

Some New Features and Developments at ANESTHESIOLOGY

Electronic Management

FOR over 3 yr, ANESTHESIOLOGY has provided authors with an on-line method for checking the status of their submitted manuscripts. We know that nearly 90% of our authors utilize this system at some time during the peer review process. For roughly a year and a half, we have been encouraging authors to submit their manuscripts electronically *via* our Web site, diskette, or e-mail. By the end of 2002, almost 90% of our papers were arriving *via* one of these routes. In January 2003, we made electronic submission mandatory for all manuscripts. This transition appears to have been totally painless. Since January, only about one manuscript per month has arrived in a paper format—and obtaining an electronic version from the authors has been straightforward. There are enormous advantages to this transition. Most importantly, having all manuscripts in an electronic format has made it possible for us to substantially speed the review process, at least for initial submissions, and it has resulted in a 7-day reduction in our median times to first decision, as well as the nearly complete elimination of truly delayed first decisions (as compared with the last few months of 2001).

This month, we take this process one step further. Since the editorial office was established in Iowa, we have used a proprietary database for managing our manuscripts. We are now switching to a Web-based commercial system (Editorial Manager [EM], Aries Systems Corporation, North Andover, MA). Authors will still be able to submit their articles *via* our “old” Web system and *via* e-mail and disk. However, they will also have the option of submitting *via* EM, and all subsequent communications with authors and reviewers will be handled through this system. This has a number of implications for both our authors and our reviewers. Most importantly, it means that both will now need to have e-mail addresses *and* Web access. Reviewer packets will no longer be sent to anyone *via* “snail mail,” and printed reviews (either mailed or sent *via* fax) will no longer be accepted. I realize that some may view this as a burden. However, most major journals have taken this approach, and have done so successfully. One of our key goals is to serve our authors better—and we believe that this is an appropriate step toward meeting this goal.

One other change will be taking place over the course of the remainder of the year, although it won't be obvious to many people. Major changes have been and are

being made in the production process at Lippincott Williams & Wilkins (LWW), changes that will enable substantial reductions in the time between when we forward a completed manuscript file to LWW and the article's appearance in print. Authors may already have noticed that page proofs (“galley”) are now being handled electronically. For many years, we've worked on an 11- to 12-week production schedule. This will quickly be shortened to about 8 weeks, and we are actively pursuing methods that may allow articles to be electronically published (on our Web site) even more rapidly.

Free Electronic Access

Since 1999, the full text of ANESTHESIOLOGY (back to 1995) has been available electronically to all subscribers, to libraries, and to nonsubscribers who pay a small fee to download individual articles. However, as we have tracked activity at our Web site, we've noted some disturbing patterns. Many (thousands) of readers have tried to download articles, only to be confronted by the pay-per-view screen. We believe that this conflicts with our greater goal of making the best quality peer reviewed material in our specialty available to the greatest number of individuals. Therefore, after over 2 yr of discussion between the editorial board and LWW, and after approval by the American Society of Anesthesiologists, we have decided to allow everyone free electronic access to articles more than 1-yr-old. Access to more recent articles will still be limited to subscribers and to those willing to pay for download. However, papers more than 1-yr-old (*e.g.*, published in July 2002 or before) will be available to all. We may sacrifice some pay-per-view revenue, but the Editors, the ASA, and LWW view this as an important service to the world's anesthesia community, as well as to nonmember readers involved in the science related to our specialty.

