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Gene Therapy for Pain

THE past quarter century has witnessed an explosion in the understanding of pain, characterized by the elucidation of anatomic pathways, and the identification of receptors, ion channels, and neurotransmitters that are involved in the transmission of nociceptive information from primary sensory neurons in the dorsal root ganglion (DRG) to the brain.[1] In parallel, it has become apparent that the emergence of chronic pain, an important and difficult-to-treat condition, involves defined alterations in nociceptive processing in the peripheral nervous system, at the level of the spinal cord, and in the brain. But despite advances in basic and clinical sciences and the concentrated efforts of many academic and pharmaceutical research laboratories, the development of novel effective treatments for chronic pain has been disappointingly slow. In part, the challenge to the development of pain therapeutics is a predictable result of the parsimonious use by the nervous system of a limited repertoire of neurotransmitters, receptors, and ion channels at multiple sites and in many pathways subserving different functions. Therefore, potent small molecules designed to interrupt nociceptive neurotransmission often have "off-target" adverse effects resulting from actions of these molecules in pathways subserving other, non–pain-related functions. In response, several groups have begun to explore the possibility of using gene transfer to achieve analgesic effects, and in this issue of the Journal, Tzabazis *et al.*[2] present the results of a study of gene transfer using a herpes simplex virus (HSV)–based vector that significantly extends the range of gene transfer in the treatment of pain.

The rationale for applying gene transfer techniques to the treatment of pain is based on the presumption that expression of transgene products (usually short-lived potent peptides) in a restricted anatomical distribution may be used to reduce pain perception through modulation of nociceptive neurotransmission at an identified site, with off-target effects limited by the limited anatomic distribution of transgene expression. Transduction of meninges accomplished by intrathecal injection of "naked" plasmid or liposome-encapsulated DNA, or by injection of recombinant viral vectors created from adenovirus or adenoassociated virus to express inhibitory neurotransmitters (*e.g.*, beta endorphin) or antiinflammatory cytokines (*e.g.*, interleukin 2 or interleukin 10) has been shown to reduce pain-related behaviors in several animal models of inflammatory and neuropathic pain.[3] These analgesic effects are presumed to result from modulation of neurotransmission at the synapse between the central afferents of first-order nociceptive neurons (whose cell bodies lie in the DRG) onto second-order neurons located in the dorsal horn of spinal cord. Modulation of nociceptive neurotransmission at that synapse in the spinal cord can also be achieved by peripheral inoculation of vectors created from recombinant HSV, relying on the natural neurotropism of HSV to achieve efficient transport from the periphery to sensory neurons in the DRG.[4] Reduction of pain related behaviors using HSV-based vectors has been demonstrated in models of chronic inflammatory and neuropathic pain with vectors expressing enkephalin, glutamic acid decarboxylase (to produce gamma amino butyric acid), glial cell–derived neurotrophic factor, interleukin 4, and the truncated soluble tumor necrosis factor receptor.[5]

In the current report, Tzabazis *et al.* used a recombinant HSV-based vector encoding an antisense sequence to the calcitonin gene–related peptide (CGRP) gene. They demonstrate that application of the vector to the skin resulted in a significant reduction in CGRP expression in primary afferents in the DRG, producing a significant attenuation in thermal C-fiber hyperalgesia after topical application of capsaicin. CGRP is expressed in 45–70% of lumbar DRG neurons, a majority of which are nociceptors. Although the precise role of CGRP in nociception has not been established, spinal delivery of CGRP antagonists has previously been shown to reduce pain-related behaviors in a variety of models, and in the mouse, strain-related differences in sensitivity to noxious heat correlates with strain-dependent differences in CGRP expression and sensitivity.[6] In contrast to the transient effects produced by spinal delivery of CGRP antagonists, HSV-mediated knockdown of CGRP expression resulted in an analgesic effect that persisted for 12 weeks. An advantage to gene transfer of an antisense sequence is that no foreign gene products are released from the transduced neurons, although it will be crucial to demonstrate in future studies that HSV-mediated knockdown of gene expression by this antisense expressing vector is limited to CGRP. Nonetheless, the observation by Tzabazis *et al.* that the HSV vector produced a significant reduction in CGRP gene expression in a majority of nociceptor afferents in the DRG after superficial application to the skin is impressive, and extension of this work to an animal model of chronic pain would serve as an important preclinical step in the development of a treatment for chronic pain.

