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To See or Not to See

THIS issue of ANESTHESIOLOGY contains two fascinating outcome studies. Cheney *et al.*[1] provide a trend analysis of the proportion of closed malpractice claims involving death or permanent brain damage reported to the American Society of Anesthesiologists Closed Claims Project. Lienhart *et al.*[2] present an innovative approach to identifying specific causes of anesthesia-related deaths in France. Both authors describe their unique sampling methodologies and peer review processes, along with some limitations, but do not fully acknowledge the effect that these limitations could have on their conclusions. Shakespeare's Hamlet pondered the question "to be or not to be," but for the readers of this issue of ANESTHESIOLOGY, to see or not to see—that is the question.

Cheney *et al.* use the American Society of Anesthesiologists Closed Claims database to determine changes in the proportion of claims for death or permanent brain damage over a 26-yr period and to identify factors associated with the observed changes. Their methodology includes a structured evaluation of adverse outcomes from 6,894 closed anesthesia malpractice claims that shows that the proportion of claims for death or brain damage decreased between 1975 and 2000. The authors conclude that the significant decrease in the proportion of claims for death or permanent brain damage from 1975 through 2000 seems to be unrelated to a marked increase in the proportion of claims where pulse oximetry and end-tidal carbon dioxide monitoring were used. That is, they could not find an association between the increase in monitoring and decrease in death or permanent damage.[1]

This should not come as a surprise, because malpractice claims, in general, may be unrelated to the quality of patient care.[3–5] In fact, one study, specific to anesthesia care, found absolutely no relation between human errors by anesthesiologists that resulted in disabling patient injuries and subsequent risk of malpractice litigation. In that study, the investigators identified 13 cases in which human error by an anesthesia provider, as determined by peer review, resulted in patient injury over a 3-yr period. None of those 13 incidents resulted in a closed malpractice claim or even a letter of intent. During that same time period, 18 cases involving legal action directed at the anesthesiologists were judged by peer review to be devoid of human error with regard to the anesthetic management.[3]

Still, the proponents of closed claims analyses argue that the use of such data circumvents the problem of gaining access to low-frequency adverse events, despite inherent limitations that must be considered when interpreting the data.[6] Among these limitations is the lack of any real denominator data. Specifically, the authors do not know how many anesthetics resulted in the number of closed claims present in their database. Instead, the authors use the total number of closed claims reported to the database annually as a denominator, and report their outcome measures as a proportion of all annual claims. The authors admit that the number of annual claims reported by a select group of insurance companies is not a random sample,[6] but have they acknowledged the impact of changing the insurance companies over time? The current study reports that the Closed Claims Project has 18 insurance organizations in its active panel, but as many as 35 insurance companies have contributed to the database over the study period. It seems likely that changing insurance companies might produce a change in the number and type of annual claims. For example, the authors excluded claims from 1970 through 1974 and 2001 because there were "insufficient" numbers (n = 21 and n = 15, respectively) per year for meaningful analysis. With so much variability in the denominator data, the readers must be cautious when interpreting trends.

Readers must also give consideration to the numerator data used by the Closed Claims Project. As noted previously, not all patient injury due to anesthesia provider error results in a claim. Also, closed claims can occur in the absence of human error.[3] For example, in the current study, overall standard of care was judged as less than appropriate in only 28% of the cardiovascular-related damaging events. Therefore, closed claims occurrences may not be a valid indicator of patient safety or quality of care. If the frequency of closed claims were a valid indicator of patient safety, one might conclude that 2001 was a very "safe" year for anesthetized patients.

The proportion of claims for death and brain damage is as likely to be affected by legal practice as it is by medical practice. Malpractice attorneys operating under a contingency-based system are becoming more inclined to pursue litigation involving disabling injury leading to lost wages in younger clients than to pursue cases involving death or permanent brain damage in older patients be-

◆ This Editorial View accompanies the following two articles: Cheney FW, Posner KL, Lee LA, Caplan RA, Domino KB: Trends in anesthesia-related death and brain damage: A closed claims analysis. ANESTHESIOLOGY 2006; 105:1081–6; Lienhart A, Auroy Y, Péquignot F, Benhamou D, Warszawski J, Bovet M, Jougla E: Survey of anesthesia-related mortality in France. ANESTHESIOLOGY 2006; 105:1087–97.