Conflict of Interest

As everyone who reads a newspaper knows, the problems of conflict of interest between manufacturers and authors, authors and reviewers, reviewers and editors, etc., continue to grow. As Larry Saidman (former Editor-in-Chief of ANESTHESIOLOGY) and I noted in an editorial published soon after I took over the editorship, this is a serious problem in our specialty.¹ To try and divorce ourselves from the sponsorship of manufacturers would be foolish; much of the progress we've made over the past decades is a direct result of the support provided by

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pharmaceutical and equipment companies. Nevertheless, ANESTHESIOLOGY has taken a strong position regarding possible conflicts of interest. My feeling has long been that the best way to deal with this is to provide the readers with a clear and unambiguous disclosure of the relationships between the authors of a paper and their sponsors. All submitted and published articles must contain such a disclosure statement, some of which are quite lengthy. Some authors have objected, unsuccessfully. We firmly believe that the honest disclosure of any and all relationships between a sponsor and an author is in the best interest of everyone.

What has been missing from this process has been a method for disclosing the conflicts of our editors and associate editors. All members of our editorial boards file yearly conflict of interest statements with the editorial office. However, these statements were not made available to authors or readers. This has now changed. Starting in early 2003, a formal conflict disclosure statement for all Editors has been posted on the Masthead of the electronic Journal, where they can be read by anyone. Statements for our Associate Editors will soon follow.

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Lung Overinflation

The Hidden Face of Alveolar Recruitment

In this issue of ANESTHESIOLOGY, Lim *et al.* provide experimental evidence that the positive pressure ventilation-induced re-aeration of a surfactant-depleted collapsed lung can be optimized by using a recruitment maneuver.¹ They also convincingly demonstrate that this potential beneficial effect is accompanied by the overinflation of other lung regions.

For the first time in an experimental study, computed tomographic sections of the whole lung were obtained at end-expiration and end-inspiration at different intrathoracic pressures. Scanning the whole lung is essential for an accurate determination of lung volumes of gas and tissue, lung aeration, and alveolar recruitment.² In a majority of patients with acute respiratory distress syn-

This Editorial View accompanies the following article: Chae-Man Lim, Sung Soon Lee, Jin Seoung Lee, Younsuck Koh, Tae Sun Shim, Sang Do Lee, Woo Sung Kim, Dong-Soon Kim, Won Dong Kim: Morphometric effects of the recruitment maneuver on saline-lavaged canine lungs: A computed tomographic analysis. ANESTHESIOLOGY 2003; 99:71-80.

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Will this eliminate all possible conflicts at ANESTHESIOLOGY? No, certainly not. But we believe it confirms our commitment to helping the reader understand what conflicts potentially exist. The responsibility for interpreting these conflicts, and determining how they might influence the science we present, is in the hands of the reader.

Our goals include continuing to pursue ways to improve all aspects of the Journal. I invite you to communicate with the editorial board members, the editorial office staff, and me. We all welcome your feedback, suggestions, and critical comments. I can't make any promises about implementing all of the suggestions that are made—but I can promise to pay attention to all constructive comments.

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Reference

1. Todd M, Saidman L. Academic-Industrial Relationships: The Good, the Bad, and the Ugly. ANESTHESIOLOGY 1997; 87:197-200

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drome (ARDS) when lying supine, lung re-aeration resulting from positive end-expiratory pressure (PEEP) decreases from the apex to the diaphragm.³ In contrast, lung overinflation predominates in caudal and nondependent lung regions.⁴ As a consequence, assessing changes in lung aeration resulting from PEEP on a single computed tomographic section presents the risk of grossly mis-estimating alveolar recruitment and lung overinflation. In their study, Lim *et al.* used a multi-detector Light Speed Scanner, which allowed scanning of the whole lung with an accurate spatial resolution (voxel size ranging between 1.2 and 1.74 mm³) during a breath-holding lasting less than 10 s.