◆ This Editorial View accompanies the following article: Tzabazis AZ, Pirc G, Votta-Velis E, Wilson SP, Laurito CE, Yeomans DC: Antihyperalgesic effect of a recombinant herpes virus encoding antisense for calcitonin gene–related peptide. ANESTHESIOLOGY 2007; 106:1196–203.

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Gene transfer for the treatment of pain is slowly moving toward the clinic. A trial using intrathecal injection of a plasmid encoding interleukin 10 to treat chronic neuropathic pain has been proposed, and a second trial to establish safety and dose range of a nonreplicating HSV vector encoding enkephalin in patients with pain caused by cancer has received sponsorship. Chronic pain represents an important clinical problem for which there is a substantial unmet need; the current report provides additional hope for the future in this regard.

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Advancing Perioperative Prediction of Cardiac Risk after Vascular Surgery

Does Postoperative N-terminal Pro-brain Natriuretic Peptide Do the Trick?

PATIENTS undergoing elective major vascular surgery still have substantial perioperative risk of myocardial infarction and cardiac death, despite decades of research focused on risk stratification and implementation of risk-reduction strategies.[1–3] This significant myocardial risk extends beyond the perioperative period. At 18 months after vascular surgery, 18.7% of patients still experience death or myocardial infarction, *i.e.*, almost 1 in every 5 subjects studied.[1]

Recent research has suggested that perioperative intervention may improve outcomes in this high-risk subset of vascular surgical patients.[4,5] Therefore, enhanced identification of patients at high risk represents a means of targeting perioperative intervention. Serum biomarkers such as C-reactive protein, serum creatinine, brain natriuretic peptides, and/or troponin may collectively represent such a method.[1,6–10]

In this issue of the Journal, Dr. Mahla *et al.*[11] further examine the utility of cardiac biomarkers to stratify perioperative risk and those patients in whom more targeted long-term interventions should be directed. In this prospective observational study, the investigators tested whether certain cardiac biomarkers (N-terminal pro-brain natriuretic peptide [NT-proBNP], C-reactive protein, fibrinogen, and serum creatinine) were predictors of adverse cardiac outcome. The study cohort consisted of 218 elective vascular surgical patients who all had a preoperative ejection fraction greater than 40% and who had a median follow-up of 2.25 yr. Twenty percent of the study cohort experienced adverse cardiac events as follows: 7% cardiac death, 15% nonfatal myocardial infarction, and 1% emergent coronary artery revascularization.

After univariate analysis, the following serum markers were predictors of adverse cardiovascular outcome: preoperative NT-proBNP, postoperative NT-proBNP, preoperative creatinine, preoperative fibrinogen, and C-reactive protein. After multivariate analysis, there were three independent predictors of adverse cardiovascular events: postoperative NT-proBNP levels of 860 pg/ml or greater (odds ratio, 4.88; 95% confidence interval, 2.43–9.81), occurrence of surgical complications (odds ratio, 2.56; 95% confidence interval, 1.11–5.90), and preoperative creatinine greater than 1.2 mg/dl (odds ratio, 1.92; 95% confidence interval, 1.02–3.62).

The significant ability of preoperative NT-proBNP to predict adverse cardiovascular outcome after noncardiac surgery has been established.[8–10] The novel observation in this outcome study is that postoperative NT-proBNP is more predictive of short-term and long-term cardiovascular morbidity and mortality than preoperative NT-proBNP.