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cause of trends toward caps on pain and suffering. Similar economic motivations might cause insurance companies that represent hospitals and physicians simultaneously to settle on behalf of the hospital with a larger award, in return for the physicians being dropped from the claim. This allows the insurance company lawyer and plaintiff's attorney to settle with the cost of only a single negotiation. The physicians are then able to continue to generate income for the hospital without wasting time in litigation. Some malpractice insurers have even offered discounted premiums to physicians who gave up their right to refuse settlement. This allowed the insurance companies to determine whether it was cheaper to settle or defend against a claim based purely on the costs of doing so. Cheney *et al.* argue that it is unlikely that plaintiff's attorneys became more inclined to sue for less serious anesthesia-related injuries over the 1975–2000 time period because premiums for professional liability insurance decreased from approximately $30,000 per year in 1985 to $20,000 in 2005. Perhaps practitioners became more inclined to settle, rather than defend against, these smaller claims when it became apparent that there was little relation between quality of care and malpractice litigation. This could have resulted in significant savings in litigation costs for the insurers and a subsequent decrease in premiums.

Although closed claims databases are an important source of outcome data for risk management, the inferences drawn in this study with respect to monitoring devices are unrealistic. If the downward trend in the proportion of claims involving death or brain damage had begun in 1985, would the authors have concluded, as closed claims investigators have in the past,[7,8] that pulse oximetry and end-tidal carbon dioxide monitoring has an impact on mechanism of injury or outcome? Closed claims analyses should never attempt to show efficacy of monitoring devices because the population denominator remains unknown. One could also argue that the numerator of adverse outcomes is equally unknown because not all adverse outcomes result in a claim, particularly a closed claim. The fact remains that we have no idea what causes a closed malpractice claim. Closed claims investigators often try to relate claims occurrences to patient management, but claims may bear little relation to any aspect of anesthesia care (not just pulse oximetry or end-tidal carbon dioxide monitoring).

In the second outcome study, Lienhart *et al.*[2] introduce new methodology to estimate the number and characteristics of anesthesia-related deaths in France for 1999. They then compare their estimate with data from a previous nationwide study by Tiret *et al.*,[9] who used different methodology between 1978 and 1982, to suggest a 10-fold decrease in the rate of anesthesia-related deaths in France during this 20-yr time frame. The authors of the current study again acknowledge many of the limitations of their methods but are confident in their conclusions because, in their opinion, many of these limitations are likely to lead to underestimates of the authors' more recent anesthesia-related mortality rate. As such, the authors' innovative approach to identifying specific causes of anesthesia-related deaths in France may be both a strength and a weakness.

As in the previously discussed closed claims study, the investigators lack denominator data. Therefore, to calculate an anesthesia-related mortality rate, they must estimate the number of patients receiving an anesthetic in France during 1999. They do this by using data from a 1996 French survey.[10] Although Lienhart *et al.* acknowledge that this is merely an estimate, they rationalize the potential effect that this could have on their conclusions by saying, "The error, if any, again seems minimal because data from the French Ministry of Health providing the number of procedures and their type do not show any increase in anesthetic activity during this small time frame." The authors go on to say that a small reduction in surgical activity, between 1% and 5%, is even suggested by the French Ministry of Health. Readers may wonder why an estimate from 1996 data were necessary if the French Ministry of Health collects this data, but let us put that aside for a moment. When the 1996 survey data were published in ANESTHESIOLOGY in 1999 by Clergue *et al.*,[10] they concluded that the number of anesthetic procedures had increased by 120% and the rate of anesthetic procedures had increased from 6.6 to 13.5 per 100 French inhabitants since 1980. Clearly, the number of anesthetic procedures has the potential to change over time and, more importantly, this change may not represent a trend, but merely normal variation. This may bring the current authors' estimated denominator into question. Still, the readers must accept that low rates are affected more by changes in numerator data than denominator data.

There are also reasons why the current study may have underestimated the numerator of anesthesia-related deaths in 1999 in comparison with previous studies. Although the current study used an elaborate peer review process to assure that cases in which the death certificate suggested potential for anesthetic involvement were analyzed appropriately, the initial screening process did not involve an anesthesiologist. The flowchart in figure 1 should really show a medical certifier (examiner) using a medical record, and possible autopsy results, to assign International Classification of Diseases, Ninth Revision (ICD-9) codes as the initial screening step.[2] Handwritten anesthesia records are notoriously inaccurate, and ICD-9 codes certainly do not allow description of all factors contributing to an anesthesia-related death. It is possible that the medical examiners were unable to capture the more subtle anesthetic contributions to perioperative deaths and these were lost to the subsequent peer review process of the investigators.