An ovine model of surfactant depletion-induced lung lavage was selected because it promotes alveolar collapse and fits the traditional concept viewing the ARDS lung as "collapsing" under its own weight. In addition, it has been shown to be the most responsive to recruitment maneuvers.⁵ Throughout the experiment, pure oxygen was administered, a condition known to potentiate alveolar collapse.⁶ The sheep were also lying supine, a posture that frequently generates atelectasis of dorsal lung regions and is well known to enhance the response to recruitment maneuvers in animals with oleic acid-induced lung injury⁷ or in patients with ARDS.⁸ In other words, the most favorable

experimental settings were selected for demonstrating the beneficial effects of recruitment maneuvers. For these reasons, the results of the present study cannot be automatically extrapolated to adults with ARDS in whom alveolar flooding rather than lung collapse is the main cause of the loss of aeration.^{9,10} Additional studies performed in oleic acid-induced injured lungs¹¹ are required to assess whether the benefits of recruitment maneuver hold true when alveolar spaces are filled with fluid, hemorrhagic edema, inflammation, and tissue debris.

The recruitment maneuver performed in the present study has several particularities that deserve to be outlined. In contrast to classic recruitment maneuvers consisting of a 40–60 cmH₂O inspiratory pressure sustained during 15–60 s,^{5,7,12–17} a 40-cmH₂O peak inspiratory pressure was applied during a 120-s period of pressure-controlled ventilation, during which PEEP was gradually increased above and then decreased to the lower inflection point + 2 cmH₂O. Theoretically, such a long-lasting maneuver should prevent the expiratory derecruitment of lung regions that are progressively reopened during the successive inspiratory phases performed at the pressure of 40 cmH₂O.¹⁸ As correctly pointed out by the authors in the discussion, lung recruitment is basically an inspiratory phenomenon occurring during tidal ventilation, whereas PEEP prevents expiratory derecruitment. However, before adopting such a recruitment maneuver in clinical practice, it seems essential to verify experimentally that it is more efficient than a sustained inflation for recruiting a surfactant-deficient collapsed lung.

An interesting result of the study, although not entirely new, is that a recruitment maneuver seems superior to a simple PEEP titration for decreasing pulmonary shunt, improving arterial oxygenation, and reopening a surfactant-deficient lung. This beneficial effect is accompanied by an increase in respiratory compliance and a decrease in plateau inspiratory pressure, reflecting the greater lung re-aeration. This finding is in accordance with previous studies demonstrating that at a given PEEP, the end-expiratory aeration is markedly influenced by the preceding end-inspiratory pressure: the higher the end-inspiratory pressure (or volume), the higher the end-expiratory aeration.^{13,19–21} In fact, as confirmed by Lim *et al.*, the administration of a recruitment maneuver boosts the ventilatory cycle onto the deflation limb of the pressure-volume curve.²² If the duration of the recruitment maneuver is long enough, then the beneficial effects may be long-lasting, as previously demonstrated in patients with ARDS.¹⁸ However, it must be outlined that the superiority of a recruitment maneuver over a simple PEEP titration for recruiting collapse prone lungs was not retrieved in patients with ARDS.²³ In a series of 17 patients whose ARDS was predominantly caused by a primary insult to the lung, Villagra *et al.*²³ compared the effects of a simple PEEP titration with the effects of a recruitment maneuver very similar to the one used by

Lim *et al.* The superimposed recruitment maneuver provided no additional increase in arterial oxygenation in most of the patients whose lungs were probably not collapsed but rather were filled with edema, blood, and inflammation. In such patients, lung recruitment could be optimized by setting the PEEP 3 to 4 cmH₂O above the lower inflection point of the pressure-volume curve.