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This important observation must be interpreted in light of the study design. The peptide, NT-proBNP, is released from cardiomyocytes in response to ischemia and myocardial stretch.[6–12] The investigators chose NT-proBNP, as compared with BNP, because of its longer half-life. Furthermore, they excluded clinical entities associated with higher levels of natriuretic peptides such as atrial fibrillation, aortic stenosis, unstable coronary syndromes, decompensated heart failure, and impaired renal function. From an anesthetic standpoint, all patients in this cohort underwent general anesthesia compared with regional anesthesia, which decreases perioperative levels of natriuretic peptides.[13]

Where do we go from here? The cumulative evidence strongly suggests that we should include serum markers to better predict the subset of high-risk patients who will experience postoperative adverse cardiovascular outcome. We have no doubt that further perioperative research will identify more candidate markers besides NT-proBNP, including not only peptides but also genetic polymorphisms.

The results from this study beg future investigation in at least three areas: (1) trials to confirm this observation across perioperative populations, (2) trials that target perioperative interventions based on this marker, and (3) trials that target further long-term consultation and/or assessment based on this marker. The remaining discussion will be stratified with respect to these stated groups.

Despite the extremely positive findings from this study, further clinical trials are required to confirm and validate these findings (group 1 of further studies). The predictive value of the generated multivariate model is robust for this data set, but whether this will generalize across different data sets is still unknown. Further studies should examine various noncardiac surgical cohorts to test the reproducibility and validity of postoperative NT-proBNP as a predictive marker of postoperative myocardial risk. Will the odds ratio still be greater than 1? That is, will a postoperative NT-proBNP of 860 pg/ml or greater still correlate with increased cardiovascular risk? Will the odds ratio be 4.88 or greater? That is, will a postoperative NT-proBNP level of 860 pg/ml or greater correlate with a $\geq$ 5 times higher risk of developing an adverse cardiovascular event? Will the confidence interval of the odds ratio be greater than 1? That is, will it be certain to a 95% confidence limit that a postoperative NT-proBNP level of 860 pg/ml or greater correlates with increased cardiovascular risk? These further studies should also examine the predictive performance of postoperative NT-proBNP with respect to patient age, anesthetic technique, and compromised organ reserve (*e.g.*, degrees of renal dysfunction, degrees of acute and chronic ventricular dysfunction).

If the elevation of NT-proBNP occurs before irreversible cardiac morbidity, it is conceivable that multimodal perioperative intervention could be implemented to prevent or limit this morbidity (group 2 of further studies). These interventions could be pharmacologic (*e.g.*, β-blockade, statins, anticoagulation), diagnostic (*e.g.*, admission to a high-care setting such as an intensive care unit, further noninvasive or invasive testing), and/or therapeutic (*e.g.*, coronary angioplasty). The study population could be stratified *post hoc*, *i.e.*, after postoperative NT-proBNP measurement. The high-risk group would be the subgroup with a postoperative NT-proBNP level of 860 pg/ml or greater. This high-risk group could then receive targeted intervention as detailed above. High-priority interventions to test would be intensive β-blockade, platelet blockade, and/or statin therapy. We anticipate that this group of studies will follow in the near future and are highly likely to document further reduction in cardiovascular risk after vascular surgery.

With regard to long-term strategies, the perioperative period could be viewed as a "stress test." The presence of markedly elevated NT-proBNP could therefore be viewed as analogous to a positive stress test result and identify high-risk patients for referral to a cardiologist or internist. This referral could trigger specific management to reduce future myocardial risk (group 3 of further studies). This kind of biomarker-driven management already exists in published guidelines for cardiologists (*e.g.*, serum natriuretic peptide and heart failure,[14] C-reactive protein and coronary disease).[15] The referral could direct long-term medical attention to aggressive risk-reduction for atherosclerotic events not only in the heart but also elsewhere in the arterial tree, such as the brain and kidney, given that atherosclerosis is a systemic disease. We anticipate that this group of studies will occur most likely as long-term follow-up of the cohorts from groups 1 and 2 of further studies.

In summary, Dr. Mahla *et al.* are to be congratulated for further refining identification of patients at high risk for both short-term and long-term postoperative myocardial mortality and morbidity. Their study not only has shaped future outcome research in this important area, but also is another step toward making the immediate perioperative period and beyond safer for our patients.

