

## Obligate Acceleromyography and Pharmacologic Reversal of All Neuromuscular Blocking Agents: Really, and Where Is the Clinical Outcome?

*To the Editor:*—The recent article<sup>1</sup> and editorial<sup>2</sup> regarding acceleromyography findings of residual paralysis hours after neuromuscular blockade (NMB) raised several questions and proposed sweeping conclusions based on results found in extubated patients on arrival in the PACU, transferred by competent anesthesiologists. The type of anesthesia and the time from discontinuation is unknown. No patient was examined prior to use of NMB for preexistent abnormalities, and it does not appear that any of the study patients required or were given reversal agents, despite the “findings” of residual NMB. I suspect that all recovered successfully and without complaint, making the relevance of “acceleromyographic quantification of residual effects” clinically irrelevant. The editorial invokes “evidence-based practice,” but the “evidence” lies outside the realm of practice. Evidence should have clinical consequence. The newest mantra of medicine was ignored: *outcome-based*. Also, because the study was not randomized and double-blind, it may be too soon to make these sweeping recommendations.

Universal reversal is offered as if no adverse effects are associated with such drugs: Hypersalivation, nausea, asystole, bradycardia and tachycardia, laryngospasm, negative pressure pulmonary edema and failure to reverse or recognize such, prolonged apnea after succinylcholine for reintubation, and so forth are potential reversal side effects. These acceleromyographic findings are extremely difficult/impossible to quantify, using the clinically commonplace mechanomyogram tactile and visual methods.<sup>3</sup> Increased utilization of complex monitoring devices is also proposed, as if no shortcomings are introduced—don't forget the costs and time involved in applying/acquiring devices and to verifying/failing to verify complete reversal! No scientific test will ever replace the clinical ability to comprehensively evaluate the patient's ability to breathe and maintain an airway or clinical experience to appreciate pharmacodynamics in medicine. *Recovery* is a composite of the clinical effects of *all* anesthetic agents, as well as the imposition of the surgical events: Indeed, frequently patients remain

intubated because of surgical trespass, narcotics, sedatives, or preoperative/perioperative infirmity.

How many study patients with residual NMB needed reversal, were reversed, or failed recovery without reversal, and based on what criteria? Did the residual effects disappear after reversal agents, and when? How did age, core temperature, body mass index, NMB agent used, and patient satisfaction correlate to the findings of individual's residual NMB hours after a single dose? Did the abdominal wound inhibit head lift in your patients, as it does in mine, and how did you control for this? How is this study *clinically* relevant: what were the outcomes? A great deal of neuromuscular and pharmacokinetic reserve is evident in many healthy, muscular patients yet not evident in debilitated geriatric patients, who will need *complete* reversal. Do we need pharmacologic reversal in every patient and can these tests actually measure clinical reversal in ALL patients? Are we recommending obligate reversal to eliminate acceleromyograph findings or clinical respiratory compromise, and what side effects will obligate reversal and acceleromyograph monitoring incur? Sometimes the enemy of “good” is “better.”

**Paul M. Kempen, M.D., Ph.D.** University of Pittsburgh School of Medicine, Presbyterian University Hospital, Pittsburgh, Pennsylvania. pkempe@pol.net

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(Accepted for publication September 26, 2003.)

## Evidence-based Practice and Neuromuscular Monitoring

*To the Editor:*—Evidence-based practice is a laudable goal, but before acting on it we must have all the evidence. Two hours after an intubating dose of an intermediate acting muscle relaxant, Debaene *et al.*<sup>1</sup> showed residual paralysis not recognized by subjective tactile or visual train-of-four monitoring. On the basis of this evidence, quantitative evaluation is recommended by the authors and is endorsed by the accompanying editorial.<sup>2</sup> Using awake volunteers, Eikermann<sup>3</sup> confirmed the presence of respiratory dysfunction detected by accelerometry that is not detected by more subjective analysis. However, what is not answered is, What is the morbidity and mortality caused by this “subjective” analysis? What is the morbidity and mortality of fixing the perceived problem? I have not seen a clinical problem with a patient intubated after rocuronium, a subjective train-of-four ratio of one at 1 hour later, and extubation without reversal. In fact, Eikermann reported, “Despite impaired upper airway function, no jaw thrust was needed, none of the volunteers reported dyspnea, and oxygen saturation remained greater than 96% at all times.” Clinically, quantitative analysis may yield false-positive test results that change our procedures

so as to increase morbidity and mortality. Reversal of clinically insignificant paralysis may increase nausea and vomiting as well as increase airway secretions that may decrease pulmonary function. In an attempt to avoid problems with muscle relaxants, intubating without relaxants may cause laryngeal morbidity.<sup>4</sup> Resources and attention may be diverted from more significant factors. Outcome studies comparing the standard train-of-four with a more precise measurement of paralysis would provide evidence as to which is the best technique. Until we have such evidence it is premature to recommend a change in practice.

