypertonic saline in patients with cerebral infarction.²

Third, and more importantly, is hypertonic saline deleterious to the brain during cerebral ischemia? Experimental evidence suggests this to be the case. Under controlled experimental conditions, in a well-characterized intraluminal suture model of focal cerebral ischemia (middle cerebral artery occlusion) in the rat, we have demonstrated that a hypernatremic state (serum Na⁺ 145 to 155 mEq/L; osmolality 310 to 320 mOsm/L) induced and maintained with continuous hypertonic saline infusion intravenously started at 2 hours of ischemia onset markedly worsened infarction volume compared with saline-treated controls.⁵ While the mechanism(s) of this deleterious effect is unclear, it was demonstrated that this was not due to unfavorable redistribution of regional cerebral blood flow during early reperfusion. Furthermore, in this study hypertonic saline did not cause neuronal or glial injury in naive nonischemic rats. Conversely, the effects of mannitol on ischemic stroke have yielded mixed results.⁶ Its neuroprotective effects in cerebral ischemia are attributed largely to its nonosmotic and rheological properties.⁶ However, our experimental study demonstrated a trend toward worsening of infarction volume with continuous intravenous mannitol infusion to achieve and maintain a target serum osmolality.⁵ It has been previously suggested⁶ that all these studies may have partial validity, and results are dependent on different experimental techniques and models used. In our opinion, the outcomes are largely dependent on the timing of onset, duration of treatment with osmotic agents, and integrity of the blood-brain barrier in relation to evolution and "maturation" of the ischemic lesion. Thus, while hypertonic saline may ameliorate elevated ICP over a short period of observation, its long-term effects (eg, "rebound" in ICP, stroke volume) remain largely unknown, especially in the cerebral ischemia paradigm. Until some of these important questions are answered with carefully performed experiments in appropriate animal models and with clinical trials, caution is advised in using hypertonic saline solutions in patients with ischemic stroke.

Wendy C. Ziai, MD
Marek A. Mirski, MD, PhD
Anish Bhardwaj, MD

Neurosciences Critical Care Division
Johns Hopkins University School of Medicine
Baltimore, Maryland

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Response

We appreciate the valid comments of the correspondents, which reinforce many of the points we made in our article.¹ We fully agree that large randomized trials are necessary to evaluate both the possible benefits and negative effects of hypertonic solutions such as hypertonic saline or mannitol in the treatment of intracranial hypertension. However, the points of criticism raised by Ziai et al miss the aim of our study. We did not attempt to evaluate the long-term effects of hypertonic saline or to compare different osmotic agents (which we did previously in a randomized study²). In this study we investigated the efficacy of hypertonic saline in patients with ischemic stroke with an acute intracranial pressure (ICP) crisis after conventional therapies, including mannitol, had failed, and our data clearly show that hypertonic saline can successfully be used in this life-threatening emergency situation. Of course, our criterion for ICP reduction to <10% of pretreatment values is arbitrary. Since no other criteria have been established yet, use of arbitrary criteria is the only way to perform this type of study. Of course, our patient population is not entirely homogeneous; in an intensive care unit setting, it is nearly impossible to establish a homogeneous patient population. This is also a critical point in a previous study on the use of hypertonic saline for brain edema by 2 of the correspondents, in which patients with traumatic brain injury, brain tumor, intracranial hemorrhage, and ischemic stroke were mixed.³ Although we certainly agree that a randomized trial would be desirable, we are doubtful that results from a “well-executed prospective, randomized, blinded trial” addressing the very specific question of our study will be available in the near future.

Stefan Schwarz, MD
Dimitrios Georgiadis, MD
Stefan Schwab, MD
Department of Neurology

Alfred Aschoff, MD
Department of Neurosurgery
University of Heidelberg
Heidelberg, Germany

- Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. *Stroke*. 2002;33:136–140.
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Laterality of Ruptured Aneurysm Has No Influence on QT Prolongation After Subarachnoid Hemorrhage

To the Editor:

We write in response to the recent interesting article of Hirashima et al, entitled “Right Sylvian Fissure Subarachnoid Hemorrhage Has Electrocardiographic Consequences.”¹ Although in this article the authors concluded that cardiac consequences are possible in patients with massive right sylvian fissure subarachnoid hemorrhage (SAH), we have some reservations about the methodology in this study, especially about the assessment of ECG.