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Anesthesia-related Maternal Mortality

A Pat on the Back or a Call to Arms?

THE article by Mhyre *et al.*[1] in the current issue of ANESTHESIOLOGY reviews anesthesia-related maternal mortality in Michigan over an 18-yr period. This is the third in a series of reviews that have examined maternal mortality in Michigan since the state began the Maternal Mortality Surveillance in 1950.

Before focusing on the current article, I would like to provide a brief overview of the evolution of anesthesia-related maternal mortality over the past three decades. Anesthesia-related maternal mortality is a remarkable success story and illustrates how a problem can be targeted and significantly reduced through scientific study followed by recommendations that alter practice patterns. Before 1984, the side effects of local anesthetics were poorly understood, and a majority of complications in obstetric anesthesia occurred in laboring patients or when epidural local anesthetics were administered for operative delivery. The first "call to arms" in obstetric anesthesia was an editorial in 1979 that raised concerns over bupivacaine- and etidocaine-induced cardiac toxicity.[2] This editorial and a second in 1984[3] that outlined investigations spawned from the former led to the eventual withdrawal of 0.75% bupivacaine in obstetrics and altered the way in which local anesthetics were administered. Instead of administering concentrated local anesthetics as a bolus, epidural catheters were tested after insertion and/or all doses were fractionated. These simple measures and the use of dilute local anesthetics solutions to achieve and maintain labor analgesia resulted in a drastic reduction in the number of anesthesia-related maternal deaths, especially during labor.[4] In fact, I am unaware of a single maternal death during labor related to local anesthetic toxicity since 1984, during which time approximately 40 million parturients within the United States received epidural labor analgesia. This achievement is deserving of a pat on the back for obstetric anesthesia.

Although anesthesia-related maternal mortality was reduced, it was not eliminated. An examination of deaths after 1984 revealed that they now occurred primarily during operative delivery and were most often associated with general anesthesia.[4] Of concern, it was noted that although overall anesthesia-related maternal mortality was reduced despite the widespread use of epidural analgesia during labor, the rate of maternal mortality associated with general anesthesia remained unchanged. The physiologic changes of pregnancy were believed to be the major contributing factors that increased the risk of either aspiration or

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failed intubation during induction. This was the second call to arms for obstetric anesthesia.

Reducing the incidence of aspiration or failed intubation by either avoiding general anesthesia or standardizing airway management became the focus of attention. Recommendations included (1) increased utilization of regional anesthesia for both vaginal and operative delivery, (2) early epidural placement in patients at highest risk for urgent cesarean delivery, (3) use of algorithms for difficult intubation with adaptations for fetal distress, (4) equipment checklists for difficult intubation carts, (5) elective fiberoptic intubation in patients with anticipated difficult intubation, and (6) use of newer devices that facilitate ventilation (*LMA*™ [The Laryngeal Mask Company Limited, Le Rocher, Victoria, Mahe, The Seychelles]; *LMA-Fastrach*™ [LMA North America, San Diego, CA]; and Combitube [Tyco Healthcare Group, LP, Mansfield, MA], to mention a few). Although it remains to be determined whether these recommendations will further reduce maternal mortality, the current article provides tantalizing evidence that this may be the case.

At first glance, the current review of maternal mortality in Michigan reconfirms much of what we believe to be true in obstetric anesthesia: that anesthesia-related maternal mortality is exceedingly rare and that labor analgesia is safe. There were only eight deaths identified in which anesthesia was the primary cause, and none occurred during labor or were associated with local anesthetic toxicity. However, a closer examination of the deaths reveals a surprising and potentially ominous signal that may once again alter obstetric anesthesia dogma: No maternal deaths were associated with aspiration or failed intubation in the current series. Instead, all eight occurred during emergence or recovery and were related to either airway obstruction or hypoventilation. Weight and race were contributing factors in that 75% of the patients who died were obese (body mass index greater than 30) and 75% were African-American. Whether this trend will be widespread or is simply an aberration remains to be seen. However, at least two alarming trends within the US population may have been confounding factors in the current series and have the potential to impact obstetric anesthesia and maternal mortality in the future: obesity and advancing maternal age.