**M. Craig Pinsker, M.D., Ph.D.** Commonwealth Anesthesia, Richmond, Virginia. mcpins@pol.net

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:454

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## Neuromuscular Monitoring Advancement

*To the Editor:*—I read with interest the editorial view of Lars Eriksson, M.D., on evidence-based practice and neuromuscular monitoring.<sup>1</sup> As Dr. Eriksson correctly presents, current subjective neuromuscular blockade monitoring is clearly inaccurate, often resulting in patients with some residual blockade in the PACU.<sup>2-7</sup> However, to conclude that “the message is short and clear—it is time to move from discussion to action and introduce objective neuromuscular monitoring in all operating rooms” is unfortunate. There are currently no published outcome studies with respect to intermediate-acting muscle relaxants and residual weakness postoperatively. The “consequences” to which Dr. Eriksson refers in his editorial have never been related to any mortality/morbidity differences. His belief that this would improve patient outcome is unsupported.

To advocate a new monitoring standard that would probably cost millions of dollars without outcome data to support such an expenditure is inappropriate. Just because other equipment has been introduced into medicine without outcome research does not justify the continuation of such behavior. That is not evidence-based medicine. Dr. Eriksson's conclusion, although quite dramatic, is not presently justified.

**Roland R. Rizzi, M.D.** Department of Anesthesiology, Lenox Hill Hospital, New York, New York. mdski@msn.com

Anesthesiology 2004; 100:454

*In Reply:*—We thank Drs. Kempen and Pinsker for their remarks on our article.<sup>1</sup> The main criticism of these two letters is that because outcome of partially paralyzed patients in the postoperative setting was not extensively evaluated, there is not enough evidence to recommend a quantitative evaluation of neuromuscular blockade or to promote universal reversal in presence of a partial paralysis at the end of the procedure. We agree with the first part of the comment. Indeed, our study was not designed to assess adverse events induced by partial paralysis. Our aim was limited to the determination of the incidence of partial paralysis at arrival in the PACU following the administration of a single dose of nondepolarizing muscle relaxant with an intermediate duration of action. This was done only to alert physicians that a time interval longer than 2 h after tracheal intubation to the end of the surgical procedure does not guarantee full recovery. Numerous studies have already demonstrated that moderate degree of paralysis (train-of-four ratio between 0.7 to 0.9) impedes physiologic pathways during early recovery. These alterations particularly affect respiratory response to hypoxemia,<sup>2,3</sup> and the ability to swallow, a mechanism involved in the upper airway protection from inhalation after extubation.<sup>4-6</sup> In our study, we tried to demonstrate that quantitative monitoring (i.e., train-of-four ratio measurement) is a valuable tool to detect a low degree of residual paralysis with a good accuracy while qualitative instrumental tests and clinical test (head-lift) are not sensitive enough. To resume, there is enough scientific evidence to think that residual paralysis is not advantageous to the patient, even if it is not necessarily deleterious. Thereafter, anesthesiologists can detect quantitatively moderate residual paralysis levels and have long known how to accelerate recovery using different reversal agents (neostigmine or

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(Accepted for publication September 26, 2003.)

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edrophonium). Therefore, and as mentioned in the editorial view accompanying our article,<sup>7</sup> why not use all of these facts to improve our patient's safety?

**Bertrand Debaene, M.D.\* Benoit Plaud, M.D., Ph.D.** \*Hopital Jean Bernard, Poitiers cedex, France. bdebaene@chu-poitiers.fr

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:455

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**In Reply:**—The interesting comments of Drs. Kempen, Pinsker, and Rizzi regarding my previous editorial in the Journal<sup>1</sup> are, to some extent, similar and offer me the opportunity to comment on this issue from another perspective.

Dr. Kempen focuses on whether we have evidence strong enough to support a change in practice. Like Dr. Pinsker, he also thinks that clinical bedside evaluation is superior to the information given by a neuromuscular monitor. He also states that the acceleromyograph is extremely difficult/impossible to quantify and that more complicated devices may lead to serious problems of costs, time consumption, and accuracy! In this matter, Dr. Kempen partly refers to a study when accelerography was not yet in routine clinical use. He also states that recovery includes recovery from all anesthetic agents, not only the neuromuscular blocking drugs. Currently, most commercially available neuromuscular monitoring principles are easy to use and have a simple and rapid setup procedure. Of course, objective neuromuscular monitoring, as mentioned in the editorial,<sup>1</sup> only detects muscular function rather than recovery from anesthesia within other organ systems (e.g., central nervous system, spinal cord). As such, neuromuscular monitoring provides important pieces of information that cannot be derived from other monitoring principles, such as capnography, spirometry, or end-tidal gas analysis. More important, it is not justified to accept a nonmonitoring attitude merely because one thinks the evidence is insufficient and without having studied the recent literature.

Dr. Pinsker touches on issues related to morbidity and mortality caused by residual block. In this context, he also states that he has not seen a clinical problem with a patient cared for in his practice, which he declares routinely lacks neuromuscular monitoring and reversal agents. He further thinks that more outcome studies are needed before a change in practice can be recommended. As a clinical anesthesiologist who routinely reads our anesthesia journals, I am surprised at this statement. Even without knowing the quality of the data and the protocols that Dr. Pinsker uses, I strongly suggest that he publish his clinical observations about the lack of any problems in his practice, because such findings are in deep contrast to several reports in the anesthesia literature.<sup>2–6</sup> Moreover, the existence of a few outcome studies<sup>5,6</sup> of the kind Dr. Pinsker wants to see must have escaped his attention. As written in the editorial, investigations of that kind<sup>5,6</sup> and many more clearly demonstrate that such practices result in residual paralysis in many patients, that residual block is a risk factor for the development of postoperative pulmonary complications, and, finally, that such block can be avoided by objective neuromuscular monitoring.