In fact, the most striking contribution of Lim *et al.* is to bring convincing evidence that providing lung recruitment may be associated with a risk of overinflating significant parts of the lungs. At a PEEP of 3 cmH₂O, 40% of the lungs were normally aerated, with a wide range of CT attentuations, indicating a nonhomogeneous regional distribution of the lung collapse. As observed in humans, in whom “focal” loss of aeration predominating in lower lobes is the most frequent morphologic pattern characterizing ARDS,²⁴ lung collapse was found predominantly in caudal and dependent parts of the lungs. According to the “sponge” theory, the “superimposed” pressure increases in dependent lung regions, which require high intrathoracic pressures to be reopened. These high opening pressures were generated during the recruitment maneuver, explaining a recruitment of caudal lung regions that was not obtained with a simple PEEP titration. Unfortunately, a high opening pressure for a collapsed lung becomes a high “distending” pressure for a normally aerated lung, and it is not surprising that both methods of recruitment induced significant lung overinflation. At end-expiration, 12% of the overall lung volume was overinflated, reintroducing a risk of ventilator-induced lung injury. These experimental findings are in accordance with several human studies that clearly reported the simultaneous onset of alveolar recruitment and lung overinflation in patients with ARDS receiving PEEP levels ranging between 10 and 20 cmH₂O.^{3,25–28} Experimentally, lung overinflation was also reported in *Escherichia coli* bronchopneumonia²⁹ and in oleic acid-induced lung injury,¹¹ two models in which alveolar flooding rather than lung collapse plays a determinant role in the loss of aeration. Interestingly, lung overinflation slightly increased at end-inspiration, reaching 14% of the overall lung volume and suggesting that tidal ventilation essentially resulted in lung recruitment. Similarly, lung overinflation was not significantly greater following the recruitment maneuver, suggesting a predominant effect on lung re-aeration.

With regard to the clinical application of recruitment maneuvers and, more generally, to the different techniques of alveolar recruitment, it seems essential to consider the risk of overdistension and to avoid focusing exclusively on the potential for recruitment.³⁰ Optimizing alveolar recruitment can be defined as providing the greatest lung re-aeration without inducing significant lung overinflation. Because a recruitment maneuver is not likely to increase lung overinflation, as demonstrated by Lim *et al.*, it could be an attractive adjunct to PEEP for optimizing the re-aeration of a collapse-prone lung.

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Intrathecal Analgesia and Catheter-tip Inflammatory Masses

The advent of intrathecal analgesic therapy, which involves delivery of analgesic agents directly into the spinal fluid *via* implanted infusion pump, has revolutionized the treatment of chronic pain. Compared to other routes of drug delivery, intrathecal administration offers the relative advantages of greater efficacy and fewer adverse effects. Compared to most interventional, ablative approaches to pain management, this nondestructive, reversible, adjustable therapy is generally very safe. However, as occurs with the maturation of many innovations in medical care, growing experience has revealed that this therapy is not without complications. One of the most potentially serious complications is the formation of an inflammatory mass at the tip of the intrathecal catheter placed to deliver analgesic agents. This issue of ANESTHESIOLOGY includes two articles authored by leaders in the field of intrathecal analgesia, who provide valuable insights into the formation of catheter tip inflammatory masses ("granulomas").^{1,2}

The phenomenon of intrathecal granuloma associated with intrathecal analgesic administration was first described in 1991 in a case report of a patient who presented with paralysis caused by an intrathecal mass that compressed and damaged the spinal cord.³ Since then, dozens of granulomas have been reported, and there is growing awareness of the causal relationship between intrathecal analgesic administration and the formation of inflammatory masses at the catheter tip. Despite growing recognition of the problem, we understand relatively little about the causes of granulomas; consequently, we do not know how best to treat or prevent these mass lesions.

Why do we need to understand the pathophysiology of catheter-tip inflammatory masses? At the very least, granulomas can result in loss of pain relief for affected patients. More important, they may cause neurologic deficit, including myelopathy and paralysis, which may not

improve despite aggressive treatment. Loss of pain relief, neurologic injury, and the need for medical and/or surgical treatment of the intrathecal mass result in personal and economic loss that compromise the utility of this pain therapy.