The authors mentioned that 26 patients had changes on admission ECG [ECG(+) group], while 92 patients did not [ECG(−) group]. The inclusion criteria for the ECG(+) group in this study were any ECG changes on admission, including T-wave inversion, QT prolongation, or ST-segment elevation or depression. However, the authors did not quantitatively assess these ECG changes. In addition, it is unclear that T-wave inversion or ST-segment changes increase susceptibility to sudden death associated with SAH. On the other hand, QT prolongation is commonly believed to cause life-threatening ventricular arrhythmias such as torsades de pointes, thus leading to sudden death associated with SAH.^{2,3}

We herein assessed the corrected QT (QTc) intervals on admission in 57 SAH patients and 57 controls (age-matched hospitalized patients) to determine whether there was any difference on the basis of the laterality of ruptured aneurysm in their QTc intervals on the first days of SAH. The SAH patients who were included in our study were admitted within 24 hours after onset of SAH to the National Defense Medical College Hospital and had a ruptured aneurysm that was located in the anterior circulation, namely, right or left middle cerebral artery (MCA), right or left internal carotid artery (ICA), or anterior communicating artery (ACoA). These 5 subgroups of the SAH group were matched for patient age, Hunt and Kosnik grade, and Fisher’s classification for CT. The exclusion criteria in our study included heart disease, previous SAH or intracerebral hemorrhaging, a young age (<19 years), pregnancy, pacemaker rhythm, or use of the following drugs: digitalis, quinidine, procainamide, or disopyramide. Measurements of 12 leads of a standard ECG were done on the first days of SAH. Two consecutive QT intervals were manually measured in all 12 leads of a standard ECG with the assessor blinded to the name and group of the patient. The QT intervals were measured from the beginning of the QRS complex to the visual return of the T wave to the isoelectric line and were corrected for heart rate with the Bazett formula: $QTc = QT / \sqrt{\text{RR interval}}$. The mean QTc interval was calculated from all QTc intervals measured. The intraobserver coefficients of variation were 1.6%, and the interobserver coefficients of variation were 1.9%. All data were compared by Student’s *t* test or ANOVA with the post hoc test of Scheffé *F*.

The mean QTc interval of the SAH group was significantly longer (466 [SD 51] ms; $P < 0.0001$, Student’s *t* test) than that of the control group (395 [SD 24] ms). However, the individual subgroup comparison showed no significant difference on the basis of the laterality of the ruptured aneurysm in the mean QTc interval (right MCA: $n = 5$, 452 [SD 47]; right ICA: $n = 12$, 468 [SD 73]; ACoA: $n = 19$, 450 [SD 45]; left ICA: $n = 12$, 498 [SD 37]; left MCA: $n = 9$, 462 [SD 36] ms). In addition, there was no particular prolongation of QTc intervals in the 2 patients with right-sided massive sylvian hematoma.

These findings suggested that there was no difference on the basis of the laterality of the ruptured aneurysm in the degree of QT prolongation on the first days of SAH. However, the amount of SAH in each of the cisterns and fissures was not measured

quantitatively in our study, and therefore there are limitations to the conclusions that can be drawn. Further studies are required to assess whether there is any right-sided dominance in cardiovascular effects, especially QT prolongation, during the acute phase of SAH.

Shinji Fukui, MD
Naoki Otani, MD
Nobusuke Tsuzuki, MD, DMSc
Hiroshi Nawashiro, MD, DMSc
Katsuji Shima, MD, DMSc
Department of Neurosurgery
National Defense Medical College
Tokorozawa, Japan

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Response

We appreciate the interesting comments of Dr Fukui and colleagues regarding our recent article.¹ First, they did not measure the amount of subarachnoid hemorrhage (SAH) in each cistern and fissure, as they pointed out. Therefore, it is difficult to discuss our results according to their data, although their study is very interesting. They have reservations about the assessment of ECG in our study. We think that the changes of ECG by sympathetic cardiovascular effects at the acute stage of SAH include not only QT prolongation but also other findings such as T-wave inversion or ST-segment elevation or depression. We also calculated QTc in this study and defined QT prolongation as QTc >0.44 in men and QTc >0.46 in women. We evaluated the changes in ECG at admission and 1 month later. When abnormal findings disappeared on subsequent ECG, we defined them as abnormality due to SAH. Although they stressed quantitative assessment of ECG changes, they did not evaluate ECG 1 month later. Therefore, we have some apprehensions, such as that QT prolongation in their study is not always due to SAH. Systolic blood pressure >160 mm Hg and the amount of SAH in the right sylvian fissure on admission were independently associated with ECG changes due to sympathetic cardiovascular effects, and we suggested that these phenomena may be via the stimulation of the right insular cortex.