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This is again rationalized by the investigators, who chose to review a sample of 500 hospital deaths in which no preselected ICD-9 codes had implicated anesthetic management as a contributor to the death. In this sample, they found no anesthesia-related deaths but reported that the upper limit of the 95% confidence interval could have produced as much as a 6.7% error. More concerning is the exclusion criteria applied during the peer review process. The investigators chose to exclude cases in which the medical history "explained why death occurred." The authors admit that these cases included very sick patients undergoing high-risk surgery. In fact, these cases are the most likely to involve human error by an anesthesiologist.[11] Eliminating the sickest patients from studies of anesthesia-related morbidity and mortality is a relatively common practice, but it negates comparison to studies in which these patients are included.[12] The authors dismiss this weakness by implying that their study is not "devoted to human error." The authors also state that because the rate of American Society of Anesthesiologists physical status III and IV patients has increased severalfold in the more recent study, to conclude that anesthesia-related mortality has declined overall, in comparison to the study by Tiret *et al.*, seems "sound." In fact, a higher proportion of these sicker patients might have led to a higher proportion of patients being excluded from the current study, even if the same methodologies had been used.

Differing methodologies create different operational definitions of anesthesia-related death, each with their own unique limitations, and readers must be acutely aware of this when evaluating comparisons. For example, Lienhart *et al.* state that the "rate of deaths totally related to anesthesia was close to other published values" and reference a study by Lagasse. In fact, Lagasse reported, in the referenced study, that no deaths were considered to be due solely to anesthetic management.[11] The current authors seem to be comparing their estimated rate of deaths partially and totally related to anesthesia, which excludes deaths where anesthetic care could have played a minor role, to the Lagasse definition that included all deaths where even minor errors by the anesthesia providers were judged to have contributed. Similarly, Lienhart *et al.* compare their findings to those of Tiret *et al.*, who did not employ the same sampling methods or exclusion criteria. This does not detract from the current study's unique methodology; it merely brings the comparisons to other studies into question. Although space limitations will not allow a lengthy discussion, suffice it to say that the limitations of the current study methodology are compounded by the limitations faced by Clergue *et al.* and Tiret *et al.* when making comparisons.

The readers should appreciate the adversity that outcome researchers must deal with to bring us answers to difficult questions. Lack of standardized definitions and methodologies, inadequate risk adjustment models, and a hesitancy to share data are some of the frustrations facing outcomes researchers in the field of anesthesiology. We must applaud the work of Cheney, Lienhart, and their colleagues who continue to push forward with the best that anesthesiology has to offer. This work brings us closer to the truth. If I may again paraphrase Shakespeare's Hamlet, we are fortunate that these investigators believe it is "nobler in the mind to suffer the slings and arrows of outrageous fortune than take arms against a sea of troubles, and by opposing end them."

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Do the Right Thing (or Do the Market Exclusivity Thing?)

(IF the title makes no sense, be patient.) In the current issue of ANESTHESIOLOGY, Petroz *et al.*[1] describe the pharmacokinetics (and, to a limited extent, the pharmacodynamics) of dexmedetomidine in pediatric patients. When dexmedetomidine was approved by the US Food and Drug Administration (FDA) for use in adults in 1999, the package insert did not offer any guidance regarding its use in pediatric patients. In the ensuing years, little has been published about the use of dexmedetomidine in infants and children. I make no judgment as to whether the drug is useful in these patients; however, if a clinician believes that dexmedetomidine would benefit his or her patient, it is difficult to obtain either guidance on dosing or a perspective on the risk–benefit ratio in children.

During the 1990s, the FDA struggled with the infrequent submission of efficacy and safety data in pediatric patients. Although many drugs were used off-label (*i.e.*, in the absence of language in the package insert describing use in a particular population) in children, dosing recommendations were often anecdotal, based on publications that may or may not have been peer reviewed. Despite journals' interest in rigorous review of data submitted for publication, reviewers' access to data (particularly that regarding safety events) is far more limited that the scrutiny the FDA applies in its reviews of clinical trials. Thus, it is not surprising that the FDA does not allow claims in package inserts based on nonaudited, published clinical reports. To improve package inserts for pediatric patients, the FDA created the "Pediatric Rule" in 1999; Congress passed the Best Pharmaceuticals for Children Act in 2002.* These initiatives informed the pharmaceutical industry that drugs that were likely to be used in pediatric patients required appropriate labeling, supported by clinical studies in the target population. As recently reviewed by Shultheis *et al.*,[2] the FDA's rules for pediatric labeling have undergone repeated challenges and revisions. However, currently, unless a drug has no potential benefit in children (*e.g.*, a chemotherapeutic agent for prostate cancer), pharmaceutical companies are expected to perform studies in children, typically after approval for use in adults. In exchange for these efforts, the government offers an enormous carrot: 6 months of additional market exclusivity (*i.e.*, thereby delaying generic competition). For drugs with annual sales of hundreds of millions of dollars, the additional period during which generic competitors can be excluded from the market represents a massive financial opportunity. In turn, many companies have performed pediatric studies to obtain this market exclusivity.

