Failure of Standards in Reporting the Composition of Artificial Cerebral Spinal Fluid in Studies of the Pial Blood Vessels

To the Editor:

Reproducible experimental results require the replication of the experimental conditions under which the experiment was first performed. Relevance to humans may depend on the degree to which those conditions resembled those to which humans are exposed. With respect to studies of vascular reactivity, a most important parameter is the composition of the fluid bathing the vessel. For vessels on the brains surface, so-called pial vessels, this fluid is the cerebrospinal fluid (CSF). Experiments studying these vessels, in vivo or in vitro, generally bathe the vessels in an artificial CSF, sometimes called a “mock” CSF, or some other fluid, sometimes called a physiological salt solution and sometimes simply a buffered solution. A question that should immediately arise, if relevance to humans is an issue, is whether the fluid used has the composition of cerebrospinal fluid, and if not, is it the composition of the experimental species’ CSF or of human CSF. At present there is no data to tell us whether or not it would be better to always replicate the composition of human CSF, even if this differs from that of the animal in use, or whether, instead, the mock CSF should resemble that of the animal itself. CSF contains urea, but not everyone adds urea to the artificial CSF, and there are no studies showing the effect of the urea on the vascular responses. Indeed there is virtually no information on the effect of altering one or more aspects of CSF composition, other than pH and changing the concentration of one ion or another so that it is clearly out of mammalian physiological range. Moreover, recent studies show that under some circumstances, when a mock CSF flows over the pial surface in a continual suffusion, some vascular responses may be dramatically altered because essential substances, not thought of as part of CSF but in the tissue and its extracellular space, may be washed away. In the absence of the requisite studies, this letter will not address the question of “which formulation of mock CSF is better—human or animal?” Nor will it address the importance, or lack thereof, of the addition of urea or of the presence or absence of continuous rapid suffusion. It will, however, direct itself to the most basic requisite for a scientific presentation—the need to describe the fluid one is using so others may replicate your experimental conditions.

Unfortunately, with respect to studies concerning cerebrovascular reactivity in vivo, our leading journals and, presumably, reviewers, and authors have been delinquent in meeting a reasonable standard for the publication of in vivo studies of pial blood vessels, a standard that is almost always met when other vessels and/or in vitro studies are the subject of the reports, and a standard that is frequently violated for pial vessels even when it is met for other vascular beds in the very same journal. It is hoped that these remarks will lead to correction of that situation.

William I. Rosenblum, MD
Department of Pathology
Medical College of Virginia
at Virginia Commonwealth University
Richmond, Virginia

Lipoprotein(a) and the Risk of Stroke

To the Editor:

Despite a number case-control studies in the literature suggesting that lipoprotein(a) is a risk factor for cerebrovascular disease, both the recent article by Glader et al and the report from the Physicians Health Study by Ridker et al failed to demonstrate an association of lipoprotein(a) and the future risk of stroke. One possible explanation discussed by Glader et al is the paucity of young stroke patients in their study population. Nagayama et al had previously reported significantly higher lipoprotein(a) levels in patients under age 45 years with athero-sclerotic stroke. In the Stroke Prevention in Young Women Study, we4 examined the role of lipoprotein(a) in a population-based study of women under the age of 45 years with ischemic stril of a both stroke and multivariate analyses, we found no significant difference in lipoprotein(a) levels between cases and age-matched controls. Even among the subset of patients with atherosclerotic stroke, we could not demonstrate an association...
with elevated lipoprotein(a) levels. The number of patients in our study with atherosclerotic stroke was small (n = 15), however, but comparable to that of Nagayama et al (n = 11).

The structure of lipoprotein(a) and its potential link to both atherosclerosis and hypercoagulability is an intriguing hypothesis, but at this time the epidemiologic basis for a relationship of lipoprotein(a) and stroke remains uncertain.