Yutaka Hirashima, MD
Nobuhisa Matsumura, MD
Masanori Kurimoto, MD
Shunro Endo, MD
Department of Neurosurgery
Shutaro Takashima, MD
Second Department of Internal Medicine
Hideki Origasa, PhD
Division of Biostatistics
Toyama Medical and Pharmaceutical University
Toyama, Japan

- Hirashima Y, Takashima S, Matsumura N, Kurimoto M, Origasa H, Endo S. Right sylvian fissure subarachnoid hemorrhage has electrocardiographic consequences. *Stroke*. 2001;32:2278–2281.

Ambulatory Carotid Stenting in Patients With Asymptomatic Carotid Artery Stenosis

To the Editor:

In a recent article by Al-Mubarak et al,¹ the authors claim to have demonstrated the feasibility and safety of performing

carotid angioplasty and stenting (CAS) as an ambulatory outpatient procedure. In our opinion, both the title of the article and the conclusion drawn by the authors are misleading and cannot be supported by the presented data.

Over a 2-year period, 341 carotid stenting procedures in 300 patients with extracranial carotid artery stenosis were performed at the authors' institution. They now report the results of a subgroup of these patients, consisting of those 92 patients (31%) who had successful CAS without complications, had a successful vascular access site hemostasis, were judged to be compliant, and had adequate care at home. On the basis of these 4 criteria, a same-day discharge was judged to be appropriate for all 92 patients of this subgroup, whereas hospitalization was required for the remaining 208 patients. No strokes, deaths, repeated procedures, or relevant access site complications occurred in the first group. However, no further information on the outcome of the latter is given.

As for the title of the article, the given data do not seem to provide any information on the true procedural safety of ambulatory CAS, since the absence of any early complication was the main inclusion criterion for the population described in the article. Moreover, it is not the short-term outcome after prospectively planned ambulatory CAS that is reported, but rather the outcome of a distinct subgroup of patients for whom an early discharge after CAS was judged feasible hours after the procedure was done. Thus, the reported data do not help to estimate the safety and risk of the procedure, nor can the true feasibility of CAS in an ambulatory setting be assessed.

By the therefore unjustified conclusion, that CAS can safely be performed even in an ambulatory setting, the general safety of the procedure in patients with extracranial carotid stenosis is implied. However, the data presented in the article are not sufficient to assess the periprocedural risk of CAS, nor do they add any new information regarding its still unproven efficacy in preventing stroke in patients with extracranial carotid stenosis compared with carotid endarterectomy (CEA). The conclusions that can be drawn from the reported data merely are that approximately 30% of patients might be safely discharged a few hours after CAS if the predefined criteria are applied and that the thereby selected subgroup seems to have a good short-term outcome.

In our opinion, the high rate (72%) of patients with asymptomatic carotid artery stenosis who were treated in this series is of particular concern. Although the authors present an impressive safety record with no neurological events or deaths occurring after 1 year, it is very unlikely that these results can be transferred to the current clinical practice. Since an asymptomatic carotid artery stenosis is associated with a comparatively low risk of stroke of only about 2% per annum,² a very low periprocedural risk is a crucial precondition for the long-term efficacy of any invasive therapy for stroke prevention. Unfortunately, as mentioned above, the current article does not present the actual rates of periprocedural complications for the complete population of 300 patients. Yet, a 30-day stroke and death rate of 7.4% is reported in another series from the same institution published in 2001, with symptomatic and asymptomatic patients having similar 30-day outcomes (8.2% versus 6.3%, respectively; $P=0.47$).³ In the International Stent Registry, Wholey et al⁴ reported a combined all-strokes-and-death rate of 3.4% within 30 days following CAS in 1361 asymptomatic patients. These numbers clearly exceed the complication rate of less than 3.0%, which is recommended by the American Heart Association as the upper limit for CEA in asymptomatic patients.⁵ Moreover, these data were collected in uncontrolled and mostly retrospective series, and even higher complication rates may be expected in a prospective controlled study in which neurologists take part in the follow-up investigations.

