David S. Warner, M.D., Editor

Baseline Cerebral Metabolic Rate Is a Critical Determinant of the Cerebral Vasodilating Potency of Volatile Anesthetic Agents

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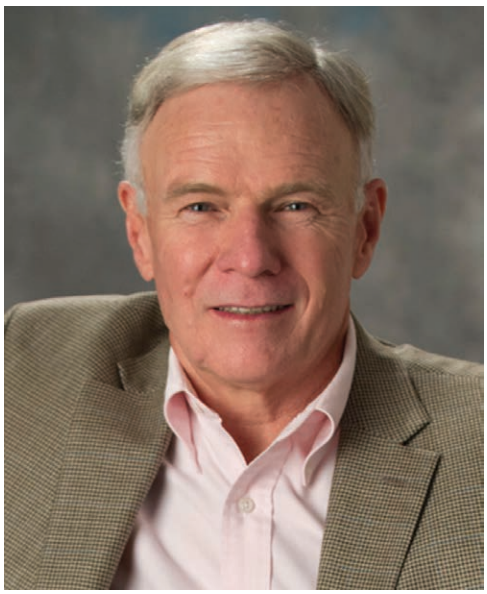
A Comparison of the Direct Cerebral Vasodilating Potencies of Halothane and Isoflurane in the New Zealand White Rabbit. By Drummond JC, Todd MM, Scheller MS, and Shapiro HM. Anesthesiology 1986; 65:462–7. Reprinted with permission.

Abstract: Halothane is commonly viewed as a more potent cerebral vasodilator than isoflurane. It was speculated that the lesser vasodilation caused by isoflurane might be the result of the greater reduction in cerebral metabolic rate (CMR) that it causes, and that the relative vasodilating potencies of halothane and isoflurane would be similar if the two agents were administered in a situation that precluded volatile-agent–induced depression of CMR. To test this hypothesis, cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen ($CMRO_2$) were measured in two groups of rabbits before and after the administration of 0.75 MAC halothane or isoflurane. One group received a background anesthetic of morphine and N_2O, which resulted in an initial $CMRO_2$ of 3.21 ± 0.17 (SEM) ml · 100 g^{-1} · min^{-1}; second group received a background anesthetic of high-dose pentobarbital, which resulted in an initial $CMRO_2$ of 1.76 ± 0.16 ml · 100 g^{-1} · min^{-1}. In rabbits receiving a background of morphine sulfate/N_2O, halothane resulted in a significantly greater CBF (65 ± 10 ml · 100 g^{-1} · min^{-1}) than did isoflurane (40 ± 5 ml · 100 g^{-1} · min^{-1}). Both agents caused a reduction in $CMRO_2$, but $CMRO_2$ was significantly less during isoflurane administration. By contrast, with a background of pentobarbital anesthesia, CBF increased by significant and similar amounts with both halothane and isoflurane. With halothane, CBF increased from 22 ± 2 ml · 100 g^{-1} · min^{-1} in the control stage to 39 ± 3, and with isoflurane from 24 ± to 38 ± 2 ml · 100 g^{-1} · min^{-1}. $CMRO_2$ was not depressed further by either halothane or isoflurane. These results suggest that the relative effects of halothane and isoflurane on CBF are dependent on the CMR present prior to their administration. When the preexistent CMR is not markedly depressed, isoflurane decreases CMR and causes less cerebral vasodilation than does halothane. When initial CMR is depressed, halothane and isoflurane have similar vasodilating potencies.

IN 1984, I learned from Robert F. Bedford, M.D., then at the University of Virginia (Charlottesville, Virginia), of a clinical investigation he and colleagues had performed on the use of isoflurane in patients with intracranial mass lesions. Before that time, and before the availability of isoflurane, anesthesiologists had generally been leery of the use of volatile agents, particularly halothane, in patients with or at risk for raised intracranial pressure. However, isoflurane in concentrations up to 1.0 minimum alveolar concentration (MAC) had been reported to have minimal effect on cerebral blood flow, and it was therefore anticipated that it could be administered without adverse effects on intracranial pressure (ICP).[1,2] But, in Dr. Bedford's investigation (eventually



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published as Grosslight *et al.*[3]), it appeared that many of the patients had not "read the memo," and sustained substantial increases in ICP in response to 1.0 MAC of isoflurane.

At that time, I was working with Michael M. Todd, M.D., at the University of California, San Diego, in Harvey M. Shapiro, M.D.'s laboratory. I owe a great deal to both of them, but it is in particular to Dr. Todd, who was my shoulder-to-shoulder compatriot during much of the 1980s, that I owe the most for my development in the neuroanesthesia "biz." We three, along with Mark S. Scheller, M.D., surmised that the net effect of volatile agents on cerebral blood flow was the sum of a direct vasodilatory effect plus an indirect effect of anesthetic-induced reduction in cerebral metabolic rate, acting *via* the coupling of cerebral metabolic rate and cerebral blood flow. We knew that the cerebral metabolic rate reduction caused by isoflurane was greater than that caused by other agents, specifically halothane. However, it seemed intuitively likely that all of the volatile agents would have similar direct cerebral–vascular smooth muscle relaxing effects, and that the final differences on cerebral blood flow might be a function of differing reductions in cerebral metabolic rate.