To my opinion, this sends a clear message to all of us who frequently read anesthesia journals.

Finally, Dr. Rizzi would like to see better outcome studies. Each publication can (and should) be evaluated in this context, which improves the discussion. The editorial<sup>1</sup> tried to do this by putting neuromuscular monitoring in perspective with intraoperative and postoperative studies, thus providing key information, even if further studies are yet to be done. In this light, there is far more scientific evidence that residual neuromuscular block affects outcome in a way that may be hazardous for some patients, with increased risk for pulmonary adverse events occurring late in the postoperative period, when most anesthesiologists are back in the operating room. Solid information<sup>1,7,8</sup> currently supports the view that failure to introduce objective neuromuscular monitoring into routine anesthetic practice represents substandard care.

Once again, explore the references and join the club! It is time for action and to provide neuromuscular monitoring in our operating theaters.

**Lars I. Eriksson, M.D., Ph.D.** Karolinska Hospital and Institute, Stockholm, Sweden. lars.i.eriksson@ks.se

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:455–6

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## Alpha-stat Induced Alkalosis: Cause of Neuronal Apoptosis after Deep Hypothermic Perfusion

**To the Editor:**—We congratulate Ditsworth *et al.* for the elegant biochemical demonstration of mechanisms triggering the apoptosis cascade to eventually cause neuronal death following deep hypothermic circulatory arrest (DHCA) in piglets.<sup>1</sup>

The authors dismissed the significantly elevated caspase-8 of the cardiopulmonary bypass (CPB) group (see their figure 5) and declined making any comments regarding it, but how do they explain it? We believe it is the key to interpreting the article in the proper perspective. It is indeed documented that ischemic damage, even though reversible, had occurred without arrest, corroborating numerous reports of the overlooked deleterious effects of  $\alpha$ -stat cooling. If circulatory arrest was not induced and  $\alpha$ -stat hypothermia was innocuous,

one would not anticipate activation of caspase-8 or -3, the case of control animals without CPB.

The authors did not find postrewarming (adenosine triphosphate [ATP]) differences between the various groups. However, the issue is the ATP during cooling just before arrest and after the arrest just before rewarming, not after rewarming, because the described caspase-8 and -3 are activated by ischemia, during which time ATP is depleted.

We postulate that the arrest (ischemic) period was the final blow to activate the pathway of caspase-3 and to trigger the irreversible apoptosis cascade whose grounds had been conditioned by the hypothermia-induced Bohr effect (tissue hypoxia caused by the increased affinity of the oxyhemoglobin), aggravated by the  $\alpha$ -stat alkalosis during induction of



hypothermia to the point of caspase-8 activation. In the context of ischemia, apoptosis and necrosis must be a continuum, the fate depending on the extent of spared ATP stores;<sup>2</sup> necrosis is found in the center of brain infarcts, and apoptosis in the surviving penumbra zone. Alkalosis within pH ranges of 7.0 to 8.0 depresses linearly creatine-kinase mediated phosphorylation ( $\sim$  P) reactions;<sup>3</sup> the extremes of pH below 7 or above 8 at which linearity is maintained is not known. During deep  $\alpha$ -stat hypothermia, the actual pH often exceeds far above 8.0; if sustained long enough the decreased synthesis will lead to  $\sim$  P depletion even without arrest, manifested as significant elevation of caspase-8 in the CPB-only group. We postulate that  $\sim$  is further consumed during the arrest to levels below the threshold limits for activation of caspase-3 and leading to the apoptosis cascade. If arrest time is limited, sufficient  $\sim$  still remains for the recovery of ATP synthesis mechanisms on rewarming and oxygenation, leading to the recovery of postrewarming [ATP] levels similar to controls, thus preventing acute cellular death by necrosis. However, because the apoptosis cascade has been already activated, those cells are destined to die 8 to 72 h post-DHCA without involving ATP at that time.

Following is a brief account of some of the widely documented deleterious effects during  $\alpha$ -stat cooling that, despite being significant, were dismissed (as with the caspase-8 in the CPB group in the authors' study) because of the overwhelming findings of circulatory arrest:

1. During cooling induction: (a) brain hypoxia,<sup>4</sup> worse with  $\alpha$ -stat hypothermia than with pH-stat hypothermia<sup>5</sup>; (b) brain lactate production<sup>6</sup>; and (c) brain glutamate and nitric oxide release.<sup>7</sup>
2. During or after rewarming: (d) brain production of hypoxanthine and xanthine.<sup>8</sup>
3. Functional outcome: (e) the time required for electroencephalographic recovery on rewarming correlated with time to electrocerebral silence, and even minimal hypocarbia increased time to electrocerebral silence;<sup>9</sup> (f) worse neurologic performance and worse brain histopathologic injury with longer pre-arrest CPB  $\alpha$ -stat cooling duration.<sup>10</sup>