In addition, there are still no controlled data available that demonstrate any benefit of CAS in previously asymptomatic patients. The only completed randomized trial comparing CEA and CAS included mainly symptomatic patients (98%) and showed similar major risks and effectiveness for both procedures.⁶ How-

ever, the study yielded periprocedural stroke and death rates of about 10% in each group, which are considerably higher than those of previous large CEA trials in symptomatic patients on which treatment recommendations are based. A similar risk increase for CAS and CEA in asymptomatic patients would be devastating, leaving not the slightest chance of any benefit from both procedures. Since these results are likely representative of clinical practice, the benefit of both ambulatory and in-hospital CAS and of CEA for asymptomatic patients is at least questionable.

Until scientifically validated data from randomized trials demonstrate a lasting benefit of CAS in asymptomatic patients, a widespread use of either ambulatory or in-hospital carotid stenting should not be encouraged. Meanwhile, CAS should be restricted to experienced centers and to randomized patients in controlled trials.

Florian Masuhr, MD

Markus Busch, MD

*Department of Neurology
Charité Medical School
Humboldt University
Berlin, Germany*

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Is Ambulatory Carotid Stenting Safe? Too Early to Say

To the Editor:

We read with interest the recent article by Al-Mubarak et al.¹ We agree that ambulatory (same-day discharge) carotid stenting is a feasible option and note the admirable absence of neurological events and deaths in this group.

Same-day discharge has important cost implications. Carotid artery stenting has already been shown to be as safe and efficacious as carotid endarterectomy² and could prove a more attractive alternative if also more cost-effective. The use of vascular closure and neuroprotection devices does not add to the cost of the ambulatory group, as suggested in the editorial comment,³ as these devices, if employed, would be used in all carotid stent patients regardless of future discharge plans. Their cost, therefore, should not be used in a cost-analysis comparison between ambulatory and hospitalized carotid artery stenting patients.

We would, however, like to add a note of caution. Hemodynamic instability, particularly hypotension, may be a consequence of carotid artery stenting.⁴ It may be that this is a benign entity, but we feel that further evaluation of the timing of these disturbances and any consequent neurological complications is required before same-day discharge following carotid artery stenting can be confidently recommended.

Fiona McKeivitt, MRCP
*Royal Hallamshire Hospital
Sheffield, England*

Trevor Cleveland, FRCS, FRCR
*Northern General Hospital
Sheffield, England*

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Response

We appreciate the interest of McKeivitt and Cleveland. We agree that hemodynamic instabilities were of particular concern in undertaking the ambulatory approach for carotid artery stenting (CAS). The most important hemodynamic instability is sustained hypotension that occurs in the immediate postprocedural period and may last up to 24 hours.^{1–3} While “transient hypotension” and brady-arrhythmia are relatively common during balloon inflation, “sustained hypotension” occurred in 10% of the patients following CAS in our early experience.¹ In our recent experience, particularly since the application of vascular closure devices and early ambulation following the procedure, this phenomenon has become very rare.

Sustained hypotension can be explained on the basis of the carotid sinus reflex arc. The baroreceptor nerve terminals located at the outer muscle layer of the carotid sinus respond to stretch and deformation of the arterial wall by transmitting impulses that inhibit the vasoconstrictor regions in the medulla oblongata, resulting in vasodilatation and hypotension. Bradycardia resulting from stimulation of the vagal regions contributes to the development of hypotension. The self-expanding stent through increased pressure on the carotid sinus wall can lead to inappropriate activation of the baroreceptors. Plaque disruption caused by balloon predilation may also enhance the pressure transmission to the carotid sinus baroreceptor. As the stent conforms to the arterial wall, the baroreceptors adapt to the sustained stimulation, gradually terminating the hypotensive response. We believe that early patient ambulation after the procedure helps counteract this hypotensive effect and may explain the rare occurrence of sustained hypotension in our recent experience. Therefore, the ambulatory approach by virtue of the early ambulation results in a low incidence of hypotension following CAS.

Although some investigators have reported adverse clinical events,^{2,3} in our large experience these hemodynamic instabilities typically resolved without complications. Careful and constant hemodynamic surveillance of all patients in the first few hours following the procedure remains crucial for early recognition and management of hypotension, hence preventing adverse clinical sequelae. If sustained hypotension develops, the patient should be hospitalized and other possible etiologies such as bleeding, volume depletion, and cardiac pathologies must be considered and carefully excluded.

