of intrathecal local anesthetics in rabbits. ANESTHESIOLOGY 1985; 63:364-70

9. Lambert L, Lambert D, Strichartz G: Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. ANESTHESIOLOGY 1994; 80:1082-93

10. Drasner K, Sakura S, Chan V, Bollen A, Ciriales R: Persistent sacral sensory deficit induced by intrathecal local anesthetic infusion in the rat. ANESTHESIOLOGY 1994; 80:847-52

11. Byers M, Fink B, Kennedy R, Middaugh M, Hendrickson A: Effects of lidocaine on axonal morphology, microtubules, and rapid transport in rabbit vagus nerve in vitro. J Neurobiol 1973; 4:125-43

12. Bainton C, Strichartz G: Concentration dependence of lidocaine-induced irreversible conduction loss in frog nerve. ANESTHESIOLOGY 1993; 81:657-67

13. Kalichman M, Powell H, Myers R: Quantitative histologic analysis of local anesthetic-induced injury to rat sciatic nerve. J Pharmacol Exp Ther 1989; 250:406-13

14. Sakura S, Bolen A, Ciriales R, Drasner K: Local anesthetic neurotoxicity does not result from blockade of voltage-gated sodium channels. Anesth Analg 1995; 81:338-46

15. Hashimoto K, Nakamura Y, Hampl K, Ciriales R, Bollen A, Drasner K: Epinephrine increases the neurotoxic potential of intrathecally administered local anesthetic in the rat. ANESTHESIOLOGY 1996; 85:A770

16. Carpenter RL: Hyperbaric lidocaine spinal anesthesia: Do we need an alternative? Anesth Analg 1995;81:1125-8

17. Sakura S, Chan V, Ciriales R, Drasner K: The addition of 7.5% glucose does not alter the neurotoxicity of 5% lidocaine administered intrathetically in the rat. ANESTHESIOLOGY 1995; 82:236-40

18. Rigler M, Drasner K: Distribution of catheter-injected local anesthetic in a model of the subarachnoid space. ANESTHESIOLOGY 1991; 75:684-92

Anesthesiology
1997; 87:472-6

Epidural Analgesia and the Incidence of Cesarean Section

Time for Another Close Look

The relationship between epidural analgesia and the incidence of cesarean section remains controversial. Three years ago, Dewan and Cohen[1] reviewed this subject for ANESTHESIOLOGY. Their editorial accompanied reports of two prospective, randomized studies that showed that early administration of epidural analgesia (*i.e.*, cervical dilation of 3-5 cm) did not increase the incidence of cesarean section in nulliparous women, when compared with early administration of nalbuphine followed by late administration of epidural analgesia.[2,3] In contrast, Thorp *et al.*[4] earlier observed that epidural analgesia resulted in an increased incidence of cesarean section in nulliparous women. They concluded that this effect may be limited by delaying administration of epidural analgesia until cervical dilation of at least 5 cm.

Subsequently, two prospective, randomized trials were performed at the University of Texas Southwestern Medical Center at Dallas. Ramin *et al.*[5] randomized 1,330 women of mixed parity to receive either epidural bupivacaine-fentanyl or intravenous meperidine analgesia during labor. Among the 664 women randomized to an offer of epidural analgesia, 232 (35%) did not receive the allocated treatment. Approximately one half of the patients refused epidural analgesia, and the rest delivered before epidural analgesia could be administered. Among the 666 women randomized to an offer of intravenous meperidine, 229 (34%) were not treated as planned. Approximately one half of those women requested and received epidural analgesia because the meperidine provided inadequate pain relief. When the authors evaluated outcome according to intention to treat, they noted that 60 (9%) of the 664 women in the epidural group, compared with 35 (5%) of the 666 women in the meperidine group, had operative delivery for dystocia ($P < 0.01$). However, the authors defined operative delivery as either low forceps or cesarean delivery. Within the intention to treat analysis, the authors did not report the number of cesarean deliveries in the two groups. Thus it

Accepted for publication May 21, 1997.

Key words: Epidural analgesia, Patient-controlled analgesia, Cesarean delivery.

Reprints will not be available.

is unclear that there was an increased incidence of cesarean section in the women randomized to an offer of epidural analgesia.