Why don't pharmaceutical companies do studies in children early and often? My two-decade experience as an academic pediatric researcher (6 years ago, I changed careers; I now consult for pharmaceutical companies) may provide some insight. Conducting studies in pediatric patients is not easy. Obtaining consent from pediatric patients was challenging in my era; I suspect that it is markedly more difficult in the current environment: Petroz *et al.*[1] report that they were able to obtain consent from only 1 of every 20 families that they approached. Second, the environment for the conduct of clinical studies in anesthesia has become more problematic with each passing year. When I started doing clinical trials in 1981, delaying the start of surgery or end of anesthesia by several minutes or more to permit data collection for a clinical trial was accepted readily by my surgical colleagues; the nursing staff and hospital administration never paid any attention. In the current cost-containment environment, I doubt that investigators are allowed any delays in the surgical schedule. Third, investigational review boards at academic institutions (at least mine, the University of California, San Francisco) supported the conduct of clinical trials in neonates, infants, and children; in particular, we were not burdened by consent forms that were so onerous that family members would automatically refuse to participate. Today, as a consultant to industry, I see consent forms exceeding 20 pages and listing so many potential risks that one can readily imagine a reflex refusal from family members. Finally, many university-affiliated pediatric anesthesia departments focus heavily on clinical care (or basic research) rather than clinical research, affording pediatric investigators relatively little opportunity to develop research careers.

Other than the opportunity for market exclusivity (and "doing the right thing"), there may be little incentive for pharmaceutical companies to perform studies in children. First, for many drugs, sales in pediatric patients will be relatively small, a combination of the relatively

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* Public Law 107-109. Best Pharmaceuticals for Children Act. Available at: www.fda.gov/opacom/laws/pharmkids/pharmkids.html. Accessed July 19, 2006.

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small number of pediatric patients and the dose per utilization (as a function of size). Second, in many instances, investigators (typically in academic settings) obtain experience and then publish (or otherwise publicize) their results, providing the clinical community with guidance on dosing and adverse effects (although, as mentioned previously, without the scrutiny that would be applied by the FDA), and the drug is used extensively in children without appropriate labeling. A few examples are evident in the anesthesia community. In 1981, Organon asked me to determine the clinical pharmacology of vecuronium in infants and children. Our study included patients as young as 7 weeks of age,[3] leading to the following text in the package insert: "See DOSAGE AND ADMINISTRATION: Use in Pediatrics subsection for recommendations for use in pediatric patients 7 weeks to 16 yr of age. The safety and effectiveness of vecuronium in pediatric patients less than 7 weeks of age have not been established."† Although that package insert has not been revised to describe use of vecuronium in neonates, I suspect that clinicians were not deterred from its use in that population. Similarly, the fentanyl label reads "safety and efficacy of fentanyl citrate in pediatric patients under two years of age has not been established"‡; despite this, fentanyl (and other members of the fentanyl family) are used widely in neonates and infants, guided by numerous publications in journals such as ANESTHESIOLOGY.

Now back to the title of this editorial. I don't know whether Abbott's sponsorship of a study of dexmedetomidine in pediatric patients was "doing the right thing" or attempting to extend its market exclusivity (and hence it profits). Regardless, publication of the study should remind members of the clinical community of the need for high-quality pediatric research to ensure that infants and children can be treated safely and effectively with the full armamentarium of drugs available for adults.

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† Vecuronium (package insert). Available at: www.bedfordlabs.com/products/inserts/Div-VCRB-P03.pdf. Accessed August 19, 2006.

‡ Fentanyl citrate (package insert). Available at: www.baxter.com/products/anesthesia/anesthetic_pharmaceuticals/downloads/fentanyl.pdf. Accessed August 19, 2006.