Nadim Al-Mubarak, MD
Gary S. Roubin, MD, PhD
Jiri J. Vitek, MD, PhD
Gishel New, MD, PhD
Sriram S. Iyer, MD

*The Lenox Hill Heart and Vascular Institute of New York
New York, New York*

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Drugs and Recovery: A Challenge for a Few?

To the Editor:

I read with great interest the recent article by Walker-Batson and colleagues,¹ in which the authors show that the administration of dextroamphetamine and speech/language therapy facilitated recovery from aphasia.

We also investigated the efficacy of high-dose bromocriptine, prescribed according to a dose-escalating protocol, combined with speech therapy in a double-blind study.² Patients showed a significant improvement in language (verbal latency, repetition, reading comprehension, dictation, and free speech) during treatment, yet we considered the study negative. The high frequency of contraindication to bromocriptine administration in the enrollment phase (44% of the aphasic patients) allowed us to treat only a small sample of patients. Moreover, we observed an elevated occurrence of side effects during the active phase of the drug.

Remarkably, none of the patients enrolled into the study of Walker-Batson et al had adverse reactions, and this makes the dextroamphetamine not only one of the most successful agents used in the treatment of aphasia but also the safest. Nevertheless, the small number of patients enrolled (n=25), in comparison with the relatively long study period (4 years) and the huge number of patients screened (n=850), confirms the necessity of being very selective before giving drugs that might enhance stroke recovery but also have serious side effects.

Therefore, we would like to stress that, even in presence of a relatively safe drug such as dextroamphetamine, to date the pharmacotherapy of stroke recovery remains a “luxury” that only few patients enjoy. This fact per se precludes studies from shifting focus from a condition of “explorative” studies to a wider condition.

Moreover, this strengthens the paradox that, despite the large number of stroke victims, we still have a small number of patients who might benefit by a specific treatment in both the acute and chronic phases.

Marta Altieri, MD
Vittorio Di Piero, PhD
Gian Luigi Lenzi, MD

Department of Neurological Sciences
University of Rome “La Sapienza”
Rome, Italy

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Response

While we agree with Drs Altieri, Di Piero, and Lenzi that the use of dextroamphetamine is not ready for wide acceptance as a standard of care for poststroke deficits, we disagree with their reasons. It is true that in our recently published study in aphasia we had specific exclusion criteria. We considered the exclusions necessary for an initial efficacy study of this type. However, the number of patients screened (n=850) compared with those enrolled (n=25) is fairly typical of stroke trials in general. The primary exclusion for the patients that we screened was history of a previous stroke with residual deficits. Those patients with radiological evidence of a previous stroke that was clinically silent were included in our sample. The second major exclusion for the patients we screened was aphasia so mild that subjects did not meet our inclusion definition. Included in our sample were many patients with medically complicated histories, ie, cardiovascular surgery, diabetes, and hypertension. In fact, the majority of the patients in our study had history of hypertension controlled by medication (>160/100 mm Hg). Thus, although admittedly small, our sample was special only in that it required a single stroke. The low-dose amphetamine (10 mg) that we administered was safe for a broad range of patients, a finding that we have previously reported (D.H. Unwin, MD, and D. Walker-Batson, PhD, unpublished data, 2000).

The reason that the use of dextroamphetamine is not ready for broad application is not that only a select group of patients can enjoy the effects. The reason that pharmacotherapy with the use of dextroamphetamine is not ready to become a standard of care is that there are still many gaps in our knowledge. Unanswered questions include the following: How long after stroke can amphetamine be administered and have an effect? What are the dosage and the number of drug administrations needed to provide optimum recovery? What is the amount of use-dependent practice or retraining that must be paired with the pharmacological intervention for optimal recovery? We are encouraged that ongoing trials (supported by the National Institutes of Health and the Medical Research Council of Canada) are exploring the efficacy of dextroamphetamine to enhance recovery from stroke. It is hoped that, in time, with collaborations between the basic science laboratory and clinicians, pharmacotherapy will become a standard of care for poststroke deficits.

Delaina Walker-Batson, PhD

The Stroke Center–Dallas
Texas Woman’s University
Department of Neurology

The University of Texas Southwestern Medical Center

Sandra Curtis, MS

The Stroke Center–Dallas
Texas Woman’s University

D. Hal Unwin, MD

Department of Neurology
The University of Texas Southwestern Medical Center
Dallas, Texas