◆ EDITORIAL VIEWS

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Bringing Light to the Dark Side

"YOUR child's heart stopped." There are few more chilling words that parents can hear as they wait for a child who is in surgery. Preventing and treating this devastating event has always been of paramount concern to anesthesiologists. In this issue of ANESTHESIOLOGY, Morray *et al.*[1] present important new data regarding anesthesia-related cardiac arrest in children. These data come from the Perioperative Cardiac Arrest (POCA) Registry during 1994-1997.

The POCA Registry is a voluntary, anonymous, American Society of Anesthesiologists-sponsored reporting system that collects data on children who have experienced perioperative cardiac arrests. Sixty-three institutions participated. Seventy-five percent were university-affiliated and 40% were children's hospitals.

Similar to other previous reports of age-related cardiac arrest, this report provides only a partial view of the problem. Not all hospitals that care for children are represented, nor are all hospitals accurately represented by the predominantly academic institutions that did participate. A great deal of information, even from the reporting centers, is not available. We are told of many etiologies for arrest, but we do not know if this list is complete (cases not submitted). Without a denominator (*e.g.*, the total number of children undergoing anesthesia or the total number of children administered a specific anesthetic), we cannot know the true incidence of different etiologies for arrest. Despite these drawbacks, valuable information is presented.

Previously, the most recent major report on anesthesia-related pediatric arrests came from the Closed Claims Project.[2] The database for that report was obtained from insurance company files after claims were settled. Respiratory-related events were shown to be the primary cause of cardiac arrest. This is not true for the POCA report, in which nonrespiratory events predominate. We do not know whether this change is absolute or whether it simply represents a difference in reporting. One hopes that, given the different time frames for the two studies, increased use of oximetry and capnometry accounts for the different results. In the current study, capnometers were used in 86% of the cases when an arrest occurred. By contrast, inadequate monitoring was thought to be a factor in 51% of the cases described in the Closed Claims report. On the other hand, the voluntary nature of the POCA database may have lead to the underreporting of respiratory events.

A significant number of events in the current study are medication-related. The single most common cause was cardiovascular depression from the administration of halothane, alone or in combination with other drugs; this accounted for 37 of the 150 anesthesia-related arrests. One half of these occurred during assisted or controlled ventilation. This suggests that, in spite of halothane's well-known ability to depress myocardial function, other factors are at work. In 1982, Friesen and Lichtor[3] reported that the greatest decrease in heart rate or blood pressure occurred 2-10 min after tracheal intubation. The combination of halothane and positive-pressure ventilation, resulting in increased uptake of anesthetic agents and decreased cardiac output because of decreased venous return, may be more important than the drug alone. The question is whether use of an alternative agent (*e.g.*, sevoflurane) would result in different data. The POCA database does not include a denominator; therefore, we do not know the relative numbers of children anesthetized with halothane and sevoflurane. It would, therefore, be inappropriate to conclude that any other anesthetic is safer than halothane for use in children.

In light of the recent Institute of Medicine report, it is interesting that medication errors are not listed as a reason for cardiac arrest.[4] Is this because of patterns of practice, or is it because of underreporting?

A number of studies have found that the youngest patients have an increased risk of arrest in the operating room. In the current study, 55% of arrests occurred in

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patients less than 1 yr old, and, more significantly, 43% occurred in infants aged 5 months or less. Why is this? Did the infants in this group have emergency procedures because of gross disorders of anatomy and physiology? Was the American Society of Anesthesiologists physical status stratification of this group different from the stratification of the population as a whole? Because the median age for halothane-related arrests was 6 months, some of these arrests (n = 13) were halothane-related, but what about the others? What is the risk of anesthesia for a healthy infant in this youngest age group undergoing elective surgery? This is a question that parents and surgeons ask all the time—but for which we have no answer. Even for emergency surgery, questions remain.

Emergency procedures were identified as a predictor of mortality. This seems obvious; patients with more serious disorders are at greater risk. But can disease be separated from emergency conditions? Are arrests and death time-related? Are procedures that are performed at 11 PM or 3 AM inherently riskier because of fatigue or fewer experienced personnel to assist when there is a problem?

Keenan *et al.*[5] reported that expertise plays a role in the incidence of critical events in children. The data presented in the current report do not shed light on this issue. The fact that the POCA Registry hospitals are predominantly university and children's hospitals, not smaller hospitals and community hospitals, leaves us in the dark on this important issue.