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Forehead Pulse Oximetry

Friend and Foe

THE use of pulse oximetry to continuously monitor blood oxygenation (Spo_2) is accepted as the standard of care during anesthesia[1] and in the postanesthesia care unit, but the pulse oximeter, like any other monitoring device, is not perfect. Problems fall into two basic categories: (1) Data failure or dropout, when no Spo_2 reading is obtainable, occurs because of either too little signal or too much noise, *i.e.*, low signal/noise ratio. (2) The Spo_2 reading displayed is spurious, *i.e.*, it does not accurately predict the fractional (Hbo_2%) or functional (Sao_2%) oxygen saturation of hemoglobin in the arterial blood. In the search for the best available signal/noise ratio, the forehead offers several potential advantages over other pulse oximetry sensor placement sites. The skin of the lower forehead just above the eyebrows may be a better location for the sensor because its blood supply is from the supraorbital artery and therefore well maintained, and the area shows less vasoconstrictor response to cold or other stimuli compared with other peripheral sites.[2] Unfortunately, the forehead site is also associated with spuriously low Spo_2 readings in some patients. In this issue of ANESTHESIOLOGY, Agashe *et al.*[3] report how use of a headband that applies up to 20 mmHg pressure on the forehead pulse oximeter sensor decreases the incidence of spuriously low Spo_2 readings that are likely related to venous pulsation artifact. These authors disclose that they are all full-time employees of Nellcor Puritan Bennett, Tyco Healthcare (Pleasanton, CA), the sponsor of this study. Nellcor manufactures the Max-Fast forehead reflectance sensor and headband that were used.

Agashe *et al.*[3] studied healthy volunteers breathing room air in the supine position and two levels of Tren-

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delenburg positions using the forehead sensor with the headband adjusted to its maximum and minimum recommended pressure limits. Spo_2 readings obtained from the forehead sensor with the subjects supine and the headband in place were used as a baseline to compare the effects of Trendelenburg on Spo_2 reading accuracy with and without use of the headband. Occurrences of spuriously low Spo_2 readings detected by forehead sensors were compared with those from digit sensors. Agashe *et al.*[3] found no difference between Spo_2 readings obtained from the forehead sensor in the supine and Trendelenburg positions when the headband was used. When it was not used, forehead Spo_2 readings obtained while subjects were in the Trendelenburg positions were significantly lower than the Spo_2 readings when the subjects were supine.

Pulse oximetry failure occurs frequently. Reich *et al.*[4] reviewed 9,203 electronic anesthesia records at The Mount Sinai Medical Center and found a pulse oximetry failure rate of 9.18%. Independent intraoperative predictors of failure included hypothermia and hypotension. Almost all of these patients had been monitored using sensors placed on the fingers or toes.

There are anecdotal reports of forehead pulse oximetry working when sensors at other sites have failed; indeed, Nellcor advertises the Max-Fast forehead sensor as "most likely to succeed in challenging conditions." However, to date, there is no published clinical study that compares the failure rate of forehead pulse oximetry sensors with other peripherally (*i.e.*, finger, toe, earlobe) placed sensors.

To properly assess the validity of data displayed by a physiologic monitor, in this case the Spo_2 reading, the clinician should understand the principles underlying the technology. The traditional two-wavelength pulse oximeter is an optical plethysmograph that measures the ratio of pulse-added absorbance (AC) to fixed absorbance (DC) of radiation at wavelengths of 660 and 940 nm. The "ratio of ratios," often termed R, where R = [(AC660/DC660)/(AC940/DC940)], is used to determine the Spo_2 reading *via* an empiric algorithm created by the pulse oximeter manufacturer. The pulse-added signal is produced by changes in volume in the vascular bed at the sensor site, due to pulsatile arterial (oxygenated) blood flow during the cardiac cycle.[5] If there are also pulsations in venous blood at the sensor site, a lower Spo_2 reading will result because the instrument is unable to distinguish arterial from venous blood pulsations. When there is a continuous column of blood between the right heart and the forehead sensor site (*i.e.*, jugular vein valve absent), venous pulsations can be transmitted from the chest.[6]

Spuriously low Spo_2 readings are therefore most likely to occur during positive-pressure ventilation, in the head-down (Trendelenburg) position, and when venous drainage from the neck is impeded. The Spo_2 underreading can be significant, depending on the venous pulse pressure and the distensibility of the venous system at the probe site. Barker[7] reported one case (anterior neck surgery) in which the Max-Fast read an Spo_2 of 60–70% for the entire case while an earlobe sensor and arterial blood gas analysis indicated saturation percents in the mid-90s.

Shelley *et al.*[8] studied the plethysmographic waveforms from reflectance pulse oximetry sensors (Max-Fast) placed on the finger, ear, and forehead of 25 patients undergoing general anesthesia. In 20 of the 25 patients, the forehead probe generated signals that were similar to the finger and the ear. In 5 patients, a more complex signal with an intermittent venous component was recorded. This component was exacerbated when the patient was placed head-down. Application of pressure to the forehead probe eliminated the venous component, whereas relieving pressure from the ear probe clip induced the venous component. The amount of pressure applied and use of a headband were not studied.[8]