Readers should consider carefully the implications of excluding one third of the patients in each group. In the epidural group, the authors excluded those women at lowest risk for cesarean section (*i.e.*, those who labored rapidly and did not request analgesia, or those who requested analgesia but delivered before analgesia could be provided). Conversely, in the meperidine group, the authors excluded the women at highest risk for cesarean section (*i.e.*, those with a longer labor and more severe pain, which may have signaled an increased risk of dystocia).

In this issue of ANESTHESIOLOGY, Sharma *et al.*[6] report this group's second randomized trial of epidural *versus* intravenous meperidine analgesia during labor. The authors randomized 715 women of mixed parity in spontaneous labor at full term to receive either epidural analgesia or patient-controlled intravenous analgesia (PCIA) with meperidine. (The authors chose PCIA so that fewer patients in the meperidine group would "cross over" to the epidural group.) Enrollment and randomization occurred when the patients were admitted from the triage area to the nurse-midwifery service at Parkland Hospital. Subsequently, an anesthesiologist offered epidural analgesia to those women randomized to the epidural group, but not to those women randomized to the PCIA group. Epidural analgesia was initiated with small boluses of 0.25% bupivacaine and was maintained with a continuous epidural infusion of 0.125% bupivacaine with 2 μg/ml fentanyl. The PCIA was initiated with 50 mg meperidine and 25 mg promethazine and was maintained by patient-controlled boluses of 10–15 mg meperidine every 10 min. Among the 358 women who were randomized to an offer of epidural analgesia, 243 actually received epidural analgesia. Of the remaining 115 women, 78 labored rapidly and never requested or received epidural analgesia, and the remaining 37 refused epidural analgesia. Among the 357 women who were randomized to an offer of PCIA, 259 women completed the study as allocated. Of the remaining 98 women, 73 women labored rapidly and did not receive any analgesia, 20 women refused PCIA, and 5 women who received meperidine PCIA "crossed over" to epidural analgesia because of inadequate pain relief.

Using an intention to treat analysis, the authors observed no difference between the two groups in the incidence of cesarean section (*i.e.*, 4% in the epidural group and 5% in the PCIA group). When the authors evaluated outcome among the nulliparous women, they again noted no difference between the two groups in the incidence of cesarean section (*i.e.*, 5% in the epidural group and 6% in the PCIA group). Women in the epidural group had lower pain scores during both the first and the second stage of labor, and women in the PCIA group had higher sedation scores. (Women in the PCIA group were "visibly sedated but . . . invariably arousable.") There was no difference between the two groups in neonatal outcome, except that more babies in the PCIA group received naloxone to reverse respiratory depression at birth.

The authors also noted no difference between the two groups in the incidence of cesarean section when they evaluated outcome for protocol-compliant patients (*i.e.*, 5% in the epidural analgesia group and 6% in the PCIA group). Among the protocol-compliant patients, the authors observed a longer first stage of labor and an increased incidence of oxytocin augmentation in the epidural group. The authors did not report the duration of the first stage of labor or the incidence of oxytocin augmentation as part of their intention-to-treat analysis.

Altogether, 213 (30%) of the 715 patients did not comply with their group assignment. This resulted in part from the fact that enrollment and randomization occurred at the time of admission to the labor and delivery unit rather than at the time that patients first requested analgesia. The 30% rate of protocol noncompliance illustrates the enormous difficulties in performing randomized trials of epidural analgesia in laboring women. Nonetheless, it remains unclear why 57 (8%) women refused the allocated method of analgesia despite their earlier consent.

The results of the present study will be welcome news for anesthesiologists who provide care for obstetric patients. However, it would be naive, and indeed a mistake, to assume that this study settles the issue in favor of epidural analgesia. Years ago, Roy Pitkin, then chair of the Department of Obstetrics and Gynecology at the University of Iowa and now Editor-in-Chief of *Obstetrics and Gynecology*, advised me that the concluding paragraph of most clinical manuscripts should begin as follows: "Under the conditions of the present study, we conclude

. . . . " What were the conditions of the study by Sharma *et al.*?[6]

Patient Population

Most of the patients were poor and either Hispanic (70%) or black (22%). Other investigators have documented a decreased rate of cesarean delivery among indigent women.[7,8]

Obstetric Management

Patients were not admitted to the labor and delivery unit until labor was well established. (The median cervical dilation on admission was 4 cm in both groups.) Labor was managed by on-site nurse midwives. Fetal assessment was provided by periodic fetal heart auscultation, and continuous electronic fetal heart rate monitoring was reserved for women with meconium-stained amniotic fluid, fetal heart rate decelerations, or inadequate progress of labor. An intrauterine pressure catheter was used to confirm adequate uterine activity. Strikingly, only 20 (5%) of the 386 nulliparous women in the two groups underwent cesarean section. A cesarean section rate of 5% in nulliparous women should give pause to all of us who provide care to obstetric patients.