It is probable that other people, perhaps many, had also entertained this idea, but a confirmatory study was in order. The method was straightforward. We measured the cerebral blood flow response to 0.75 MAC of halothane and isoflurane, first against a background nitrous oxide–narcotic anesthetic, which causes minimal reduction of cerebral metabolic rate, and then against a background of pentobarbital, titrated to deep electroencephalographic burst suppression, which entails a substantial reduction of cerebral metabolic rate. The results were consistent with the prediction. Against the nitrous oxide–morphine background, isoflurane reduced the cerebral metabolic rate for oxygen much more than halothane did, and was associated with less (actually, no) cerebral blood flow augmenting effect. But against background major cerebral metabolic rate suppression by pentobarbital, isoflurane and halothane had identical (and substantial) cerebral blood flow augmenting effects (fig. 1).[4]

Were I to have the opportunity to repeat the study these 30 yr later, I doubt that I would do it very differently. What would be different are the title of the paper and the figure. In fact, there was no figure in our 1986 paper! A graphic depiction would have made the message much easier to grasp (fig. 1). With respect to the title, I erred again. It is now the fashion with the title to ballyhoo the results of the investigation with a tabloid style statement or a provocative question. A well-chosen title captures more readers on the first pass and more MEDLINE searchers on later occasions. It should have been, "The Critical Role of Cerebral Blood Flow: Cerebral Metabolic Rate Coupling in Determining the Effect of Volatile Agents on Cerebral Blood Flow," or something similar. I suspect that as a result of those deficiencies, many clinicians also did not "get the memo." The residents I deal with regularly recite the line, "sub-MAC concentrations of

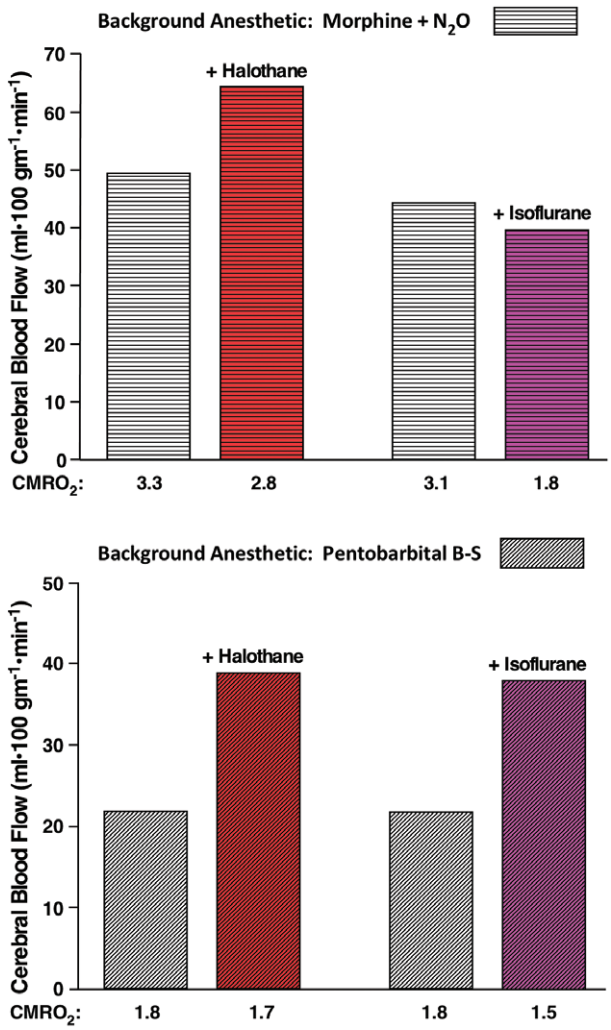

Fig 1. The effect on cerebral blood flow and cerebral metabolic rate for oxygen (ml of oxygen consumed per 100 g of brain per min) of 0.75 minimum alveolar concentration of halothane (*red*) and isoflurane (*magenta*) when superimposed on a background anesthetic of morphine and nitrous oxide (*top*) or pentobarbital (*bottom*), with the latter administered in sufficient dose to achieve deep electroencephalographic burst suppression. B-S = burst suppression; $CMRO_2$= cerebral metabolic rate for oxygen.

contemporary volatile agents do not increase CBF [cerebral blood flow]". What I see some of my faculty colleagues doing reflects the same belief and, on numerous occasions, I presented American Board of Anesthesiology oral exam candidates with hypothetical brain herniating into the surgical field, but could not, by any matter of begging, persuade them to discontinue the isoflurane. (I have no idea where the idea that isoflurane is the preferred volatile agent for neuroanesthesia obtained its currency, but isoflurane was always the agent of choice.)

There are, of course, factors other than cerebral blood flow that might contribute to the effects of a volatile agent on ICP, most notably effects on cerebral blood volume, some of which may occur independent of effects on cerebral

blood flow. However, when confronted with a patient in whom intracranial compliance is exhausted (and, yes, I know that "elastance" is the correct term in this context), and in whom cerebral metabolic rate may already have been suppressed by either disease processes or the drugs used to treat them, or in whom pathology may have interfered with the physiology of cerebral blood flow–cerebral metabolic rate coupling, it still seems prudent to this clinician to avoid volatile agents—at least until the cranium is open and the effect on the brain can be observed directly. I acknowledge that the admonition about impaired coupling is not entirely straightforward. We are not sure how coupling works in the first place; *ergo*, it is inevitably uncertain just which physiologic disturbances will render it unreliable. But in the face of known cerebral metabolic rate suppression and/or possible disruption of coupling, volatile agents should be viewed as potentially much more potent cerebral vasodilators than is the case in physiologically and metabolically normal brain.

Why revisit 30-yr-old physiology? Perhaps because a recent publication[5] reported patient responses to sevoflurane that were presaged by the 1985 observations of Grosslight *et al.*[3] The contemporary authors studied the use of sevoflurane as a sedative agent for patients who had sustained either acute stroke or subarachnoid hemorrhage and observed ICP crises in some patients. In their report, the experience of Grosslight *et al.*[3] was not cited and the "Discussion" section did not make mention of the possibility that the physiology recounted above might have contributed to the observations. Perhaps it is not a bad moment for a revisitation.

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