The results of Agashe *et al.*[3] suggest that use of a headband that applies 10–20 mmHg pressure to the forehead probe provides a potential solution to the problem of spuriously low Spo_2 readings in patients in whom venous pulsations are likely to occur. Their study has several limitations. First, the subjects were awake, healthy volunteers rather than potentially very sick patients undergoing general anesthesia with positive-pressure ventilation. Second, the subjects breathed room air and had baseline Spo_2 values of 98%. Because the pulse oximeter is used clinically to detect hypoxemia, performance under such conditions must be evaluated. Third, it is unclear from this study whether a headband tension of 10–20 mmHg reliably prevents spurious readings in all patients. The current Nellcor sensor application guide that describes how the sensor and headband are to be applied states, "Forehead sensors are contraindicated for patients in Trendelenburg's (head-down) position." Fourth, headband pressure may cause injury to the tissue under the forehead sensor, particularly in patients where perfusion is suboptimal. Indeed, Shelley *et al.*[8] noted that use of their setup in a subsequent study resulted in a burn on the forehead of one of their research subjects. This occurred with the probe secured by a Tegaderm dressing and without application of external pressure. When such a sensor is used, the skin at the site must be checked at regular intervals.

The place of forehead reflectance pulse oximetry continues to be the subject of discussion. We look forward to the results of further investigations. In the meantime, the educated user will recognize the potential advantages of forehead pulse oximetry as well as the limitations and potential hazards, and interpret the data accordingly.

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In Hot Pursuit

DENBOROUGH and Lovell[1] first reported a myopathy associated with anesthesia nearly 50 yr ago. Despite great strides made in the diagnosis and management of malignant hyperthermia (MH) over the ensuing three decades, the cause itself remained obscure until DNA-based technologies were brought to bear on its many mysteries. To some, the outcome of these investigations may now appear as a surfeit of riches. For example, the number of polymorphisms (*i.e.*, multiple alleles, or DNA sequence variations, of genes within a population) in the gene encoding the calcium release channel (*RyR1*) of skeletal muscle that are purported to cause MH in at least one human now stands above 100, with more published seemingly by the month.[2–4] As acknowledged by the authors of these and similar reports, a causative role in MH for most of the newly detected nucleotide polymorphisms remains to be proven beyond reasonable doubt. But for one at least, *i.e.*, that causing a substitution of a cysteine for arginine at amino acid position 163 (R163C) of the human RyR1 protein, the case is all but closed. In this issue of ANESTHESIOLOGY, Yang *et al.*[5] use gene targeting to create a mouse line that expresses the human R163C mutation and that exhibits signs of MH at both biochemical and whole animal levels of resolution. Below, the methods underlying this achievement and its broader implications are framed in brief.

To investigate traits correlated with specific nucleotide substitutions, exogenous DNA carrying the polymorphism of interest may be transfected into cultured cells capable of differentiation into an adult mouse. The consequences of the DNA sequence variation may then be compared between manipulated and unmanipulated mice with otherwise identical genetic backgrounds. Gene targeting is the method of introducing a transgene into a desired position of the host genome for site-directed mutagenesis. In embryonic stem (ES) cells, gene targeting creates a mouse in which all of the nucleated cells, including those in the germ line, carry a mutant version of the gene of interest. To generate germ line chimeras, ES cells isolated from a mouse blastocyst are engineered to undergo homologous recombination. This is most often accomplished, as in Yang *et al.*, by electroporation of a cloned region of DNA (*i.e.*, a partial sequence of the *RyR1* gene constructed in a targeting vector also carrying genes encoding selectable neomycin and *HSV-tk* markers) that is closely related or identical to an endogenous region in the genome of the ES cells (in the current case, 129Sv ES cells). Treated ES cells, *i.e.*, the rare 1 in 1,000 cells in which recombination has occurred between the introduced gene and its corresponding chromosomal homolog, are selected in culture from the untreated ES cells, and from those carrying nonhomologous insertions.

The modified and selected ES cells are then injected into the blastocyst of a preimplantation embryo from a different mouse strain (in the current case C57BL/6 blastocysts) and surgically reimplanted into a pseudopregnant foster mother to produce an animal in which the nucleated cells are altered at the desired site. Coat color (*i.e.*, yellow agouti mottling) is used as a marker to determine whether the modified ES cells have contributed to the germ line of the chimera. First-generation offspring are usually heterozygous for the targeted mutation. Backcrossing and interbreeding of chimeras produces mice that may be heterozygous or homozygous for the genetic modification as desired. If mutagenesis results in inactivation of gene expression, the mutation is termed a *knock-out*. If the altered gene retains its ability to express a functional, albeit modified, protein, the mutation is termed a *knock-in*. As might be surmised,

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erisks for failure are inherent at each step of the way, with no *a priori* guarantee that the transgenic mouse will have a relevant, or even identifiable, phenotype.