Anesthetic Management

The authors' technique of epidural analgesia (*i.e.*, 0.25% bupivacaine followed by 0.125% bupivacaine with 2 μg/ml fentanyl) probably represents a "middle-of-the-road approach" in contemporary practice. Some anesthesiologists now provide epidural analgesia with a more dilute solution of bupivacaine (a few patients actually walk), but other anesthesiologists continue to use a more concentrated solution. In the present study, the anesthesiologists titrated the epidural infusion to maintain a T-10 sensory level. (This implies that the anesthesiologist checked the sensory level at regular intervals—an attention to detail that is overlooked by a disappointingly large number of practitioners.) In contrast, the authors' meperidine PCIA regimen differs strikingly from the way that intravenous opioid analgesia is provided in most obstetric units in the United States. Obstetricians often administer homeopathic doses of opioid, which result in modest sedation but little analgesia in laboring women. In the present study, 61 (24%) women in the PCIA group received more than 200 mg meperidine.

Altogether, many anesthesiologists may find it difficult to extrapolate the conditions of the present study to their own practice. Nonetheless, it is hard to reconcile the present study with claims that "epidural analgesia has made a significant contribution to the cesarean section epidemic in the United States."[9]

What is the current state of affairs regarding this contentious issue? The following summary includes some of my personal opinions on this subject.

1. Most studies suggest that laboring women who request and actually receive epidural analgesia are more likely to undergo cesarean section than those who do not. This does not establish a cause-and-effect relationship. The presence of severe pain during early labor may signal an increased risk for prolonged labor and operative delivery.[10]
2. Several retrospective, population-based studies suggest that the introduction of an epidural analgesia service, or the increased use of epidural analgesia, does not increase the cesarean section rate.[11–13]*
3. Epidural analgesia during labor is not a generic procedure. Many practitioners believe, as do I, that the epidural administration of a dilute solution of local anesthetic (*e.g.*, 0.0625–0.125% bupivacaine) is less likely to increase the cesarean section rate than administration of a more concentrated solution (*e.g.*, 0.25–0.5% bupivacaine). Some retrospective studies support this hypothesis, but it remains unproved by prospective, randomized trials.[14,15]†
4. Among women in spontaneous labor, it seems reasonable to delay administration of epidural analgesia until labor is well established. However, it is unnecessary to await an arbitrary cervical dilation of 5 cm.
5. In some patients, use of epidural analgesia may increase the likelihood of vaginal delivery. For example, the availability of epidural analgesia may encourage women with a history of previous cesarean section to attempt vaginal birth after cesarean. Similarly, some obstetricians allow a trial of labor in

* Robson M, Boylan P, McParland P, McQuillan C, O'Neill M. Epidural analgesia need not influence the spontaneous vaginal delivery rate [Abstract]. Am J Obstet Gynecol 1993; 168:364.

† Naulty JS, March MG, Leavitt KL, Smith R, Urso PR: Effect of changes in labor analgesic practice on labor outcome [Abstract]. ANESTHESIOLOGY 1992:77:A979.

women with a breech presentation only if the patient receives epidural analgesia.[16]

