Letters to the Editor

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What Causes the Acute Blood Pressure Elevation After Stroke?

To the Editor:

In an insightful editorial1 to a recently published paper by Mattle et al.,2 Lindsberg raises a central question as to why blood pressure increases in the acute phase of stroke. The Cushing reflex is suggested as a possible mechanism because it results in sympathetic nervous system activation; however, this reflex is typically described as occurring in the face of raised intracranial tension.3 The purpose of this letter is to suggest that the central nervous system (CNS) ischemic response may be responsible for the marked sympathoexcitation leading to marked blood pressure elevation in acute stroke. This reflex leads to marked activation of the sympathetic nervous system and serves to eventually optimize cerebral perfusion.3 Fundamentally, the Cushing reflex and the CNS ischemic response are the same in that they are both triggered by cerebral ischemia. Cushing reflex is a variant of the CNS ischemic response because raised intracranial tension diminishes blood flow to brain cells.3 Hypoxia has been demonstrated to excite vasomotor neurons raising sympathetic outflow to blood vessels.4 Although chemoreceptors typically are described as being located in the carotid and aortic bodies and in the brain stem, there is increasing evidence that all cells are capable of metering oxygen tension and eliciting appropriate responses to optimize the supply-demand relationship that is inextricably linked to homeostasis.5

E. Sankaranarayanan Prakash, MD
Madanmohan, MD
Department of Physiology
Jawaharlal Institute of Postgraduate Medical Education and Research
Pondicherry 605006, India.

Response:

I thank the authors Prakash and Madanmohan for an interesting remark. The physiological reason for immediate hypertension in acute stroke is intriguing. Although hypoxia, increase of intracranial pressure, and very low systemic arterial pressure are known to stimulate the cerebral ischemic response (CIR) by activating the neurons of the vasomotor center located within the ventrolateral medulla,6 occlusion of a single cerebral artery causes focal ischemia that generally does not rapidly induce any of these stimuli to the medullary vasomotor center. Experimental studies in animals related to cerebral ischemia and the CIR have used experimental setups that cause global cerebral ischemia or systemic hypoxia,1–3 which directly influence those medullary oxygen sensing neurons. Translation of results from experiments in anesthetized animals into the clinical situation in conscious humans may be tricky. Furthermore, acute stroke does not reproduce CIR in its entirety; what is missing are bradypnea and bradycardia as found in classical Cushing reaction. This supports that higher cerebral centers, probably those influencing the rostral parts of the reticular formation such as hypothalamus, cingulate or other cortices, stimulate the vasomotor center4 and produce CIR during focal cerebral ischemia only for its one component, hypertension. Clamping of one common carotid artery in anesthetized dogs causes only 6 to 10 mm Hg increase in blood pressure, which quickly normalizes after release of the clamp,2 and the same holds true for humans during carotid endarterectomy, indicating functioning carotid sinus baroreceptor reflex to the vasomotor center.5 This procedure does not normally cause significant cerebral ischemia. However, if in awake patients undergoing carotid endarterectomy blood pressure paradoxically falls even moderately to clearly nonhypotensive levels, and a sudden neurological deficit develops to indicate cerebral ischemia, the deficit is completely corrected by fast-acting hypertensive drugs.6 Therefore, the immediate hypertension after occlusion of a cerebral artery would indeed seem to serve a meaningful function for brain protection. I agree that it is the increased sympathetic vasomotor excitation that most likely transmits this obviously very important hemodynamic response.

Perttu J. Lindsberg, MD, PhD
Department of Neurology,
Helsinki University Central Hospital
Neuroscience Program
Biomedicum Helsinki
Helsinki, Finland


What Are High-Flow and Low-Flow Oxygen Delivery Systems?

To the Editor:

We read with interest the article, “A Pilot Study of Normobaric Oxygen Therapy in Acute Ischemic Stroke.”1 However, we have certain reservations with the terminology and the method of oxygen delivery used by the authors.