Cerebral oxygen needs below 18°C could *theoretically* be met by the dissolved oxygen on which  $\alpha$ -stat strategies rely,<sup>11</sup> but dissolved oxygen cannot satisfy requirements at temperatures higher than 18°C, at which the role of oxyhemoglobin (whose dissociation is carbon dioxide-dependent or pH-dependent) is greater. Significant brain lactate production starts during cooling well before arrest,<sup>6</sup> coinciding with brain hypoxia<sup>4,5</sup> and excitotoxicity.<sup>7</sup> Regardless of the temperature, the  $\text{Ca}^{2+}$  extrusion pump is impaired by alkalosis. Alkalosis increases *N*-methyl *D*-aspartate currents sensitizing to glutamate,<sup>12,13</sup> thus facilitating the intracellular  $\text{Na}^+$  and  $\text{Ca}^{2+}$  influx that cause cytotoxic edema, especially on reperfusion, which is minimized by acidosis.<sup>14,15</sup> Mild acidosis reduces glutamate neurotoxicity by decreasing the activation of *N*-methyl *D*-aspartate receptors and, consequently, reducing  $\text{Na}^+$  and  $\text{Ca}^{2+}$  influx, thus minimizing oxygen-glucose deprivation excitotoxic and reperfusion neuronal injury.<sup>12-16</sup>

The issue is preserving the metabolic machinery integrity and  $\sim$  P levels during cooling induction. For millions of years, nature<sup>17</sup> has exploited the protective hyperpolarizing effects of hypothermia due to increased  $\text{Na}^+$  efflux<sup>18</sup> and increased  $\text{Cl}^-$  conductance<sup>19</sup> of eucapnic ventilation-induced acidosis, which is equivalent to pH-stat perfusion management. Such a strategy maintains aerobic metabolism and integrity of energy requiring membrane pumps, regardless of age,<sup>17</sup> while fully taking advantage of metabolic depression and decreased release of excitatory aminoacids<sup>20</sup> induced by hypothermia.

Our contention that brain hypoxia (Bohr effect) develops with  $\alpha$ -stat cooling severely enough to cause injury well before arrest induction has been corroborated by the authors' elegant study. pH-stat management was demonstrated to be superior both functionally and histopathologically by the same group,<sup>5,21</sup> and it is regrettable that pH-stat-managed (CPB and DHCA) piglets were not included in this study, for we believe that caspase-8 in a CPB group and apoptosis in a DHCA

group would have been prevented or greatly minimized. Supplementary intravenous taurine further potentiated, equivalent to 1.2°C, the protection afforded by pH-stat hypothermia.<sup>22</sup>

**Tadaomi A. Miyamoto, M.D.\* Koho J. Miyamoto, M.D., Ph.D.**

\* Kyoto University, Graduate School of Medicine, Kyoto, Japan.  
tkmiyamo@f3.dion.ne.jp

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:457

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**In Reply:**—We thank Dr. Tadaomi A. Miyamoto and Dr. Koho J. Miyamoto for their interest in our work. We share their perception that the use of pH-stat management during cardiopulmonary bypass (CPB) for cardiovascular surgery in neonates confers neurologic protection compared with the use of  $\alpha$ -stat management during CPB.<sup>1–3</sup> However, we do not agree with their theory that  $\alpha$ -stat management during CPB cooling “primes the system” for neuronal apoptosis after deep hypothermic circulatory arrest. This theory is based on their selective interpretation of caspase-8 data in our study and altered brain bioenergetics data in other studies.<sup>4,5</sup>

First, we cannot conclude that caspase-8 was elevated following  $\alpha$ -stat CPB cooling. Although caspase-8 was elevated in Western blot analysis, as the authors point out, we did not find increased caspase-8 by immunohistochemistry or enzyme assays in the same brain specimens. Thus, the evidence for caspase-8 elevation was not conclusive. Moreover, we observed no functional impairment, histopathologic damage, or caspase-3 activation following deep hypothermic CPB using  $\alpha$ -stat management.

Second, the experimental evidence for brain energetic failure during  $\alpha$ -stat CPB cooling is conflicting. During  $\alpha$ -stat CPB cooling, adenosine triphosphate is preserved and cerebral hemoglobin oxygenation increases.<sup>6</sup> Whereas early work suggested cytochrome aa<sub>3</sub> reduction during  $\alpha$ -stat CPB cooling (supporting the idea of bioenergetic failure), recent work refutes the validity of these cytochrome aa<sub>3</sub> measurements.<sup>2,7,8</sup>

In summary, our interpretation of the literature is that pH-stat management for CPB provides neurologic protection for neonates through multiple mechanisms, but  $\alpha$ -stat management does not, in and of itself, induce neurologic injury.