6. The use of epidural analgesia during labor likely decreases the requirement for administration of general anesthesia, with its attendant risks of failed intubation and aspiration, in parturients who require emergency cesarean section. In some cases, failure to administer epidural analgesia during labor may increase maternal risk during a subsequent emergency cesarean section.
7. Pain relief *per se* is a worthy goal. In their earlier study, Ramin *et al.*[5] acknowledged, "Pain relief during labor is of paramount importance, and in most circumstances the . . . increased risk of cesarean delivery associated with epidural analgesia is a secondary consideration." In 1992, the American Society of Anesthesiologists and the American College of Obstetricians and Gynecologists issued a joint statement that included the following observation: "There is no other circumstance where it is considered acceptable for a person to experience severe pain, amenable to safe intervention, while under a physician's care."[17] All women should have access to effective pain relief during labor.
8. Some third-party payers and managed health plans now limit access to, or deny reimbursement for, epidural analgesia during labor. Restricted access to epidural analgesia will result in unnecessary pain and dissatisfaction for obstetric patients, and is unlikely to affect the cesarean section rate significantly. Johnson and Rosenfeld[18] observed an abrupt decrease in the use of epidural analgesia in their hospital as a result of TennCare, a state-funded health insurance plan for Medicaid and uninsured patients in Tennessee. However, that did not result in a decreased incidence of cesarean section in their patients.
9. Even if it were shown that the contemporary use of epidural analgesia results in a small increase in the cesarean section rate, it is unclear how many women—who now choose epidural analgesia—would voluntarily opt for nothing or intravenous opioid analgesia, which is less effective and provides marked sedation.
10. Maternal administration of high doses of opioids may result in substantial neonatal effects (*e.g.*, respiratory depression, prolonged neurobehavioral changes). These effects have been largely ignored in this debate.
11. Maternal-fetal factors and obstetric management, not epidural analgesia, are the most important determinants of the cesarean section rate.

David H. Chestnut, M.D.
Departments of Anesthesiology and
Obstetrics and Gynecology
University of Alabama at Birmingham
Jefferson Tower, Room 920
619 South 19th Street
Birmingham, Alabama 35233-6810
Electronic mail: dchestnut@ms.jt.anes.uab.edu

References

1. Dewan DM, Cohen SE: Epidural analgesia and the incidence of cesarean section: time for a closer look [Editorial]. ANESTHESIOLOGY 1994; 80:1189-92

2. Chestnut DH, Vincent RD, McGrath JM, Choi WW, Bates JN: Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are receiving intravenous oxytocin? ANESTHESIOLOGY 1994; 80:1193-200

3. Chestnut DH, McGrath JM, Vincent RD, Penning DH, Choi WW, Bates JN, McFarlane C: Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are in spontaneous labor? ANESTHESIOLOGY 1994; 80:1201-8

4. Thorp JA, Hu DH, Albin RM, McNitt J, Meyer BA, Cohen GR, Yeast JD: The effect of intrapartum epidural analgesia on nulliparous labor: a randomized, controlled, prospective trial. Am J Obstet Gynecol 1993; 169:851-8

5. Ramin SM, Gambling DR, Lucas MJ, Sharma SK, Sidawi JE, Leveno KJ: Randomized trial of epidural versus intravenous analgesia during labor. Obstet Gynecol 1995; 86:783-9

6. Sharma SK, Sidawi JE, Ramin SM, Lucas MJ, Leveno KJ, Cunningham FG: Cesarean delivery: A randomized trial of epidural versus patient-controlled meperidine analgesia during labor. ANESTHESIOLOGY 1997; 87:487-94

7. Neuhoff D, Burke Ms, Porreco RP: Cesarean birth for failed progress in labor. Obstet Gynecol 1989; 73:915-20

8. Haas JS, Udvarhelyi S, Epstein AM: The effect of health coverage for uninsured pregnant women on maternal health and the use of cesarean section. JAMA 1993; 270:61-4

9. Thorp JA, Hu DH, Albin RM, Meyer BA, Cohen GR, Yeast JD, Hendrick J, McKenzie DR, Gerald KB: Epidural analgesia and frequency of cesarean section [Letter]. Am J Obstet Gynecol 1994; 171:1396-410

10. Wuitchik M, Bakal D, Lipshitz J: The clinical significance of pain and cognitive activity in latent labor. Obstet Gynecol 1989; 73:35-42

11. Gribble RK, Meier PR: Effect of epidural analgesia on the primary cesarean rate. Obstet Gynecol 1991; 8:231-4

12. Socol ML, Garcia PM, Peaceman AM, Dooley SL: Reducing cesarean births at a primarily private university hospital. Am J Obstet Gynecol 1993; 168:1748-58

13. Lagrew DC, Morgan MA: Decreasing the cesarean section rate in a private hospital: success without mandated clinical changes. Am J Obstet Gynecol 1996; 174:184-91

14. Parker RK: Influence of labor epidural management on outcome in obstetrics [Abstract]. Regional Anesth 1992; 17:S31

15. Pratt SD, Soni AK, Sarna MC, Parker RA, Oriol NE: Ultra low dose labor epidural solution affects obstetric outcome but not anesthesiologist work load: A preliminary report of a review of 2511 patients [Abstract]. Anesth Analg 1997; 84:S403.

