

## CORRESPONDENCE

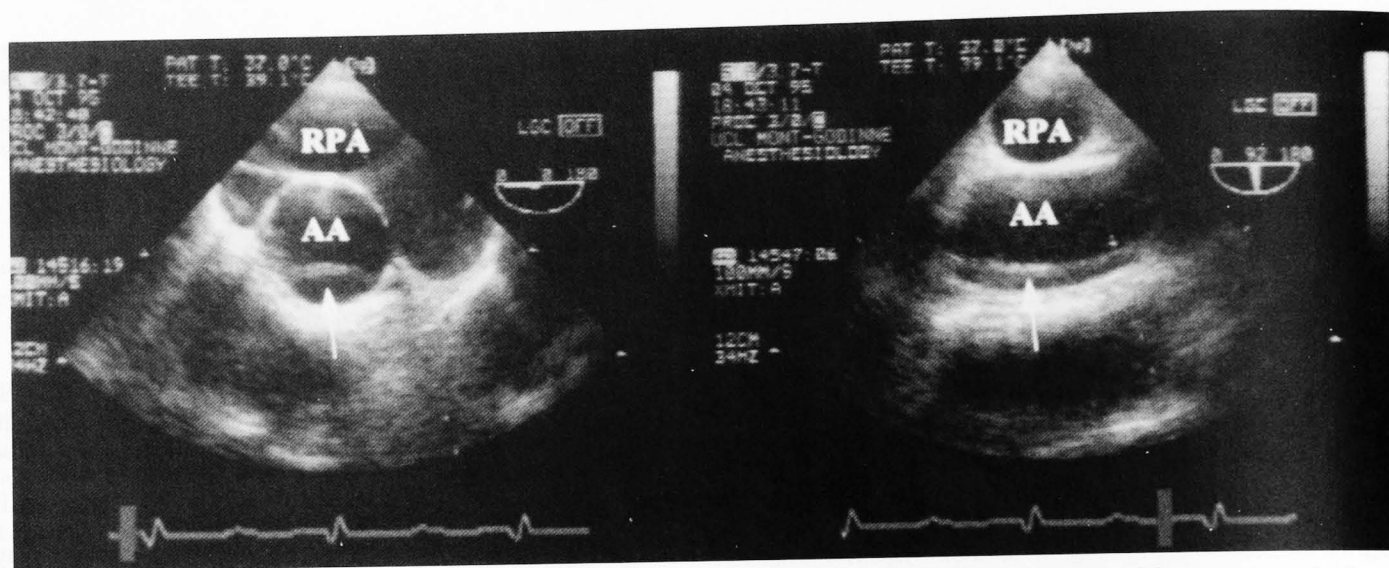


Fig. 1. Two-dimensional transesophageal echocardiographic basal transverse and longitudinal views of the great vessels showing linear reverberation in the ascending aorta (arrow). AA = ascending aorta; RPA = right pulmonary artery.

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## Preemptive Analgesia Implies Prevention

*To the Editor:*—The editorial by Kissin<sup>1</sup> rightly calls attention to the many difficulties facing the investigator who seeks to demonstrate the clinical phenomenon of preemptive anesthesia. To his balanced words, I add that I believe semantic confusion has arisen because of misuse of the word "preemptive." Increasingly, this word is equated by those who conduct clinical trials or review the literature with "preoperative" or "pre-incision." In the animal literature, however, the term "preemptive" refers to measures that prevent sensitization of cells within the spinal cord dorsal horn and other key sites within pain pathways. By definition, preemptive interventions in animal models must be accomplished before the onset of nociception. Conversely, preoperative or pre-incisional measures that could not possibly be viewed as preventing dorsal horn sensitization have been tested as if they were preemptive in the preceding sense. For example, the administration of single dose of a nonsteroidal antiinflammatory drug, or a single low dose of an opioid preoperatively, have been evaluated in clinical trials whose results are then discussed as tests of "preemptive analgesia."

It is clear from the preclinical literature that preemptive means "preventive," not simply "before." Preemptive analgesia, like many other potentially worthwhile advances in medicine, would be abandoned if its initial, sometimes uncritical implementation were viewed as a final test of its value. Cardiopulmonary bypass, blood transfusion, organ transplantation, and the use of muscle relaxants are but a few examples. Kissin does well to caution his colleagues that even effects that do exist and that may be of extreme importance are not always evident. For these reasons, we should not allow linguistic imprecision to compound our difficulties when evaluating this important concept.