**Andreas W. Loepke, M.D., Ph.D.,\* Dara Ditsworth, B.A., B.S., John C. McCann, B.S., C. Dean Kurth, M.D.** \*Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, Ohio. andreas.loepke@cchmc.org

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:457

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## Residual Neuromuscular Blockade: Importance of Upper Airway Integrity

**To the Editor:**—Eikermann *et al.* are to be commended for rekindling interest in the importance of upper airway obstruction with residual paralysis.<sup>1</sup> Previous observations in partially paralyzed volunteers indicated that although expiratory muscle strength was more impaired than inspiratory strength, expiratory flows were relatively more well maintained than inspiratory flows.<sup>2</sup> These decreased inspiratory flows could not be simply attributed to decreased effort or driving pressure. Rather, flows are reduced out of proportion to the diminished inspiratory muscle strength. The inspiratory flow patterns suggested a variable extrathoracic obstruction that was most likely the result of weakened airway abductor muscle activity during inspiration. Consequently, many patients who may demonstrate inspiratory muscle strength (maximal inspiratory pressure) ample for ventilation may still have diminished strength in muscles necessary for upper airway protection.<sup>3</sup>

Also implicit in the Eikermann study<sup>1</sup> is the relatively poor sensitivity of forced vital capacity and its inspiratory subdivision as indicators of neuromuscular block, or more specifically, respiratory muscle weakness. The relationship between vital capacity and respiratory muscle strength in supine partially curarized subjects is curvilinear.<sup>4</sup> That is to say, relatively large decrements in respiratory pressure generation must occur before volume reductions result. Thus, the relative preservation of vital capacity does not indicate a similar preservation of respiratory muscle strength as is often assumed. Such assumptions appear to be

valid in the rather clinically irrelevant upright seated position.<sup>5</sup> In supine subjects, whose mechanics are likely to be similar to Eikermann *et al.*'s semirecumbent subjects,<sup>1</sup> the greater efficiency of the diaphragm and the diminished contribution of rib cage expansion provide better preservation of lung volume.

**Thomas J. Gal, M.D.** University of Virginia Health System, Charlottesville, Virginia. tjgbmw@earthlink.net

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:458

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**In Reply:**—We appreciate Dr. Gal's interest in our work.<sup>1</sup> In our study, inspiratory flow was more affected by residual paralysis than expiratory flow. We agree that it is unlikely that persistent inspiratory flow impairment was evoked by residual blockade of inspiratory respiratory muscles, which are believed to be least affected by curarization.<sup>2</sup> Rather, pharyngeal muscle dysfunction shown to persist after recovery of thumb muscles from partial neuromuscular blockade is likely responsible.<sup>3</sup> However, to our knowledge the dose-response relationship or recovery profile of neuromuscular blocking agents at pharyngeal muscles has not yet been studied. In fact, it is unclear whether relaxation of a particular airway abductor muscle is responsible for persistent extrathoracic airway obstruction. Furthermore, there are no data on the time course of the suggested upper airway obstruction over the respiratory cycle. Therefore, Dr. Gal's hypothesis, that persistent inspiratory flow limitation during partial paralysis is due to variable extrathoracic obstruction as the result of weakened airway muscle activity during inspiration, is yet to be confirmed.

We cannot (and did not intend to) pinpoint to which degree the effects of relaxation on pulmonary function are evoked by diminution of respiratory strength and/or upper airway obstruction. Irrespective of responsible mechanisms, our data show that respiratory function can still be seriously impaired despite recommended neuromuscular function test results suggesting adequate neuromuscular recovery.

We agree with Dr. Gal that sensitivity to detect residual paralysis by forced vital capacity measurements is low. Our data suggest that measurements of forced inspiratory flow and assessment of the ability

of normal swallow may be more sensitive.<sup>1</sup> In turn, however, our data also indicate that a marked forced vital capacity decrease may occur even with minimal neuromuscular blockade, suggesting impaired muscle strength.<sup>4</sup> As respiratory muscle weakness can result in an ineffective cough with inability to clear secretions from the airways,<sup>5</sup> we consider forced vital capacity recovery relevant for preventing pulmonary complications.

**Matthias Eikermann, M.D.,\* Harald Groeben, M.D., Jürgen Peters, M.D.** \*Universitätsklinikum Essen, Essen, Germany. matthias.eikermann@uni-essen.de

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(Accepted for publication September 26, 2003.)

Anesthesiology 2004; 100:458

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## Genetic Markers: Not Yet Ready for Prime Time

**To the Editor:**—In their recent review, Ziegeler *et al.*<sup>1</sup> present their view of the future of medicine in which assessment of perioperative risk and prediction of perioperative outcome soon will be enhanced through genotyping of patients. However, the quick jump from increased genetic knowledge to improved health is not assured, as was recently pointed out by Floyd Bloom, President of the American Association for the Advancement of Science.<sup>2</sup> For example, knowledge of the specific mutation responsible for Huntington disease has not led to prevention, better treatment, or even an animal model for this condition. The authors also state, "Increasing evidence suggests an association between APO ε4 genotype and neurocognitive dysfunction after CPB."<sup>1</sup> I should regard the supporting evidence for this conclusion to be, at best, uncertain given that the association between genotype and neurocognitive dysfunction could be demonstrated in only the first of three publications on the subject.<sup>3-5</sup>

David C. Warltier, M.D., Ph.D., served as acting Editor-in-Chief for this exchange.

**John Butterworth, M.D.** Wake Forest University School of Medicine, Winston-Salem, North Carolina. jbutter@wfbmc.edu

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(Accepted for publication October 29, 2003.)