First, regarding the terminology of “high-flow” oxygen used by the authors, the authors mention the flow rates but not the oxygen delivery system used. An oxygen delivery system is a device used to administer, regulate, and supplement oxygen to a
subject to increase the arterial oxygenation. In general, the system entrains oxygen and air to prepare a fixed concentration required for administration. Oxygen delivery systems are generally classified as low-flow or variable-performance devices and high-flow or fixed-performance devices. Low-flow systems provide oxygen at flow rates that are lower than patients’ inspiratory demands; thus, when the total ventilation exceeds the capacity of the oxygen reservoir, room air is entrained. The final concentration of oxygen delivered depends on the ventilatory demands of the patient, the size of the oxygen reservoir, and the rate at which the reservoir is filled. At a constant flow, the larger the tidal volume, the lower the FiO₂ and vice versa. In contrast, the high-flow systems provide a constant FiO₂ by delivering the gas at flow rates that exceed the patient’s peak inspiratory flow rate and by using devices that entrain a fixed proportion of room air.

Second, the authors have also not mentioned how they gave oxygen at flow rates of 45 L/min. The standard flow meters are calibrated to flow rates of oxygen at 15 L/min, although if one turns the thumbscrew of the valve wide open, a much greater flow is delivered.

Also, there is a tendency to confuse flow systems with oxygen concentrations. However, both are mutually exclusive in that a high-flow system, viz. Venturi mask, can deliver FiO₂ as low as 0.24, whereas a low-flow system like a nonrebreather mask can deliver FiO₂ as high as 0.8. Thus, if the ventilatory demand of the patient is met completely by the system, then it is a high-flow system. In contrast, if the system fails to meet the ventilatory demand of the patient, then it is classified as a low-flow system.

Ritesh Agarwal, MD, DM
Dheeraj Gupta, MD, DM, FCCP
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research
Chandigarh, India


Response:
We thank Drs Agarwal and Gupta for giving us the opportunity to elaborate on our method of oxygen delivery. As stated in our article, we delivered humidified oxygen at flow rates of 45 L/min through a simple facemask. “High-flow” refers to the high flow rates of oxygen used in the trial. Because the peak inspiratory flow rate of a resting individual is typically below 30 L/min, delivering oxygen at higher flow rates (eg, 45 L/min) precludes contamination of oxygen within the facemask with room air, so that the effective FiO₂ is close to 1.0. The high flow rates were achieved by substituting the standard flowmeter (calibrated to 15 L/min) with a commercially available flowmeter that can deliver flow rates as high as 75 L/min (Timer Classic Series Flowmeter model O-75; Allied Healthcare Products, Inc.). This flow meter can only be attached to an oxygen wall outlet; therefore, during the short period of patient transport to the magnetic resonance imaging suite, we used the standard 0 to 15 L/min flow meter attached to oxygen cylinders and maximized oxygen delivery by fully opening the outflow valve and using a nonrebreather facemask (with this method, the effective FiO₂ is 0.8 to 0.9). Although we were able to achieve encouraging results using this simple methodology, we emphasize that further studies, in unselected stroke populations, are needed to establish the safety and efficacy of high-flow oxygen before it can be used as an acute stroke therapy.

Aneesh B. Singhal, MD
Stroke Service
Massachusetts General Hospital
Boston, Mass


Thromboprophylaxis in Stroke Patients
To the Editor:
The risk for venous thromboembolism (VTE) in medical patients, including those with stroke, is similar to that in moderate-risk surgery patients. In contrast to surgical patients, prevention of VTE has been less characterized in hospitalized medical patients because trials are generally limited in number and smaller in size. However, the rationale for thromboprophylaxis is based on solid principles and scientific evidence, including the high prevalence of VTE, the clinically silent nature of the disease, and the morbidity, costs, and potential mortality associated with unprevent ed thrombosis. Anticoagulants can significantly reduce the risk of VTE after stroke, but this benefit is offset by a small but definite risk of serious hemorrhages. Accordingly, there is good evidence that mechanical methods of prophylaxis (eg, graduated compression stockings, intermittent pneumatic compression, and venous foot pumps) are effective means for preventing VTE in several clinical settings, including medical patients, with little limitations and without any associated risk of bleeding. Therefore, the use of physical method of prophylaxis is currently considered an acceptable option, especially in patients at higher risk of bleeding, or when used in combination with anticoagulant prophylaxis to improve efficacy. Yet, the clinical staff must select the correct size of the device and must properly apply them to achieve definite advantages on prevention.