In 48 cases, arrest was attributed to cardiovascular causes. The most disturbing feature of this number is that an exact cause of cardiac arrest could not be determined in 18 cases, despite adequate monitoring and *post mortem* studies. Although this again may have been related to the voluntary nature of the reporting (and perhaps a tendency to exclude data from reports), it suggests that significant events that we cannot explain occur in operating rooms. At a time when we are close to sequencing the human genome, this should be troubling to us as physicians.

Where do we go from here? Important questions are raised by the current study and previous studies that we must answer.

1. When performing an inhalation induction, is sevoflurane safer than halothane?
2. What is the risk of arrest caused by anesthetic agents in healthy infants aged less than 12 months, and less than 6 months, undergoing elective or emergency surgery? This has a large bearing on the performance of certain potentially valuable procedures (*e.g.*, cochlear implants).
3. Does the previous pediatric experience of the anesthesiologist play a role in determining the incidence of arrests?
4. Can we improve our understanding of the causes of perioperative anesthesia-related arrests and thereby reduce the number of cases in which the etiology is unknown? Without such information, our ability to reduce the incidence of these events will be severely compromised.

The answers to these questions cannot be gained from retrospective studies, from registries such as the POCA Registry, or from other studies with incomplete datasets. The only approach likely to succeed will be large, multicenter, prospective epidemiologic studies in which some information is collected for all anesthetics administered to children in participating centers. This effort can and should be carried out by members of the anesthesia community, rather than by a state or federal agency. Such studies will be expensive (costing millions of dollars), and funding from the National Institutes of Health or other large organizations will be needed. However, the POCA Registry provides the critical pilot data needed to design such studies. Its participants also provide the core group of people needed to plan and perform the work. Although this would be an enormous effort, it is feasible, it is fundable, and it is clearly worthwhile.

Administration of anesthesia and the anesthetized state are not risk-free. The data from the POCA Registry have shed important light on this issue in the pediatric population. However, we are still walking around a darkened room with only a flashlight. Now is the time to take the next step in understanding the causes of arrests and, from this information, to try to create solutions to diminish this problem.

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The Three Components of Hyperoxia

The Good

Clearly, increasing inspired oxygen concentration can have beneficial effects during the perioperative period, including improved oxygen delivery to tissues and decreased incidence of wound infections associated with specific surgical procedures.[1] The work by Dr. Kotani *et al.*[2] published in this issue of ANESTHESIOLOGY shows that exposure to 100% oxygen during prolonged major procedures inhibits, but does not prevent, a decrease in antimicrobial function in alveolar macrophages (MØ) after surgery. In this study, there did not appear to be long-term pulmonary problems resulting from this therapy in otherwise healthy patients.

A greater increase in proinflammatory cytokines was observed in the group of patients administered 100% oxygen, compared with the group administered 30%. Increasing either tumor necrosis factor (TNF)-α or interferon (IFN)-γ improves antimicrobial pulmonary host defense in a number of animal models challenged with pathogenic bacteria. TNF-α is needed for neutrophil influx after intratracheal gram-negative challenge. Additionally, TNF-α and interleukin (IL)-1β are potent activators of neutrophils and MØ and are needed for transmigration of MØ and neutrophils to the site ofinfection. These proximal proinflammatory cytokines also enhance innate defenses by increasing phagocyte-induced killing of bacteria.

Chemokines that recruit and activate neutrophils (*e.g.*, IL-8) are also increased in the lungs after intratracheal instillation of *Escherichia coli* lipopolysaccharide or intact bacteria and increase neutrophil killing of *E. coli in vitro*. Additionally, inhibition of chemokine bioactivity in experimental *Klebsiella pneumonia* decreases neutrophil recruitment and bacterial clearance.[3] Finally, IL-12-induced IFN-γ release primes the MØ for enhanced TNF-α and IL-1β synthesis, thereby increasing MØ and neutrophil bactericidal activity. Therefore, hyperoxia-induced increases in proinflammatory cytokines are predicted to enhance antibacterial host defenses, as suggested by the authors.

However, increasing proinflammatory cytokines is a double-edged sword. For example, transient transgenic expression of TNF-α using defective adenovirus constructs protects against pulmonary *Klebsiella* challenge, but dosage is critical.[4] Higher expression of TNF-α is not beneficial. Furthermore, if the animals did not receive pulmonary bacterial challenge, a mild chronic inflammatory response could be detected in the lungs in response to the increased expression of TNF-α from the transfected respiratory epithelial cells.

The Bad

Increased ambient oxygen increases the rate of production of toxic reactive species. This occurs primarily

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