Anesthesiology 2004; 100:458-9

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**In Reply:**—Dr. Butterworth questions whether the use of genetic information from clinical studies to examine the impact of genetic variability on disease characterization and outcome, or *functional genomics*, is ready for "prime time." However, before replying to that

question, a brief review of the history of genetics may be in order. On April 14, 2003, the Human Genome Project announced the complete sequencing of the human genome† just 11 days shy of the fiftieth anniversary of Watson's and Crick's seminal description of the DNA double helix. During this brief timespan, we have witnessed the use of genomics for the rapid identification of newly discovered pathogens, such as that involved in the severe acute respiratory syndrome (SARS); the use

† Available at: <http://www.genome.gov/11006929>. Accessed October 8, 2003.



of gene-expression profiling to assess cancer prognosis and guide therapy; the use of genotyping to stratify patients according to the risk of a disease, such as prolonged QT interval syndrome or myocardial infarction; the use of genotyping to increase our understanding of drug pharmacokinetics and pharmacodynamics; and the use of genetics for tissue engineering and the cloning of several different species.<sup>1-4</sup> Recently, the National Human Genome Research Institute announced the formation of the International HapMap project, which will attempt to improve the ease and accuracy of human genetic risk profiling by creating a haplotype map consisting of approximately 500,000 tag single nucleotide polymorphisms from the more than 10 million that exist within the human genome. Even in diseases such as Huntington chorea, in which identification of the specific causative mutation has yet to lead to improved treatment, patients and their families have benefited from genetic counseling.<sup>5</sup> *All of these mind-boggling accomplishments have occurred within a single generation.*

Is perioperative functional genomics ready for prime time? Maybe not quite yet. But one thing is assured: If genetic advances continue to occur at the current rate and the discipline of anesthesiology remains

on the sidelines, we may very well find ourselves in the scientific "reruns" instead of at the forefront of novel, cutting-edge research.

**Stephan Ziegler, M.D., Byron E. Tsusaki, D.O., Charles D. Collard, M.D.\*** \*University of Texas Health Science Center at Houston and Baylor College of Medicine, and Texas Heart<sup>®</sup> Institute, St. Luke's Episcopal Hospital, Houston, Texas. ccollard@heart.thi.tmc.edu

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(Accepted for publication October 29, 2003.)

Anesthesiology 2004; 100:459-60

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## Base Excess and Strong Ion Difference: Clinical Limitations Related to Inaccuracy

*To the Editor:*—The problem of method-related errors, arising from different measuring technologies on calculation of the anion gap and the strong ion difference, was clearly demonstrated in patients in a recent study by Morimatsu *et al.*<sup>1</sup> Mean values differed significantly, in some cases leading to a diverging assessment of the acid-base or electrolyte status. To a clinician, however, this is not acceptable.

All quantities, including the base excess (BE), used for diagnosis of nonrespiratory acid-base disturbances (*e.g.*, metabolic, renal, or intestinal) are calculated quantities. Hence, each quantity must be assessed for reliability and associated diagnostic interpretation (normal range and normal values: mean  $\pm$  SD; pathologic range). This greatly depends on the inaccuracy and imprecision of each of the measured primary values used in the particular calculation and on how these are propagated. BE is usually obtained with arterial blood from measured pH, partial pressure of carbon dioxide (Pco<sub>2</sub>), and hemoglobin-concentration in a blood gas analyzer, the strong ion difference from measured plasma electrolyte concentrations (*e.g.*, Na, K, Cl, lactate).

For clinical practice, we propose the whole blood BE, which should be preferably used depending on the following considerations:

**Inaccuracy of calculated BE:** If correctly calculated, BE can be obtained from measured pH, Pco<sub>2</sub>, oxygen saturation, and total hemoglobin in any blood sample (venous or arterial). Over the whole range (−30 to +30 mmol/l), mean inaccuracy is less than 1 mmol/l.<sup>2</sup>

**Normal values for BE and variability:** Normal values for BE in arterialized capillary blood of men ( $n = 20$ ) are  $-0.1 \pm 1.2$  mmol/l, and of women ( $n = 20$ ),  $-1.0 \pm 1.1$  mmol/l.<sup>3</sup> Variability of BE in healthy individuals is very low and could be reproduced if calculated also from measurement in venous blood. Typical results (mean  $\pm$  SD) as obtained with blood from the vena cubitalis (50 healthy volunteers: colleagues and medical students) are shown in Table 1. Values for pH, Pco<sub>2</sub>, partial pressure of oxygen, and oxygen saturation were measured in a blood gas analyzer (AVL OMNI 9; Roche Diagnostics, Mannheim, Germany), calibrated with two precision buffers for pH (Radiometer phosphate buffer S 1500; S 1510), and the mean calculated BE was  $-0.1 \pm 1$  mmol/l. It should be noted that the SD of BE is still low, even though measured values used in the calculation varied largely (Table 1).

**Tolerable values of inaccuracy:** Representative normal values and maximal inaccuracy of the measured acid-base and electrolyte variables in blood, as tolerated by the recommendations of the German

**Table 1. Normal Values for the Base Excess (BE) from Venous Blood ( $n = 50$ )**

	Mean	$\pm$ SD
pH	7.352	0.023
Pco <sub>2</sub> , mmHg	51.2	4.9
Po <sub>2</sub> , mmHg	28.6	10.2
So <sub>2</sub> , %	49.2	22.0
BE, mmol/l*	−0.10	1.0

\* BE is calculated from measured venous pH, Pco<sub>2</sub>, So<sub>2</sub>, and total Hb.