Robert J. Wityk, MD
Department of Neurology
Johns Hopkins Hospital
Baltimore, Maryland

Steven Kittner, MD
Department of Neurology
and Department of Epidemiology and Preventive Medicine
University of Maryland at Baltimore
Baltimore, Maryland

Steven Kittner, MD
Department of Epidemiology and Preventive Medicine
University of Maryland at Baltimore
Geriatrics Research, Education, and Clinical Center
Baltimore Department of Veterans Affairs Medical Center
Baltimore, Maryland


Intrathecal Sodium Nitroprusside Improves Cerebral Blood Flow and Oxygenation in Refractory Cerebral Vasospasm and Ischemia in Humans

To the Editor:

With great interest we read the article by Thomas et al recently published in Stroke. The authors proposed the intrathecal administration of the nitric oxide donor sodium nitroprusside (SNP) as a novel means to treat refractory cerebral vasospasm. However, although amelioration or even reversal of large cerebral vessel constriction was shown by cerebral angiography, the article failed to provide data on the acute and long-term effect of SNP on cerebral vasospasm-associated ischemia and hypoxia. Therefore, in addition to their report, we here show the effect of intrathecal SNP on episodes of severely reduced cerebral blood flow and brain tissue oxygenation in a patient suffering from refractory cerebral vasospasm.

Multimodality Neuromonitoring During Intrathecal Treatment With SNP

<table>
<thead>
<tr>
<th></th>
<th>MABP, mm Hg</th>
<th>ICP, mm Hg</th>
<th>CPP, mm Hg</th>
<th>rCBF, mL/100 g/min</th>
<th>ptiO2, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>During HHH therapy</td>
<td>141</td>
<td>16</td>
<td>125</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Before delivery of 20 mg SNP*</td>
<td>111</td>
<td>15</td>
<td>96</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>30 min after 20 mg SNP ICV</td>
<td>102</td>
<td>21</td>
<td>82</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>3 h after 20 mg SNP ICV†</td>
<td>107</td>
<td>13</td>
<td>94</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>30 min after additional 16 mg SNP ICV</td>
<td>97</td>
<td>12</td>
<td>85</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>24 h after additional 16 mg SNP ICV</td>
<td>103</td>
<td>15</td>
<td>88</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>48 h after additional 16 mg SNP ICV</td>
<td>106</td>
<td>23</td>
<td>83</td>
<td>17</td>
<td>23</td>
</tr>
</tbody>
</table>

All parameters were sampled continuously at the bedside at 1 Hz. For each time point represented, the values were averaged over 50 seconds. Severe ischemia and hypoxia were defined as rCBF < 6 mL/100 g/min and ptiO2 < 10 mm Hg. ICV indicates intracerebroventricular administration.

*After discontinuation of HHH therapy; †prior delivery of additional 16 mg SNP.
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Peter Vajkoczy, MD
Ulrich Hubner, Dr Ing
Peter Horn, MD
Christian Bauhuf, MD
Claudius Thome, MD
Lothar Schilling, MD
Peter Schmiedek, MD
Department of Neurosurgery
Michael Quintel, MD
Department of Anesthesiology
Klinikum Mannheim
University of Heidelberg
Mannheim, Germany


Response

Dr Vajkoczy and colleagues present an intriguing observation that appears to have been beneficial to the patient. Although we are cautious in interpreting these limited experiences in terms of efficacy, these results corroborate our clinical experience with intrathecal SNP in several ways. (1) As illustrated in our recent article1 referenced by these authors, improvement in CBF6 was suggested by acceleration of cerebral circulation time at the same MABP and ICP. This sometimes occurred without a dramatic change in the caliber of cerebral conductance vessels and was interpreted by us as evidence of dilated collateral circulation below the level of angiographic resolution. The same inference, ie, increased regional cerebral blood flow, applies to the enhanced angiographic blush observed in treated patients (Figure 1). (2) MAB remained relatively stable, and ICP remained within normal range. (3) The improvement in measured parameters was accompanied by clinical improvement, suggesting minimal or no neurotoxicity. Indeed our most recent experience with treating patients by this method in the intensive care unit without angiography has been noteworthy for several episodes of profound and rapid neurological improvement within several hours of treatment, sometimes without a clear relationship to the vessels deemed constricted by transcranial Doppler (J. Thomas et al, unpublished observations). Such observations also suggest an effect at the level of collateral circulation. (4) The effect of the first treatment by these authors was transient, and vasospasm returned, supporting the hypothesis that it is indeed a substrate-dependent phenomenon that is liable to recur until the substrate (oxyhemoglobin[1]) is exhausted.2