Approximately 92 cases of catheter-tip inflammatory masses have been reported on a voluntary basis in the literature, to manufacturers of the infusion pumps, and to the U.S. Food and Drug Administration.⁴ On the basis of the number of pumps implanted, the incidence of granuloma formation is estimated to be 0.04% after 1 yr of therapy, increasing to 1.15% after 6 yr of therapy.⁴ These figures undoubtedly underestimate the true incidence, because voluntary reporting probably reveals only a small fraction of the total number of granulomas. The number of patients developing granulomas is almost certain to increase during the coming years. The annual rate of growth of number of pumps implanted each year for the treatment of chronic pain is approximately 12% (Robert Coffey, M.D., Medtronic, Inc., Minneapolis, Minnesota, verbal communication). In contrast to the early days of intrathecal analgesic therapy, when this modality was restricted generally to the treatment of pain in cancer patients with relatively short life expectancies, intrathecal analgesic therapy is currently used most often for the treatment of chronic noncancer pain in patients with relatively long life expectancies, and these individuals may receive intrathecal drugs for long periods of time. Thus, an ever-increasing number of patients will be exposed to intrathecal analgesics for increasingly greater lengths of time; the number of patients developing granulomas is expected to rise accordingly.

In this issue, Gradert *et al.*² and Yaksh *et al.*¹ describe the formation of intrathecal granulomas in sheep and dog models, respectively. These two reports provide, for the first time, detailed information about the development of these lesions, the factors associated with their development, and a possible explanation of the pathophysiology of granulomas. The results described in these articles correspond to descriptions of granulomas in humans, with the exception of the more rapid time course of granuloma formation (within 4 weeks) in the animal models. Granulomas have been reported to occur in humans within several weeks after initiation of therapy but in general do not occur until months or years of therapy have elapsed.⁴ Despite this difference, the models described by Yaksh and Gradert provide a means for us to understand the etiology of these inflammatory masses, which will enable us to develop effective strat-

This Editorial View accompanies the following articles: Yaksh TL, Horais KA, Tozier NA, Allen JW, Rathbun M, Rossi SS, Sommer C, Meschter C, Richter, PJ, Hildebrand KR: Chronically infused intrathecal morphine in dogs. ANESTHESIOLOGY 2003; 99:174-87; and Gradert TL, Baze WB, Satterfield WC, Hildebrand KR, Johansen MJ, Hassenbusch SJ: The safety of chronic intrathecal morphine infusion in a sheep model. ANESTHESIOLOGY 2003; 99:188-98.

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gies to treat them and, ideally, minimize or eliminate their occurrence.

As reported in these two articles, these intraspinal lesions are inflammatory masses that develop in response to the intrathecal administration of opioid agents, perhaps mediated *via* immune responses. Granulomas have not been reported to occur as a result of intrathecal infusion of nonopioid agents such as baclofen. Clinical data and the research reports within this volume of the journal indicate that granulomas occur at higher rather than lower doses and concentrations of opioid. Unfortunately, neither the articles presented here nor clinical data provide insight into whether opioid concentration or total dose is more (or equally) important in the genesis of granulomas. Particularly intriguing is the observation by Yaksh *et al.* that a nonopioid agent (clonidine) delivered concurrently with opioid might have a protective effect.

The information provided by these two sets of authors has significant implications for the management of patients receiving intrathecal analgesics. The results support recommendations published recently in an effort to increase awareness of intrathecal granulomas and their treatment and prevention.^{4,5} In particular, the findings reported by Gradert *et al.* and Yaksh *et al.* support the consensus recommendations^{4,5} that the total daily dose and the concentration of intrathecal opioid should be kept as low as possible to reduce the likelihood of granuloma formation.

What are the important messages associated with the articles published here? First, catheter-tip inflammatory masses are a potentially serious complication. Given the adverse impact of granuloma formation on the success of intrathecal analgesic therapy (including the potential for permanent neurologic injury), we must understand the pathophysiology of intrathecal granulomas and work toward eliminating them as a complication of therapy. We can accomplish this with good-quality basic science investigations, such as those published in this issue, com-

bined with clinical observations. Second, granulomas may become more common as physicians who manage intrathecal analgesic infusions become more aggressive with the therapy, administering higher doses, which require higher concentrations, and for longer durations. Third, physicians who manage patients receiving intrathecal analgesics must be highly aware of the possible development of intrathecal granulomas and must perform regular surveillance of their patients to detect these masses early, before serious complications arise. Patients who are suspected of harboring intrathecal granulomas must be evaluated and treated promptly to minimize the possibility of permanent neurologic deficit.