Obesity in America is reaching epidemic proportions.* It was estimated in 2003 that 32.2% of adults older than 20 yr were obese. The problem is prevalent throughout the United States, and the percentage is expected to continue increasing in the future. Obesity increases the risk of comorbidity, including diabetes, hypertension, and respiratory disease such as obstructive sleep apnea. In addition, obesity is an independent risk factor for cesarean delivery and increases obstetric, neonatal, surgical, and anesthetic risk.[5] Obesity associated morbidity is so problematic that our governing bodies are developing recommendations to assist with the care of these patients. The American College of Obstetricians and Gynecologists Committee Opinion #315: Obesity in Pregnancy, recommends consultation with an anesthesiologist before delivery as one of six major recommendations,[6] and the American Society of Anesthesiologists recently published Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea.[7] Not only are women becoming more obese, they also more often delay pregnancy until after age 35 years, and because advancing maternal age associates with additional risks,[8] every indication suggests that our patients will weigh more and present at an older age with additional coexisting disease in the future. I predict that these trends will affect each and every anesthetic practice and will not be limited to obstetrics.

With respect to obstetric anesthesia, if these trends hold true, they threaten to reverse three decades of reductions in anesthesia-related maternal mortality unless drastic measures are taken to reduce risks associated with larger, older, and sicker patients. Rather than resting on our laurels, it is time for a new call to arms. It is incumbent on each anesthesia practice to establish protocols that not only reduce anesthetic risks during labor and during induction, should general anesthesia be necessary, but also reduce risks associated with emergence from general anesthesia and during recovery. These protocols must also include measures that specifically address the peripartum and perioperative risks associated with obesity and obstructive sleep apnea with a special focus on reducing the risks of airway obstruction and hypoventilation after delivery and surgery. Unlike the two previous calls to arms, which were relatively easy to achieve because they primarily involved changes to anesthesia care, the current challenges outlined in this editorial will be significantly more difficult to achieve. Although not an impossible task, they will require coordinated and multidisciplinary efforts that involve anesthesia, obstetrics, primary care, nursing, and administration. Obstetric anesthesia has responded to challenges in the past, and I have every reason to believe we will do so once again.

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At the Threshold of Noninvasive Functional Hemodynamic Monitoring

THE number of novel noninvasive hemodynamic monitoring gizmos currently available and being developed is amazing. Independent of their accuracy in measuring what they say they measure, how they are used in clinical decision making is potentially more important because monitoring devices will only improve outcome if coupled to a treatment that itself improves outcome. For example, the continuous measure of cardiac output did little to improve patient outcomes until it was used as part of the measure of whole body oxygen delivery (Do_2) as a targeted resuscitation algorithm in high-risk surgical patients before surgery. This approach, called *preoptimization*, reduces postoperative morbidity[1] and mortality[2] and also reduces overall hospital cost.[3] Although several modifications of the same approach have been used, all employ a volume challenge until cardiac output no longer increases and then add inotropes and/or vasopressors to reach their targeted Do_2.[4] However, although volume loading is the traditional means to start resuscitation, fully half of all critically ill patients are not volume responsive, making this approach less efficient[5] and potentially dangerous. If one could determine volume responsiveness before therapy, an appropriate and effective treatment algorithm could be used to drive these proven therapeutic approaches.[6] Such a sensitive and specific parameter is known: assessment of arterial pulse pressure variation (PPV) during positive-pressure ventilation.[7] A PPV of greater than 13%, when averaged over 3–6 breaths of a tidal volume of 5–8 ml/kg, is predictive of an increase in cardiac output of greater than 15% in response to a volume challenge of 250 ml colloid.[8] However, such analysis requires the insertion of an arterial catheter, which itself is both time-consuming and associated with measurable morbidity. If a noninvasive means could be used to measure the same effect on PPV, it would be very useful clinically. Until recently, the only device available to make such measurements was a finger plethsomgraph.[9] However, this device is relatively expensive, is not universally available in operating rooms and other acute care monitoring environments, and may not maintain accuracy as vascular tone varies.[10] However, pulse oximetry is noninvasive, universally available, easy, and inexpensive to use. Furthermore, the pulse oximetry plethysmographic waveform amplitude is an essential variable in calculating pulse oximetry saturation and reflects the pulsatile change in tissue density during the cardiac cycle. Therefore, it is not surprising that the pulse oximetry plethysmographic waveform should resemble the arterial pulse pressure waveform in both shape and amplitude variation. However, there is no relation between absolute arterial pressure and the pulse oximeter signal, only in their variation over the ventilatory cycle. It follows, therefore, that if this relationship is not only qualitative but quantitative, it may be used as a surrogate measure of arterial pulse pressure variation and thus define preload responsiveness. Solus-Biguenet *et al.*[11] first described this phenomenon. They showed that pulse oximeter plethysmographic waveform amplitude variation (POV) predicted preload response in patients undergoing hepatic resection. In this issue of ANESTHESIOLOGY, Cannesson *et al.*[12] extends these observations to show that POV can predict fluid responsiveness in a fashion similar to PPV across a wide range of surgical patients. These findings, when coupled to the preoptimization resuscitation protocol approach, may represent a highly cost-effective means to reduce anesthesia stress and decrease mortality, morbidity, and cost of surgery. Although such a prospective study must be performed, there are still specific issues with the use of POV that must be considered.