It is also interesting that the reported patient was initially treated with intra-arterial papaverine, the effect of which was not lasting. This has also been our experience with papaverine. Finally, a caveat regarding conclusions drawn from relatively few patients is in order. Our purpose in the referenced article was to emphasize the apparent safety of intrathecal SNP in initial trials, and not its efficacy. It does appear that the treatment may be efficacious in some patients, even dramatically so, but we have seen two patients whose established vasospasm has not responded to this treatment, and the reasons for this are still unclear. Several points are worth mentioning in this regard. (1) Dosage must be scrupulously controlled to avoid hypotension, but nitric oxide may be rapidly absorbed by the hemoglobin in the subarachnoid clot, thereby making elevated dosage not only possible but necessary. This problem of a hemoglobin “sink” might theoretically be aggravated by intraventricular hemorrhage if the preparation is being administered intraventricularly. (2) The relatively slow rate of infusion of very small volumes of SNP makes photo-inactivation of the compound a very serious threat. For this reason even the smallest gap in light protection (foil wrap) must be avoided. This risk cannot be overemphasized. (3) It has been our experience that if vasospasm severity exceeds a certain threshold, it may be impossible to reverse with this treatment. For this reason we begin treatment immediately after treatment. Several additional treatments were required in the intensive care unit over several days. The patient made a full neurological recovery and has returned to work as a computer systems analyst.

Figure 1. Left ICA AP cerebral angiogram of a 40-year-old man presenting with delayed neurological deficit after aneurysmal subarachnoid hemorrhage. The patient developed dysphasia and right hemiparesis. The most pronounced angiographic effect was not dramatic dilation of constricted large conductance vessels, but of small collaterals resulting in enhanced angiographic blush (arrows) and decreased cerebral circulation time (indicated in figure). Blood pressure and ICP were unaffected by treatment. A, before treatment; B, immediately after treatment. Several additional treatments were required in the intensive care unit over several days. The patient made a full neurological recovery and has returned to work as a computer systems analyst.
Letters to the Editor

The Relative Contributions of the Anterior and Posterior Circulations to Global Cerebral Blood Flow

To the Editor:

We read with interest the report by Scheel and colleagues1 of the duplex ultrasound derived volumetric flows of the anterior and posterior components of the cerebral circulation published in Stroke. In discussing their main finding that the anterior circulation contributes 76% and the posterior circulation 24% to the total global cerebral blood flow, we would like to point out that these contributions are not definitive and require further validation and monitoring of pharmacological and endovascular therapeutics for stroke.

We published a report in 19952 of our findings from a similar investigation in a series of 21 healthy adults describing the relative flow contributions of the anterior and posterior circulation to the total global cerebral blood flow. We found that the anterior and posterior circulations contributed 82% and 18%, respectively, to total global cerebral blood flow, which is in close agreement with the findings of Scheel and colleagues. We also noted that these relative flow contributions were independent of gender and in precise concordance with the expected blood flow distribution based on the differences in the measured internal lumen diameters of the internal carotid arteries and vertebral arteries. The absolute values, however, for the volumetric flow rates differed between the 2 studies, with our reported values uniformly lower by about 40%, despite the use in both studies of a similar time-averaged velocity calculation throughout the cardiac cycle of all particles within the sample volume overlaying the entire lumen. Our report discussed the numerous potential causes and sources of systematic error, and such considerations in combination with the lack of a gold standard by which to determine absolute or actual flow suggests to us that duplex-derived direct flow measurements be used as indices of flow magnitude rather than true determinations of actual flow. We agree with the authors that a reliable, noninvasive index of regioselective blood flow could provide clinically relevant information to benefit patients in the intensive care unit. Improvements in the understanding and measurement of all components of the cerebral circulation should particularly improve validation and monitoring of pharmacological and endovascular therapeutics for stroke.