16. Chestnut DH: Epidural and spinal anesthesia/analgesia: effect on the progress of labor and method of delivery, Obstetric Anesthesia: Principles and Practice. Edited by Chestnut DM. St. Louis, Mosby-Year Book, 1994, pp. 403–19

17. American Society of Anesthesiologists and American College of Obstetricians and Gynecologists. Pain relief during labor. 1992

18. Johnson S, Rosenfeld JA: The effect of epidural anesthesia on the length of labor. J Fam Prac 1995; 40:244–7

Anesthesiology
1997; 87:476–8

Scuds, Scads, and Other Air-borne Hazards

By the turn of the millennium, more than 1,000,000 predominantly aged patients will require cardiac surgery annually throughout the world. The cost of this health care likely will exceed 25 billion dollars, with a substantial portion of the overall expense attributable to management of the perioperative morbidity associated with cardiac procedures. For example, serious adverse central nervous system (CNS) events occur in approximately 6% of patients undergoing coronary artery bypass graft surgery; in addition, less apparent cognitive dysfunction occurs in 20–79%, persisting for 2 or more months in 15–57%.[1] A recent study reports that adverse CNS events after coronary revascularization greatly increase the duration of hospitalization and therefore health care costs.[2] Type I (focal injury, stupor, coma) and type II (deterioration in intellectual function, memory deficit, seizure) adverse events not only double the the average length of hospital stay, but also the amount of time spent in intensive care. This report confirms a previous finding that suggests patients with either type I or type II adverse CNS events require a longer hospitalization than those who suffer a postoperative myocardial infarction, left ventricular failure, or renal dysfunction after coronary revascularization.[3] Thus, postoperative CNS morbidity arguably represents the most economically and emotionally costly consequence of cardiac surgery.

The pathophysiology of perioperative adverse CNS events is complex and incompletely understood, but probably includes phenomena that can precipitate focal or global cerebral injury.[4] Focal injury is likely the end-result of marked and persistent hypoperfusion or flow obstruction produced by macroemboli (> 200 micron) consisting of atheromatous material, large air bubbles, or intracardiac thrombi. Subtle nonfocal neurologic symptoms may be the result of microembolism of air, fat, or blood element aggregate. During cardiopulmonary bypass (CPB), air entrained during manipulation of the heart and great vessels, gaseous emboli produced in the extracorporeal circuit, and air bubbles produced by cavitation phenomena in either the patient or bypass circuit circulate to the brain. Cerebral micrographs obtained from animal and human autopsy specimens demonstrate the diffuse presence of small capillary and arteriolar dilations (SCADS) after CPB, probably representing lodgement of gas bubbles or fat particles (fig. 1).[5] Several studies suggest that the magnitude of postoperative cognitive dysfunction may be predicted by the volume of the embolic load, as detected by isonation of

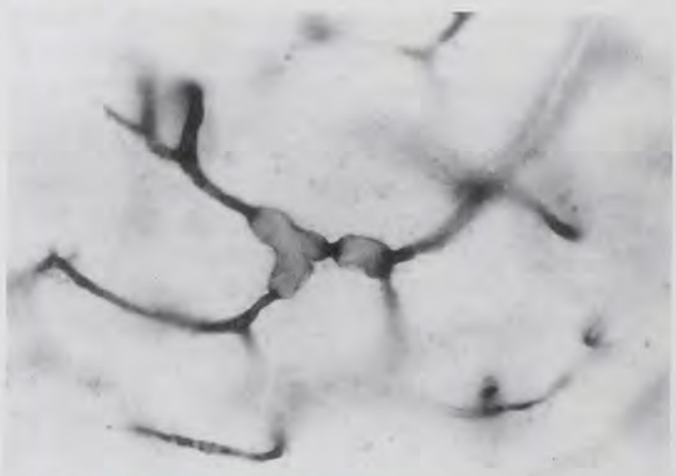

Fig. 1. Photomicrograph demonstrating putative embolic material lodged at the bisection of a cerebral capillary of a patient after cardiopulmonary bypass (CPB). This type of lesion is only present in patients or animals undergoing CPB or proximal aortic instrumentation and is thought to represent the site of air or lipid microemboli. (Courtesy of Dr. Dixon Moody).

Accepted for publication June 2, 1997.

Key words: air embolism, doxycycline, leukocytes, rabbits, somatosensory-evoked potentials.