First, the pulse oximeter plethysmographic waveform displayed on the monitoring screen and reported by all commercially available pulse oximeters is a highly processed pulse density signal. The displayed pulse density signal is not really the absolute pulse density change but a time-averaged and mean-adjusted signal wherein the actual mean density is held constant but the dynamic changes in density are reported for quality control purposes. If no pulsatile signal is sensed, the pulse oximeter is unable to calculate oxygen saturation measured by pulse oximetry. The raw plethysmographic signal is

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much more variable. Therefore, the findings of both Solus-Biguenet *et al.*[11] and Cannesson *et al.*[12] must be validated in the setting of other pulse oximeter devices and different patient groups. Furthermore, the manufacturers of the various pulse oximeters must reintroduce the graphic display of POV as part of their usual output both onto the screen and into recoverable data logs.

Second, pulse oximeter plethysmographic density will be a function of tissue (nonchanging signal) and blood (changing signal) inputs, and its pulsatility will be primarily a function of changing blood density. Therefore, one must ask: What determines the blood density change over the sensing region? Clearly this will be a function of both perfusion pressure and vasomotor tone. As upstream vasomotor tone increases, for example, pulse oximeter plethysmographic changes would decrease for the same pulse pressure, and *vice versa* with vasodilation. Accordingly, it would be interesting to see the relation between PPV and POV as cardiovascular conditions are varied by pharmacologic intervention and disease. Clearly, this new use of pulse oximetry is exciting and potentially very important. Let us define its value carefully and, if it is proven to be useful, apply this new use of an established monitor broadly to help both monitor and guide resuscitation.

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Tidal Volumes in Patients with Normal Lungs

One for All or the Less, the Better?

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.

MECHANICAL ventilation (MV) using tidal volumes (V_T) of not more than 6 ml/kg predicted body weight (PBW) has been shown to result in reduction of systemic inflammatory markers, increased ventilator-free days, and reduction in mortality when compared with V_T of 12 ml/kg PBW in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (table 1).[1,2] In the low V_T group, V_T was reduced further to 5 or 4 ml/kg PBW if necessary to maintain plateau pressure (P_{plat}) at less than 30 cm H_2O.[1] However, decreasing V_T did not improve outcome in three other controlled trials investing V_T in ALI and ARDS patients, which was explained by differences in study design (table 1).[3–5] Using V_T of not more than 6 ml/kg PBW comparing a high positive end-expiratory pressure (PEEP)–low inspiratory oxygen fraction (F_{IO_2}) with a low PEEP–high F_{IO_2} strategy to prevent hypoxemia did not demonstrate advantageous of higher PEEP levels in ALI and ARDS patients.[6] The lack of effect of higher PEEP levels was partially explained by the resulting higher P_{plat}. A secondary analysis of the ARDS Network database showed a beneficial effect of V_T reduction from 12 ml/kg to 6 ml/kg PBW even in patients with low P_{plat} ranging between 16 and