Pco<sub>2</sub> = partial pressure of carbon dioxide; Po<sub>2</sub> = partial pressure of oxygen; So<sub>2</sub> = oxygen saturation.

Medical Association (Bundesärztekammer 2002, Köln, Germany) for the electrolyte concentrations in the plasma are Na  $142 \pm 2.8$  mmol/l (2.0%); K  $4.5 \pm 0.2$  mmol/l (3.7%); Cl  $103 \pm 4.1$  mmol/l (4%); and lactate  $1.5 \pm 0.1$  mmol/l (6%). Using these figures, the normal value of the strong ion difference (Na + K − Cl − lactate) is calculated as  $42 \pm 5.0$  mmol/l, with high inaccuracy from propagation of errors. Hence, reliability is strongly reduced, dominated by the largest errors (Na:  $\pm 2.8$  mmol/l; Cl:  $\pm 4.1$  mmol/l).

In comparison, normal BE is  $0 \pm 2.2$  mmol/l when calculated from normal values of pH  $7.40 \pm 0.02$ , Pco<sub>2</sub>  $40 \pm 1.6$  mmHg (4%), hemoglobin  $15 \pm 0.3$  g/dl (2%), and full oxygen saturation  $\sim 100\%$ . Reliability of BE is mainly affected by the inaccuracy of measurement for pH and Pco<sub>2</sub>, whereas that for hemoglobin is negligible.

**BE as a prognostic factor:** The diagnostic use and prognostic value of BE is well documented. Among 10 clinical hemodynamic and 20 blood laboratory parameters tested, change in BE proved to be the best predictor of blood volume changes in a canine hemorrhagic shock model.<sup>4</sup> In critically ill patients BE has been established as an independent predictor of mortality<sup>5</sup> and endpoint of resuscitation. On the basis of 8,200 polytrauma patients, statistically selected out of 15,200 from four clinical studies, mortality increased significantly with a decrease in BE, *e.g.*, approximately by 25% if the assessed BE was  $-6$  mmol/l within the first 24 h after admission (see figure 4 in reference 6).<sup>6</sup>

**Conclusions:** Because mortality may increase considerably ( $\sim 8\%$ ) when BE is decreased by only 2 mmol/l, the clinical requirements for

reliability (inaccuracy, imprecision) should be high ( $\leq 2$  mmol/l). By using present standard measuring technology, this is met only for the BE and not for the strong ion difference or lactate alone. The latter should be used only as secondary parameters in combination with the BE for a differential diagnosis, e.g., nonrespiratory acidosis correlated to lactate, hyperchloremia, or anion gap.<sup>7</sup>

**Rolf Zander, Prof. Dr. med. Werner Lang, Dr. rer. nat.\***

\*Institut für Physiologie und Pathophysiologie, Johannes Gutenberg-Universität Mainz, Mainz, Germany. wlang@uni-mainz

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(Accepted for publication September 6, 2003.)

Anesthesiology 2004; 100:460

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## Alternative Formula for Laryngeal Mask Airway™ Size Selection

**To the Editor:**—Size selection of the Laryngeal Mask Airway™ (*LMA™*; Laryngeal Mask Company Limited, San Diego, CA) is important for avoiding complications and is based on patient body weight.<sup>1</sup> The previously proposed formula for determining the appropriate *LMA™* size<sup>2</sup> is impractical because it contains the square root of the patient's body weight. We advocate here an alternative formula: *LMA™* size = 1 + BWru/20, where BWru indicates body weight (in kilograms) rounded up at the first digit. For example, if a patient's body weight of 14 kg (BWru) is 20 because 14 can be rounded up to 20 at the first digit, the calculation would be as follows: *LMA™* size = 1 + 20/20 = 1 + 1 = 2.

If the calculation of *LMA™* size shows 3.5 or 4.5, we choose *LMA™* #3 or #4. This manner of size selection agrees with the recommendation by Brimacombe and Brain.<sup>1</sup> Alternatively, if the calculated *LMA™* size is 3.5 or 4.5, we can also use *LMA™* #4 or #5. This size selection

is similar to the sex-based *LMA™* size recommendation for adult patients.<sup>3</sup>

Our formula is convenient for pediatric patients, although it cannot be used in infants weighing less than 5 kg. In addition, the formula does not require a pocket calculator.

**Shuichi Hirai, M.D.,\* Reiko Nakamura, M.D., Nobuhiro Maekawa, M.D.\*** Kagawa Medical School, Kagawa, Japan. shina\_mon@hotmail.com

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(Accepted for publication June 20, 2003.)

Support was provided solely from institutional and/or departmental sources.

Anesthesiology 2004; 100:460-1

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## Delayed Postoperative Arousal following Remifentanyl-based Anesthesia in a Myasthenic Patient Undergoing Thymectomy

**To the Editor:**—Remifentanyl (Ultiva; GlaxoSmithKline, Middlesex, UK) is an "ultra-short"-acting opioid that is rapidly hydrolyzed by circulating and tissue nonspecific esterases. Discontinuation of remifentanyl infusion will be followed by a rapid recovery regardless of the duration of infusion.<sup>1</sup> The present report used the remifentanyl-based technique of anesthesia, without the use of muscle relaxants, in a myasthenic gravis patient undergoing transternal thymectomy. However, the patient manifested unexpected delay of postoperative arousal for 12 h. This is the first case report about a significant delay of postoperative arousal following discontinuation of remifentanyl infusion.