In the work of Yang *et al.*, the gamble has paid off. The authors demonstrate that the human R163C *RyR1* is transcribed and its protein is expressed in the transgenic mice; that the heterozygous mice become acidotic and febrile and die on exposure to halothane; that dantrolene is fully prophylactic if given before halothane exposure; and that corresponding biochemical changes are observed in myotubes and sarcoplasmic reticulum membranes isolated from the mutant mice. These observations are significant for several reasons. First, the causal property of at least one human *RyR1* mutation other than that shared with a spontaneous animal model (*i.e.*, the pig) cannot be doubted. Parallel investigations for all putative human MH mutations, *RyR1* or otherwise, are not likely to be forthcoming given the prohibitive time, costs, and risks involved. As the authors have proposed, the creation of transgenic mice with mutations selected from each of the recognized human *RyR1* hot spots are well warranted. In turn, a subset of polymorphisms selected for gene targeting that are disproportionately represented in a given human population might also be appended. Expression of the R614C mutation in mice that causes MH as an autosomal dominant trait in humans, and as an autosomal recessive trait in pigs (*i.e.*, R615C), would be of particular interest. Will one or two copies of the mutant gene be necessary and sufficient for expression of MH in the mouse? These and related investigations will be key to detecting differences, if any, between human MH-associated *RyR1* mutations expressed in the mouse in their anesthetic drug and dose dependencies, baseline and trigger calcium kinetics, severity of the clinical phenotype, and the like.

Second, as the authors point out, a well-established mouse model has certain advantages over the pig in the planning and conduct of experiments aimed at the contingencies of applied MH research. Among other factors, lower costs, larger sample sizes, and ease of sharing between investigators afforded by murine experiments will facilitate screening of newly introduced inhalational anesthetics, drugs of abuse, and drugs active at the neuromuscular junction for the capacity to trigger MH. As well, a convenient small animal model should speed validation of novel diagnostic tests for the detection of MH susceptibility in humans.

Third, a well-controlled murine model (*i.e.*, human polymorphisms expressed in a highly stable mouse background) may play a crucial role in refining knowledge of the mechanisms of excitation–contraction and their disruption by pharmacologic interventions and genetic variations. Basic MH research is characterized by a large number of "known unknowns." For example, how do potent anesthetic agents interact with RyR1 and other constituents of the skeletal muscle triad? In multiple species, why does this interaction become lethal in the presence of genetic polymorphisms that otherwise have no measurable influence on the quality of life or on life expectancy? How do divergent mutations in *RyR1* present a similar or even identical phenotype? What processes underlie rapid recovery from a catastrophic MH event but leave no residua? Why does the risk for human MH decrease by an order of magnitude with age? Multiple insights into the pathogenesis of MH remain to be disclosed, and it is reasonable to expect that murine models such as that developed by Yang *et al.* will play a central role.

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Statins

The Next Advance in Cardioprotection?

CME This editorial accompanies the article selected for this month's *Anesthesiology* CME Program. After reading the article and editorial, go to http://www.asahq.org/journal-cme to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

WITH the publication of the Coronary Artery Revascularization Prophylaxis trial, suggesting a lack of efficacy of coronary revascularization before noncardiac surgery, there has been increasing interest in identifying medical strategies to reduce perioperative cardiovascular risk in noncardiac surgery. Until recently, the therapy that has been most widely studied has been the use of β blockers in high-risk patients undergoing noncardiac surgery[1]; however, recent evidence suggests that β-blocker therapy alone may not lead to the improvement in outcome initially suggested. In this issue of ANESTHESIOLOGY, Hindler *et al.*[2] evaluate the efficacy of another class of cardioprotective agents. Using meta-analysis, the efficacy of statin therapy to improve outcomes after cardiac, vascular, or noncardiac surgery was evaluated. Statin therapy was associated with a 44% reduction in early postoperative mortality, irrespective of the type of surgical procedure involved. In a case–control study of 2,816 patients undergoing major vascular surgery, perioperative mortality in patients receiving statins was reduced 4.5-fold as compared with that in patients who did not take this medication.[3] Interestingly, the results of this study implied that statins and β blockers may produce independent but additive effects to decrease overall cardiovascular risk. Given the multifactorial etiology of perioperative myocardial infarction,[4] a multimodal approach seems to be the best means of improving outcome.