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Table 1. Randomized and Controlled Trials Comparing High *versus* Low Tidal Volume Ventilation in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome

	V_T, ml/kg		RR, breaths/min		PEEP, cm H_2O		$Paco_2$, mmHg		Mortality, %	
Trial	Low	High	Low	High	Low	High	Low	High	Low	High
Brochard *et al.*,[4] 1998 (n = 116)	7.1	10.5	NA	NA	10.6	10.8	60	41	46.6	37.9
Stewart *et al.*,[3] 1998 (n = 120)	7.2	10.8	23	17	8.7	8.4	54	46	50.0	47.0
Brower *et al.*,[5] 1999 (n = 52)	7.3	10.2	NA	NA	8.0	8.0	50	40	50.0	46.0
Amato *et al.*,[2] 1998 (n = 53)	6.0	12.0	20	17	16.4	8.7	55	33	38.0	71.0
ARDSnet,[1] 1998 (n = 861)	6.0	12.0	30	17	9.2	8.6	43	36	31.0	39.8

ARDSnet = Acute Respiratory Distress Syndrome Network; High = high tidal volume group; Low = low tidal volume group; NA = not applicable; $Paco_2$ = arterial carbon dioxide tension; PEEP = positive end-expiratory pressure; RR = respiratory rate; V_T = tidal volume.

26 cm H_2O before V_T reduction.[7] In this issue of ANESTHESIOLOGY, Schultz *et al.*[8] suggest the use of low V_T ventilation with PEEP levels above 5 cm H_2O in patients without ALI or ARDS in absence of large-scale prospective randomized trials.

Schultz *et al.* argue that in critically ill patients requiring MV for pulmonary edema, chronic obstructive pulmonary disease, congestive heart failure, aspiration, pneumonia, and trauma and after surgery not fulfilling ARDS criteria, mortality is associated with application of high V_T and P_{plat}.[8,9] Two retrospective analyses identified high airway pressures and V_T as independent risk factors for development of ALI and ARDS in patients requiring MV for acute respiratory failure.[10,11] It is of importance that these analyses included patients who were critically ill and had obviously either cardiopulmonary disease or ventilatory dysfunction and had thus *per se* a certain risk to develop ALI or ARDS. In an international cohort of unselected ARDS patients, neither P_{plat} nor V_T but use of low or no PEEP was associated with adjusted mortality.[12] Recent surveys demonstrated that V_T in critically ill patients is on average approximately 7–8 ml/kg BW but that still V_T between 12 and 18 ml/kg BW are used with low or nil PEEP.[13] Based on these data, it seems justified to request protective ventilator strategies in risk patients routinely and not to wait until the ALI or ARDS criteria are fulfilled. Although we do not have evidence that the ventilator settings suggested by Schultz *et al.*, which are essentially based on the ARDS Network protocol, are the best way to ventilate patients at risk for ALI or ARDS, they may prevent harm from the use of too-high V_T and low or nil PEEP levels.

Potential adverse effects of protective MV should be considered in all critically ill patients. Hypercapnia may cause increased intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal blood flow, and release of endogenous catecholamines. Moreover, MV with low V_T and P_{plat} may promote atelectasis formation and increase requirements for higher F_{IO_2} and PEEP. To counteract cardiovascular depression caused by higher PEEP levels, fluid loading frequently associated with a positive fluid balance and/or catecholamines may be required. Therefore, all of these variables must be carefully considered and balanced when reducing V_T in individual patients.