On this premise, we are rather surprised by the conclusions of the article of Grandi and colleagues, which recently appeared in this journal. After reviewing nearby 60 clinical investigations, the authors selected results of two trials to draw the conclusion that there is a lack of evidence on the balance of risk and benefit of these methods to prevent VTE in stroke. We agree with the first part of this statement because results on the efficacy of mechanical prophylaxis might be underestimated for the less intensive and reliable investigation when compared with anticoagulant-based options. However, we do not perceive the medical risk, besides discomfort, costs and resource utilization, of using such devices in stroke patients.

Current guidelines issued by the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy, recommend the use of mechanical methods of prophylaxis primarily in patients who are at high risk of bleeding. This might apply to stroke patients, where the contra-indication to anticoagulant therapy is rather frequent. Additionally, to our knowledge, physical methods have little limitations and no side effects. Therefore, although the influence of stocking use on outcomes is not definitely ascertained and the preventive benefit on VTE might be circumscribed to select medical setty, we find no clinical motivation to discourage the adoption of such a measure. In fact, we should consider that the relative low expenditure of some of these methods, especially the
graduated compression stockings, might be entirely outweighed by the considerable economical savings achievable from preventing episodes of VTE.

**Association Between SNP in Exon 28 of COL1A2 and Ultrastructural Connective Tissue Alterations in Skin Biopsies**

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Abnormal Morphology of the Dermal Connective Tissue (n=28)</th>
<th>Normal Morphology of the Dermal Connective Tissue (n=26)</th>
<th>Healthy Control Subjects (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG (%)</td>
<td>18 (64)</td>
<td>15 (58)</td>
<td>69 (56)</td>
</tr>
<tr>
<td>GC (%)</td>
<td>10 (36)</td>
<td>10 (38)</td>
<td>47 (37)</td>
</tr>
<tr>
<td>CC (%)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>9 (7)</td>
</tr>
</tbody>
</table>

Response:

To respond to the letter of Prof Lippi, we want to say that we performed a Cochrane Review in which our aim was to assess the effectiveness and the safety of physical methods in patients with a recent stroke. We have to consider that only unconfounded randomized controlled trials compared physical methods for prevention of DVT with control in which prophylaxis was started within 7 days at the onset of stroke. We found only 2 randomized trials in acute stroke, and they do not provide conclusive evidence on the balance of risk and benefit.

As you know, besides discomfort, compression stockings are not indicated in patients with a diabetic neuropathy or a sensory polyneuropathy. We know what current guidelines recommend, but if we consider the evidence-based medicine, we are not sure that compression stockings work, so we are waiting for CLOTS Trial results to review them and to arrive to a conclusive evidence.

**Collagen Morphology Is Not Associated With the Ala549Pro Polymorphism of the COL1A2 Gene**

To the Editor:

We read with interest the study by Yoneyama et al. concerning the genetics of intracranial aneurysms (IA). These authors found a significant association between IA and the collagen α2 (I) gene (COL1A2). Previously, they mapped a candidate locus for intracranial aneurysm to chromosome 7q11 and suggested the tropoelastin encoding gene (ELN) as a possible candidate. Mutations in ELN, however, were not identified. Moreover, the association between ELN and IA was not confirmed in a subsequent European study. The COL1A2 gene that was proposed as susceptible gene for IA subsequently is also located on chromosome 7q. However, it is separated from ELN by a considerable genetic distance of approximately 25 cM.