Intrathecal therapy has been a tremendous advancement in the field of pain management. Yaksh *et al.* and Gradert *et al.* are to be commended for their attention to the complication of intrathecal catheter-tip inflammatory masses. Their work, and future efforts directed toward determining the causes, treatment, and prevention of this disorder, will allow physicians to offer this therapy with greater confidence in its ability to provide safe and effective pain relief.

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Perioperative Genomics

Venturing into Uncharted Seas

Since its inception, the science and art of anesthesiology have been challenged and stimulated by the extraordinary variability in patient response. Patients exhibit untoward, and often unpredictable, responses to surgical procedures and to the pharmacopoeia employed in the perioperative period. As our technology and scientific understanding have become more refined, so has our ability to identify patients at risk for specific postoperative complications related to these interventions. Yet, our predictive capacity remains far from omniscient.

In this issue of ANESTHESIOLOGY, Ziegeler *et al.*¹ examine some of the recent developments in our quest to use the information unleashed by advances in human genetics to identify patients at risk. The findings highlighted catalog some of the initial efforts of those wrestling with a new and challenging field (coined *functional genomics*).^{2,3} This field has the potential to establish a firm rationale behind many unexplained risks related to anesthesia and surgery that the field has long dismissed as “idiopathic,” or even as “acts of God.” The review summarizes a number of statistical correlations between DNA sequence variations common in the population (single nucleotide polymorphisms, or SNPs), and important clinical outcomes in perioperative medicine. The challenge will be to move from these intriguing statistical correlations to an operational understanding of how genetic variability can be used in a practical manner to guide therapy, predict outcome, and improve patient care.

Studies and reviews in this field herald a new age of preoperative risk factor identification,^{2,3} as molecular medicine broadly focuses on generating predictions regarding clinical outcome on the basis of each individual's unique DNA sequence. Ziegeler *et al.* ably define for us the essential genetic parlance, and then review the recent literature associating genetic variation to clinical outcomes with relevance to perioperative medicine. Given the extraordinary rate at which the information on genetic associations is expanding, concurrent with the increasing Web-based availability of healthcare data to physicians and their pa-

tients, clinicians may soon find it necessary to navigate this literature on a routine basis. Moreover, just as we routinely judge when a particular (new) drug therapy should become part of our own practice, as industry moves to make genetic screens available and relatively inexpensive, we will soon be called to judge when identification of particular genetic variants should be integrated into our routine preoperative evaluation practices.

In view of these emerging trends, guidelines are being developed to assist clinicians and scientists in evaluating the impact of genetic association studies.³ A guiding principle is that results obtained in a single population require confirmation and validation in distinct, unrelated populations. In perioperative medicine, a statistical linkage between a genetic variant and a clinical outcome in a cohort of patients, particularly when operated on by a specific surgical team, requires validation in another population who have undergone surgery in a different center, by a different surgical team. This provides assurance that the genetic association is not spurious; that is, not related to an (unidentified) environmental variable that happens to correlate with the outcome of interest. Recent work from our own center⁴ exemplifies this caution, where linkage between the factor V Leiden polymorphism and a nearly 30% reduction in blood loss following cardiac surgery was demonstrated. This result was obtained in more than 500 patients operated on by our clinical team; hence, validation in other centers and patient populations will be required before prospective screening of patients can be recommended.⁴ At the same time, the risks conferred by genetic variants must be dovetailed into our existing knowledge of nongenetic clinical risk factors. Given the vast number and complexity of clinical variables that influence a clinically apparent surgical outcome (*i.e.*, neurologic injury following heart surgery), assignment of a genetic variant as a truly independent risk factor requires rigorous, prospective clinical trials involving exceedingly large numbers of patients (usually thousands). Moreover, demonstrating that a statistically significant outcome risk associated with a genetic variation is truly a *causative* risk requires accompanying basic science investigations aimed at correlating the impact of the DNA sequence change on protein function, and thus human physiology, in a manner that correlates in a meaningful way with the clinical outcome in question.