Robert A. Boyajian, MS, MD
Division of Neurology
Department of Medicine

Shirley M. Otis, MD
Department of Medicine
Division of Neurology
Vascular Laboratory
Scripps Clinic
La Jolla, California

References


Jeffrey E. Thomas, MD
Division of Cerebrovascular Surgery and Interventional Neuroradiology, Department of Neurological Surgery
Thomas Jefferson University and Wills Neurosensory Institute
Philadelphia, Pennsylvania


Figure 2. Electron microscopic appearance of rat cerebral cortex 7 days after intraparenchymal and intraventricular administration of SNP in concentration identical to that in human patients (4.0 mg/mL). The ultrastructural architecture is preserved; synaptic vesicle and cell membranes are intact (Erol Veznedaroglu, MD, unpublished data). Magnification ×30 000.
Response

We regret that the publication of Boyajian et al1 escaped our notice—just as the paper we published a year2 before that apparently eluded theirs. In 1994 we first reported on global cerebral blood flow volume examinations in 48 healthy adults (mean age 35±12 years), where we found a mean contribution of 76% by the anterior and of 24% by the posterior circulation. Global cerebral blood flow volume was 701±104 mL/min, corresponding to a cerebral blood flow of 50–54 mL/100 g/min (assuming a mean adult brain weight of 1300–1400 g). In a study on children and adolescents,3 the mean contribution of the posterior circulation to global cerebral blood flow volume declined significantly from 31% at the age of 4 years to 24% at the age of 18 years. During the same period, cerebral blood flow volume decreased significantly (3–9.9 years, 821±116 mL/min; 10–18 years, 727±106 mL/min).

In a recent interobserver study,4 the reproducibility of global cerebral blood flow volume measurement was shown to be comparable to that of global cerebral blood flow measured with 15O-labeled water positron emission tomography. In this study, the ratio of anterior to posterior circulation flow volumes was already estimated to be 76% to 24% by both examiners.5 In the article discussed here,6 the mean contribution of the posterior circulation to cerebral blood flow volume remained constant (24%) from 20 to 85 years of age, whereas global cerebral blood flow volume decreased from 730±87 mL/min (age group 20–39 years) to 603±106 mL/min (age group 60–85 years).

The flow volumes measured by Boyajian et al in the internal carotid arteries on both sides (147 and 143 mL/min, respectively) and in the vertebral arteries (34 and 32 mL/min, respectively) of healthy young adults are much lower than those found by our group.2,5,6 They add up to a mean global cerebral blood flow volume of 356 mL/min, which would correspond to a very low global cerebral blood flow of 25–27 mL/100 g/min. Most publications on normal cerebral blood flow in healthy adults, however, report reference data of ~50 mL/100 g/min.7 We can explain this difference only with a systematic error of flow volume measurement. In contrast to Boyajian and Otis, we are convinced that cerebral blood flow volume can be measured quantitatively, as long as a meticulous examination technique is observed. In a first attempt to pave the way for using this method in clinical routine, we studied cerebral blood flow volume in patients with vascular dementia, where a marked decrease of cerebral blood flow volume was found.8 At present we are in the process of establishing bedside cerebral blood flow volume monitoring in neurointensive care patients. We would like to encourage neurologists, child neurologists, and neurosurgeons to learn and apply this technique, because we firmly believe in the great potential benefits of the clinical and scientific application of this method.

Martin Schöning, MD
Peter Scheel, MD
Department of Child Neurology
Children’s Hospital of the University of Tübingen
Tübingen, Germany

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William I. Rosenblum

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