So how might statins reduce perioperative cardiovascular morbidity and mortality? Since their discovery several decades ago, statins have become widely prescribed to decrease low-density lipoprotein cholesterol. In the Heart Protection Study,[5] cardiovascular event reduction was similar in patients treated with statins regardless of baseline low-density lipoprotein cholesterol concentration. The results of this and other studies have stimulated an interest in mechanisms responsible for the cardioprotective effects of statins that might occur independent of reductions in low-density lipoprotein cholesterol.[6]

Statins have been shown to modulate vascular function by increasing expression of nitric oxide synthase and enhancing nitric oxide production. Increases in nitric oxide reduce endothelial dysfunction, attenuate leukocyte–endothelium interactions, and decrease platelet aggregation. Statins have also been demonstrated to scavenge reactive oxygen species, decrease endothelial cell apoptosis, and produce antithrombotic effects. Statins exert antiinflammatory effects that contribute to atherosclerotic plaque stability. In addition, statins reduce vascular smooth muscle proliferation in response to injury and may contribute to a decrease in the incidence of restenosis after percutaneous coronary intervention.[7] The direct cardioprotective effects of statins may be particularly important in disease states (*e.g.*, diabetes mellitus) in which endogenous signal transduction responsible for normal protection against ischemic injury is impaired.

Despite recent studies advocating the benefit of perioperative statin therapy, the American Heart Association Clinical Advisory on the Use and Safety of Statins concluded that it may be prudent to withhold statins during hospitalization for major surgery.[8] Statins are associated with several important skeletal muscle side effects, including muscle weakness, cramps, myalgias, elevations of creatine kinase, myositis, and rhabdomyolysis.[9] Minor muscle symptoms occur in approximately 1% to 5% of patients taking statins, a rate that is similar to that with placebo. The incidence of fatal rhabdomyolysis has been estimated to be 0.15 deaths per 1 million statin prescriptions. The mechanism of this devastating statin-induced muscle injury is unclear, but inhibition of signaling pathways, mitochondrial dysfunction, or altered P-450 metabolism have been implicated as potential etiologies. Several cases of postoperative rhabdomyolysis have been reported in patients receiving statins before surgery.[10] Precipitating factors in these cases may have included prolonged immobilization, the lithotomy position, preoperative myopathy, and prolonged use of statins.

Despite the American Heart Association Clinical Advisory, acute withdrawal of statin therapy may pose a significant risk to patients with cardiovascular disease. Cardiac event rate was investigated in 1,616 patients

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admitted with an acute coronary syndrome.[11] Statin treatment was associated with a threefold reduction in 30-day mortality as compared with patients who did not receive these drugs. In contrast, mortality rates were dramatically increased by nearly sevenfold in patients in whom statin therapy was withdrawn during or after admission to the hospital. The mechanism for this deleterious effect remains unclear, but experimental evidence suggests that acute statin withdrawal enhances oxidative stress and produces endothelial dysfunction.[12] In a study of statin use in 211 patients undergoing major vascular surgery, there were no occurrences of muscle symptoms, and incidence of moderate or severe increases in creatine phosphokinase were not different in statin users compared with nonusers.[13] The current meta-analysis clearly supports the potential benefits of continuing perioperative statin therapy.

The beneficial effects of initiating statin therapy immediately preoperatively is less clear. Experimental results in animals suggest that statins administered days before a myocardial ischemia and reperfusion event or upon reperfusion alone are protective. However, only two randomized trials[14,15] in which statin therapy was initiated approximately 30 days before elective surgery are included in the meta-analysis. Statins did not alter mortality rate in either trial; however, neither study was adequately powered to address this outcome. The combined endpoint of death, myocardial infarction, angina, and stroke was decreased by nearly 70% in patients undergoing vascular surgery.[14] Although relatively few patients were studied, the results suggest that short-term initiation of statin therapy might be effective to decrease cardiovascular risk in high-risk patients. The optimal duration of preoperative statin treatment remains unclear.

In summary, statins are an important class of drugs that decrease cardiovascular morbidity and mortality, produce favorable actions on lipid metabolism, enhance nitric oxide–mediated pathways, reduce inflammatory pathways, and produce direct cardioprotective effects. The results of the current meta-analysis by Hindler *et al.*[2] highlight the potential for statin therapy to positively impact cardiovascular risk reduction in patients undergoing cardiac and noncardiac surgery. Although there remains a small risk of rhabdomyolysis in patients in whom statins are continued in the perioperative period, the current review demonstrates that the mortality rate may be substantially increased in patients in whom statins are withdrawn. Therefore, it is time to reevaluate the perioperative use of statin drugs. In contrast to previous advisory statements, it would seem prudent to reintroduce statin therapy as soon as possible in patients chronically treated with this drug, and consideration should be given to preoperative initiation of statin therapy in high-risk patients.

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