Another question is whether protective ventilation is beneficial in patients with healthy lungs requiring short-term MV during anesthesia. Besides airway closure and reduced lung volumes in the supine position, distortion of rib cage (and lung), cephalad shift of the diaphragm, surfactant alteration, blood shift from abdomen to thorax, or a combination of these contribute to atelectasis formation in 90% of the patients during anesthesia.[14] In the 1960s, use of large V_T of approximately 15 ml/kg BW was advocated to reopen collapsed lung tissue and prevent impaired oxygenation during anesthesia.[15] Cyclic opening and closing caused by recruitment and derecruitment of small airways or lung units may lead to increased local shear stress (atelectrauma), which has been suggested to contribute to lung damage even in the absence of high P_{plat}.[16] However, for identical V_T and PEEP, reducing respiratory frequency attenuates or delays damage, provided that tidal ventilatory stress is sufficiently high.[17] This indicates that the doses of stress will matter. Whereas a ventilator cycle is repeated 20,000–40,000 times per day for a longer period in critically ill patients, probably not more than 900 cycles are commonly applied per 1 h of anesthesia. PEEP levels up to 10 cm H_2O are necessary in healthy patients during anesthesia to keep open those units that are most likely to close. However, any lung-protective benefit of PEEP is expected to be unimpressive when P_{plat} is modest or when the lung contains few recruitable units. Atelectatic area on computed tomography slice near the diaphragm is generally approximately 5–6% of the total lung area but can exceed 15–20% during uneventful anesthesia.[14] This may explain why in patients with healthy lungs undergoing elective major thoracic or abdominal surgery, MV with V_T of 12–15 ml/kg PBW and nil PEEP did not result in different pulmonary or systemic levels of inflammatory markers when compared with V_T of 6 ml/kg PBW and PEEP of 10 cm H_2O.[18]

Individual factors such as obesity, pneumoperitoneum, preexisting disease, and some surgical interventions may aggravate atelectasis formation. In addition, a variety of cofactors apart from ventilator settings such as position-

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ing; systemic inflammatory response depending, for example, on the amount of surgical trauma; and higher precapillary[19] and lower postcapillary[20] pulmonary vascular pressures are important for generation or prevention of ventilator-induced lung injury. As highlighted by Schultz *et al.*, smaller randomized controlled trials of perioperative ventilatory strategies during major surgery revealed nonuniform results.[8] The impression is that ventilatory strategy is more relevant during surgery that triggers a higher inflammatory response, such as esophagectomy or cardiac surgery. However, these studies where not designed or powered to draw clinically relevant conclusions on clinical outcome measures, but studied inflammatory markers that are likely to but not proven to be surrogate markers of clinical outcome. To avoid high plateau pressures during one-lung ventilation, it has been suggested to use V_T of 5–6 ml/kg BW with PEEP in the absence of auto PEEP and to limit P_{plat} to less than 25 cm H_2O during one-lung ventilation.[21] However, application of PEEP in the dependent ventilated lung may increase pulmonary vascular resistance in this lung, diverting blood flow to the nonventilated lung, and thereby increasing intrapulmonary shunt and hypoxemia.

Although V_T of more that 10 ml/kg PBW are probably seldom used during anesthesia, there is no sound scientific basis to consider further V_T reduction necessary when P_{plat} is not higher than 16 cm H_2O to prevent lung injury.[8] Hypercapnia and its side effects can be generally prevented by moderate increased respiratory rates due to reduced carbon dioxide production during anesthesia. To counteract atelectasis formation during MV with low V_T and P_{plat}, higher F_{IO_2} and PEEP may be required. Especially in the presence of hypovolemia or shock, already moderate PEEP levels require fluid loading resulting in a positive fluid balance, which is a significant risk factor for major and minor morbidity and gastrointestinal paralysis after colorectal and major surgery.[22] To what extent postoperative complications are caused by respiratory dysfunction and ventilator settings during anesthesia is not yet clear.

Therefore, it is essential to tailor ventilator settings during anesthesia to the specific physiologic changes caused by surgery and preexisting disease of the patient, while treating the lungs gently. It may be concluded so far that the more ill the patient is, the more relevant the ventilatory strategy may be.

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