Yoneyama et al found a particularly strong association with the Ala549Pro encoding SNP in exon 28 of COL1A2 (rs42524). Synthetic collagen-related peptides for both alleles showed differences in thermal denaturation, which might suggest an altered stability of the collagen fibril. These findings suggest, according to the authors, that the functional SNP28 of COL1A2 has an impact on collagen structure with possible effects on the integrity vessel wall and proneness to IA formation. The presence of morphologic aberrations in the dermal collagen fibrils in patients with IA previously suggested that genes involved in the biosynthesis of collagen might be among the susceptibility genes for IA.

These findings motivated us to look for a possible association between the COL1A2 SNP28 (rs42524) and the presence of an abnormal ultrastructural morphology of collagen fibrils in a series of well-characterized skin biopsies from German patients with cervical artery dissections. We did not find such an association (Table), because the genotypes of rs42524 are similar in both groups (patients with abnormal connective tissue morphology vs patients with normal connective tissue morphology). Moreover, we did not find significant genetic differences between a series of 125 healthy control subjects and a larger sample of 98 consecutive patients with cervical artery dissections (skin biopsies were studied in 54 of these 98 patients). These findings suggest that the morphologic connective tissue abnormalities, that are typically found in patients with IA as well as in patients with cervical artery dissections, are not associated with the COL1A2 SNP28, at least not in a German sample of patients with cervical artery dissections. We, therefore, have difficulties believing that the Ala549Pro encoding SNP in exon 28 of COL1A2 has a significant impact on the rigidity or the elasticity of the vascular wall, because we do not find an association with collagen fibril morphology. The interesting results of the thermal denaturation of short-model peptides by Yoneyama et al are unlikely to explain the complex structural and functional features of in vivo collagen fibrils in human adults.


Response:

We gratefully acknowledge that Drs. Arnold, Grond-Ginsbach, Haussler, and Brandt have thoroughly read and made comments on the article researched and written at our institution.1

Regarding their comparison of patients with intracranial aneurysms (IA) with those with cervical artery dissection (CAD), we would like to remark that their findings and arguments are based on the examination of patients with CAD. To our knowledge, there have been a number of publications, also by the authors themselves,2 that cannot lead to a connection between mutations seen in patients with intracranial aneurysms and CAD, eg, as is the case in endoglin,3,4 and several matrix-metalloproteinase genes.5–7 Several publications have also shown the varying results of genetic research within different ethnic groups.8–11 Moreover, the 7 of 21 patients with IA presenting morphologic aberration in the dermal collagen fibrils, that Grond-Ginsbach et al refer to, were presumably of white origin and some of them harbored multiple aneurysms. The skin tissue of an affected patient could substantiate our suspicion of abnormal ultrastructural morphology. This group can hardly be compared with patients of German/white origin with CAD in the lack of comparative data.

We do agree with the authors that to what degree the amino acid substitution of Ala to Pro at 459 has an effect on human structures, especially the extracellular matrix, remains to be examined. Presumably, the altered protein function is so subtle that it does not show its detectable effect in skin. On the other hand, the authors described that even in patients with a PEDS type IV-like electron microscopic morphology, sequencing of the encoding region of the COL3A1 gene revealed no mutations.12 This could mean that in white patients with multiple aneurysms, the presence of ultrastructural skin aberrations similar to those seen in Ehlers-Danlos disease could be given. This does not conclude, however, that in Japanese patients with intracranial aneurysms, there is a similar abnormal ultrastructural morphology. This group can hardly be compared with patients of German/white origin with CAD in the lack of comparative data.

Regarding the ultrastructural change within the vessel wall of intracranial aneurysms, light and electron microscopy of the tissue of an affected patient could substantiate our suspicion of the collagen1A2 being responsible for the change in the extracellular matrix.

Boris Krischek, MD
Ituro Inoue, MD, PhD
Division of Genetic Diagnosis
Institute of Medical Science
University of Tokyo
Tokyo, Japan

Hidetoshi Kasuya, MD, PhD
Department of Neurosurgery
Neurological Institute
Tokyo Women’s Medical University
Tokyo, Japan

Impact of Surgical Treatment of Unruptured Aneurysms

To the Editor:

In the June 2004 issue of *Stroke*, Britz et al1 provide us with a clear example of misleading information and nonscientific analysis. The credibility and authority enjoyed by *Stroke*, combined with a craving for any possible enlightenment on the management of unruptured intracranial aneurysms, strengthen the impact of such a publication and justify the necessity to critically review this work.