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## Treatment of Intracranial Hypertension with Indomethacin

*To the Editor:*—Recently, Nilsson *et al.*<sup>1</sup> concluded that intravenous infusion of indomethacin in doses of 0.3 and 3 mg/kg/h, but not 0.1 mg/kg/h, caused a constriction of precapillary resistance vessels that resulted in a substantial decrease in cerebral blood flow (CBF) accompanied by a progressive increase in cerebral arteriovenous oxygen difference, a decrease in jugular venous pH, and slowing of electroencephalographic activity, indicating cerebral ischemia. In addition, they found a progressive increase in intracranial pressure (ICP) during and after indomethacin infusion in two pigs, suggesting that the vasoconstriction was so pronounced that ischemic lesion had developed. The authors did not find that their studies supported the clinical use of indomethacin in the treatment of intracranial hypertension due to head injury.

The authors analyzed our article,<sup>2</sup> in which we studied the effect of indomethacin (30 mg intravenously, followed by 30 mg/h for 7 h) in five patients with severe head injury with resistant intracranial hypertension. All patients had focal cerebral contusion and edema, with compression of the ventricular system and basal cisterns. On average, we found an instantaneous decrease in ICP from 28 to 17 mmHg (mean value) accompanied by a decrease in CBF, an increase in the arteriovenous oxygen content difference (AVDO<sub>2</sub>) at 2 h of indomethacin administration, and a decrease in arteriovenous lactate difference (at 15 min). At conclusion of the study, 1–6 months after head trauma, all patients had regained consciousness. We concluded that the effect of indomethacin on intracranial hypertension in patients with severe head injury was promising, but the cerebral vasoconstrictor effect of indomethacin was potentially dangerous because it might provoke cerebral ischemia. However, subsequent followup of these patients revealed nothing that could obviously be linked to indomethacin use. Our preliminary result was confirmed recently in another clinical study.<sup>3</sup> Since then, we compared the effect of indomethacin with that of acute hyperventilation in patients with severe head injury, and found that 30 mg indomethacin as a bolus injection caused a decrease in ICP comparable with a decrease in PaCO<sub>2</sub> of 0.88 kPa. In the same study, the degree of change in AVDO<sub>2</sub>, jugular venous saturation, arteriovenous lactate difference, and lactate/oxygen index did not differ between hypocapnia and indomethacin.<sup>4</sup> These studies were supplemented with other studies of healthy volunteers, in which hypoxia and hypercapnia restored the indomethacin-induced CBF decrease,<sup>5</sup> and a dose-response study in which 0.1 mg/kg/h indomethacin reduced CBF significantly.<sup>6</sup> In another clinical study, the effects of 30 mg indomethacin during craniot-

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omy for cerebral tumors subjected to normocapnic isoflurane anesthesia were studied. Indomethacin reduced ICP effectively and prevented cerebral swelling after opening of the dura.<sup>7</sup> A decrease in CBF was also observed, not below that of ischemic threshold, defined as 10 ml/100 g/min during isoflurane anesthesia.<sup>8</sup>

We agree with Nilsson *et al.*<sup>1</sup> that indomethacin-like hyperventilation results in precapillary vasoconstriction, and that the decrease in CBF eventually may cause concern in regard to sufficient blood flow supply. However, their results in an experimental model of a focal mass expanding lesion in pigs cannot be transferred to the complicated pathophysiologic events of severe human head injury. In our experience of continuous intravenous indomethacin treatment of intracranial hypertension in severe head injury, the ICP-reducing effect is sustained and the increase in AVDO<sub>2</sub>, the jugular venous lactate, and electroencephalographic activity are transitory. There are reasons to believe that indomethacin may prove helpful in the treatment of intracranial hypertension, but more work is needed. We find that 0.2 mg/kg indomethacin followed by a continuous infusion of 0.1 mg/kg/h, like acute hyperventilation, can be used in patients with acute or sustained ICP-hypertension associated with a high venous oxygen saturation (>60%), and/or relatively high CBF (>40 ml/100 g/min). This dose is lower than that found to elicit electroencephalographic changes in experimental studies.<sup>1</sup> However, indomethacin, like hyperventilation, should be used with caution, if at all, in patients with low jugular venous saturation, low CBF, or cerebral spasms. In our experience, the same reservation is justified in patients with hemorrhagic hypovolemic hypotension accompanied by intracranial hypertension. We consider indomethacin to be contraindicated in cardiac ischemia, renal insufficiency, and bleeding gastric ulcer.

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