Most genetic association studies focus on DNA polymorphisms, genetic variants that are relatively common in the population, occurring at an incidence of greater than 1%. As such, these variants are often clinically silent and are

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manifest only during adverse circumstances (*i.e.*, surgery, exposure to a new drug, etc.). This contrasts with rare, disease-associated sequence variants, denoted *mutations*, that may occur only within a single family and often provoke pathophysiology (*i.e.*, Marfan syndrome). As such, the usually silent phenotype of a polymorphism suggests that these variants, when present, usually do not cause adverse outcome in 100% of patients exposed to an intervention; rather, the presence of the genetic variant contributes a small but statistically significant increase in risk within a large population. Hence, the predictive value of most polymorphisms for guiding therapy toward improved outcome, or even as a basis for counseling patients on their perioperative risk, requires rigorous assessment relative to standard practice in prospective trials. A contemporary example of this deficiency lies in the undefined risk for untoward, life-threatening arrhythmias (Torsades de Pointes) during drug therapy with agents that prolong the electrocardiographic Q-T interval. This concern is highlighted in the ongoing debate over the safety of droperidol administration for postoperative nausea and vomiting.⁵ Recent studies make it clear that clinically silent polymorphisms in cardiac potassium channels, not detectable on a screening electrocardiograph, can sometimes mediate exceptional (and unpredictable) Q-T prolongation and Torsades on drug administration, even at low doses.^{6,7} Conversely, only a small minority of patients carrying these sequence variants demonstrate adverse responses, and the studies to demonstrate the predictive value of prospective identification of these “risk” polymorphisms have not been performed. Without trials firmly establishing the *value* of prospective identification, it is difficult to justify routine patient screening for particular DNA variants.

With this scientific rigor in mind, it is understandable that career geneticists have limited enthusiasm for the initial wave of genetic association studies, because of concerns that spurious associations may pervade the literature, only to be found invalid on subsequent attempts at validation.^{8,9} The design and publication of genetic association studies, particularly as they relate to studies of perioperative risk, must take into account rational selection of candidate genes, corrections for population ethnicity, sufficiently large sample sizes, publication of negative as well as positive results, statistically sound methods for dealing with issues of multiple testing, use of intermediate endpoints and surrogate markers, and validation in independent populations.^{8,9}

Historically, our efforts to refine the identification of perioperative risk factors have resulted directly in important advances in patient management. One of the best examples of this progress is the clinical identification of patients at risk for perioperative myocardial injury. Important clinical predictors of myocardial events were first described in the 1970s.¹⁰ As our diagnostic and informatics technology became more advanced, additional risk factors and their interactions were described.¹¹ These culminated

in the creation of practice guidelines, published initially by the American College of Cardiology and American Heart Association Task Force in 1996¹² and revised last year.¹³ As our confidence in genetic associations increases, and the number of variant alleles with predictive value for guiding rational therapy expands, we can foresee an analogous need to develop consensus-based genetic risk factor practice guidelines. Anesthesiology as a specialty is called to provide leadership in these efforts, and is even now supporting the training of young investigators through the Foundation for Anesthesia Education and Research and other major research organizations. At the same time, as our specialty embraces the excitement and “glitz” of genetic medicine, it must be ever cognizant of the profound economic and social consequences genetic associations may have on individuals and on populations. These ethical issues demand ardent adherence to the most rigorous standards of evidence-based practice, as well a strong dose of healthy skepticism, as we journey into the uncharted sea of perioperative genomics.

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