I would like to rephrase the problem on which the authors focused:


My hypothesis is that physicians tend to offer a preventive but risky treatment to patients who are most likely to benefit. I believe this hypothesis to be reasonable; in fact, this is all that was shown by the study. If we are to retrospectively compare patients who underwent operation to those who were denied surgery for the same condition, we may end up dividing the population into 2 groups: patients that are likely to survive the intervention and that have a health status conducive to a life expectancy long enough to justify major surgery; and those exposed to higher surgical risk attributed to a more fragile health condition, with a lesser life expectancy.

The method used is a retrospective analysis of demographic and survival data. The results are: Group 2 patients, who were more often younger women (by 10 years), privately insured, with fewer comorbidities, survived at an improved rate as compared with Group 3 patients, older men, publicly insured, with more comorbidities. Since the logic behind this study is circular, the fact that the results confirm the hypothesis is fortunate. The data are empirical but only confirms that in Washington between 1987 and 2001 younger, healthier females would have a longer life expectancy than older, sicker men. But this does not tell us anything about aneurysms.

Somewhat more informative is the high mortality of surgical clipping, as compared with previously published rates,2,3 a common finding when one compares published data with the “real world,” as acknowledged in the text. Given this, it would then seem surprising that the authors conclude that this study supports early surgical management of unruptured aneurysms. The data, invalid from a scientific perspective, collected in a retrospective fashion, with all the potential errors well known to clinical investigators, is interpreted in favor of the biased opinions of the authors: the increased mortality following surgical clipping of unruptured aneurysms, as compared with an estimate of a corresponding population without aneurysms, “must” be related to an unrecognized comorbid state. The alternate hypothesis, that increased mortality is caused by surgery itself, seems so obviously wrong in the eyes of the authors that it is not even mentioned. On the other hand, decreased mortality in the surgical group, as compared with unoperated patients, “must” be credited to surgery. The fact that the 30-day mortality of untreated unruptured aneurysms was extraordinary (7.6%, while annual rupture rates are between 0.05 and 2%), and higher than the surgical mortality (5.5%), should be sufficient to show the flawed nature of the methodology, and raise the suspicion that the data has nothing to do with aneurysms.

There are many other methodological concerns with this work, such as the inclusion of code ICD-9 437.3 (unruptured aneurysm) as an “event” included in neurological causes of death (another example of circular logic), as well as other codes related to dementia, multiple sclerosis, Parkinson disease and carotid stenosis etc. These are errors committed by the authors, masked by undefined codes, and while they may give indications as to why patients had imaging studies, during which an unruptured aneurysm was found, these inclusions as “neurological-related causes of death”, falsely suggest to readers a causal relationship between mortality and treatment (or not) of the unruptured aneurysm.

Most importantly, works such as this, suffering from systematic errors in study design, comfort our biased opinions and have the potential to contribute to the resistance to clinical trials in this field. We must have the strength to acknowledge our doubts and a strong determination to distinguish desires, beliefs, and facts. There is still no definite scientific evidence to support the surgical or endovascular management of unruptured aneurysms.

Nothing short of rigorous scientific methods could give us valid insight to the crucial question: “Should we treat unruptured aneurysms?”

Phenytoin and Cognitive Decline

To the Editor:

We read with great interest the article by Naidech et al1 on the association of phenytoin exposure and cognitive disability after subarachnoid hemorrhage. The authors speculate on a number of reasons for this association, to which we would like to add the possibility of a pharmacokinetic interaction compromising the protective effects of nimodipine.