A 19-yr-old female patient (body weight, 57 kg) presented with myasthenia gravis (Osserman 2A) associated with a thymoma. Pyridostigmine, 60 mg, four times daily was administered for 2 months, to be followed by transternal thymectomy. The pyridostigmine regimen was maintained until the morning of surgery.

Premedication was limited to 0.2 mg intramuscular glycopyrrolate and 1 mg intravenous midazolam. Anesthesia was induced with 100 mg lidocaine and 2 mg/kg propofol intravenously, to be followed by 3.0  $\mu$ g/kg remifentanyl over 30 s, and tracheal intubation. Anesthesia was maintained by sevoflurane 1-2% in 100% oxygen, supplemented with remifentanyl infusion (0.1-0.25  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>). Neuromuscular transmission was monitored by electromyography using a Datex relaxograph (NMT-100-23-01; Datex-Ohmeda Division, Instrumentarium Corp, Helsinki, Finland), using the electromyographic response to ulnar nerve stimulation by the train-of-four. Intraoperatively, blood pressure ranged between 75/30 mmHg and 105/55 mmHg, heart rate ranged between 55 and 90 bpm, and electromyography showed normal T1/control and T4/T1 ratios. The duration of surgery was 2 h. Thirty minutes before the end of surgery, 5 mg intramuscular morphine was administered. Twenty minutes before the end of surgery, sevoflurane was turned off, and on completion of surgery remifentanyl infusion was discontinued. The total dose of remifentanyl administered throughout surgery amounted to about 2,000  $\mu$ g.

Support was provided solely from institutional and/or departmental sources.

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Ten minutes after discontinuation of remifentanyl, the patient started to breathe spontaneously, to respond to painful stimuli, and to buck on the tube. The trachea was extubated and the patient was transferred to the recovery room while receiving oxygen *via* a facemask. In the recovery room, the patient exhibited sleepiness, pinpoint pupils, and sluggish response to light glabellar tap or loud auditory stimulus, but she responded to painful stimulus (Ramsay scale 5). Her blood pressure ranged between 70/40 mmHg and 90/60 mmHg; the heart rate ranged between 50 and 60 bpm. The patient maintained spontaneous breathing at a rate of 8–10 breaths per minute. Her oxygen saturation measured by pulse oximetry while breathing room air was 90%; arterial blood gases showed  $PO_2$  78 mmHg,  $P_{CO_2}$  44 mmHg, and pH 7.32. Oxygen saturation increased to 97% with oxygen *via* facemask. After 12 h, the patient started to respond to verbal stimuli and to have adequate spontaneous breathing, as evidenced by increased respiratory rate and by oxygen saturation of 95% while breathing room air.

Remifentanyl is an esterase-metabolized opioid.<sup>1</sup> The esterase-based metabolism of remifentanyl makes its pharmacokinetics independent of end organ failure<sup>2,3</sup> and results in a half-life of about 9–11 min.<sup>4</sup>

Our myasthenic patient had been receiving pyridostigmine for 2 months previous to the morning of surgery. Postoperatively, the patient remained somnolent for 12 h. This delayed postoperative arousal could not be attributed to the propofol, sevoflurane, or the small dose of morphine administered during surgery. Also, myasthenic respiratory depression was excluded because the T4/T1 ratio was greater than 0.9. The delayed arousal may be attributed to a possible inhibition of the nonspecific esterases hydrolyzing remifentanyl by pyridostigmine.

Pyridostigmine is the traditional antiacetylcholinesterase that is used orally for the symptomatic management of myasthenia gravis. In addition to its antiacetylcholinesterase effect, Baraka *et al.* showed that pyridostigmine inhibits the plasma pseudocholinesterase (butyrylcholinesterase) by about 70%,<sup>5</sup> which explains the low plasma cholinesterase activity and the prolonged neuromuscular block of succinylcholine in myasthenia gravis patients pretreated by pyridostigmine.<sup>6</sup> However, remifentanyl does not appear to be a substrate for butyrylcholinesterases.<sup>7,8</sup> It is possible that pyridostigmine is a nonselective esterase inhibitor that may inhibit not only the acetylcholinesterase

and butyrylcholinesterase enzymes, but also the nonspecific esterases that metabolize remifentanyl with a subsequent delayed arousal.

Naloxone was not administered to confirm the diagnosis in our patient, and the blood concentrations of remifentanyl were not measured. Therefore, the supposition that because pyridostigmine inhibits acetylcholinesterase and butyrylcholinesterase it might also inhibit the enzymes responsible for remifentanyl's metabolism is purely speculative. However, the present report calls to our attention that myasthenia gravis patients maintained on a pyridostigmine regimen up to the morning of surgery may be extremely sensitive to drugs metabolized by nonspecific esterases such as remifentanyl.

**Anis S. Baraka, M.D., F.R.C.A.,\* Sanie' T. Haroun-Bizri, M.D., Frederic J. Gerges, M.D.** \*American University of Beirut, Beirut, Lebanon.abaraka@aub.edu.lb

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(Accepted for publication September 16, 2003.)