Phenytoin induces the hepatic microsomal enzyme system (cytochrome P-450 isozymes). Induction of the CYP isozyme system may begin within 48 hours of phenytoin administration.2 Nimodipine is a high extraction ratio drug and undergoes extensive first-pass metabolism in both the intestinal wall and liver. The oral bioavailability of nimodipine is less than 13%. The metabolism of nimodipine is mediated primarily by cytochrome P-450 (CYP 3A4). Indeed, it is reasonable to speculate that a pharmacokinetic interaction may exist between these 2 agents that may result in reduced efficacy of nimodipine.

A study evaluating nimodipine pharmacokinetics in a group of epileptic patients found that comedication with the CYP inducers phenytoin or carbamazepine resulted in a decrease of the area under the concentration time curve (AUC) of nimodipine of approximately 85%.3 In other words, treatment with an inducing antiepileptic drug such as phenytoin significantly reduces nimodipine bioavailability. In this same trial, patients receiving concomitant valproic acid (an antiepileptic drug that does not induce CYP 3A4) did not result in a reduction in nimodipine AUC. The clinical implications of this are that nimodipine oral doses may need to be substantially increased to compensate for this reduced bioavailability.

Vasospasm and infarction are predictors of cognitive outcome after subarachnoid hemorrhage.4,5 Any protective effect conferred by nimodipine in this setting6 may therefore have been mitigated by the coadministration of phenytoin.
Letters to the Editor

Recovery From Aphasia After Decompressive Surgery in Patients With Dominant Hemispheric Infarction

To the Editor:

The stroke patients with space occupying supratentorial lesions have poor prognosis. Despite the treatment procedures, the mortality of such patients is up to 80%, and the survivors usually have severe morbidity such as aphasia. In recent years, decompressive surgery was used for the treatment of space occupying supratentorial infarctions. 

Kastrau et al reported recovery from aphasia in 13 of 14 patients with large hemispheric infarctions after decompressive surgery. However, the study was performed by a neurolinguistic center, and the patients were first evaluated 538 days (ranges 105 to 1207 days) after the decompressive surgery, then the recovery from aphasia was determined within the following period. Same authors also reported that most of the recovery from aphasia occurs within the early period after the event. In our hospital (University of Trakya, School of Medicine), 29 patients underwent decompressive craniectomy between August 1999 and December 2003, 8 of the patients who survived had dominant hemispheric infarction, and all had recovery from aphasia within the six-month period after the event. Initial neurological examination of the 8 patients revealed global aphasia. Six months after surgery, 5 of the patients had Broca aphasia and the remaining 3 patients had slight recovery from global aphasia. We think that evaluating recovery from aphasia may have great value if performed in the early stages after stroke.

The authors reported that the contralateral activation in homologous areas of speech processing and the perilesional activation in the ipsilateral speech areas may have value for recovery from aphasia, and we also have the same opinion about the improvement process.

Age was reported the most valuable parameter for recovery from aphasia by Kastrau et al, but the mean age of the elderly patients was 43.9±5.2 years. Although the mean age of our patients (53.7±7.5 years) was older than Kastrau’s patients, evident recovery from aphasia was observed in our patients after six months.

Although the study of Kastrau et al is the first study about the recovery from aphasia after decompressive surgery, a study that also evaluates the other factors affecting cerebral perfusion (eg, the duration from the event to the surgery, stroke severity at the time of surgery, and the discovery of herniation) may have more value.

Andrew M. Naidech, MD, MSPH
Northwestern University Medical School
Chicago, Ill


Response:

We thank Drs Lock and Gidal for their insightful comments and agree that inhibition of nimodipine may be another potential mechanism for phenytoin’s association with poor outcome after subarachnoid hemorrhage (SAH). Unfortunately, nimodipine levels are not routinely available. This may be a subject for further study.

Because cerebral infarction is hardly the only predictor of poor outcome after SAH, decreased effectiveness of nimodipine is unlikely to be the only culprit. Fever, physiological derangement, pneumonia, and hyperglycemia all require neurologic critical care management and impact outcomes.

Andrew M. Naidech, MD, MSPH
Northwestern University Medical School
Chicago, Ill

What Are High-Flow and Low-Flow Oxygen Delivery Systems?
Ritesh Agarwal and Dheeraj Gupta

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