

## Mechanical Ventilation–induced Lung Release of Cytokines

### *A Key for the Future or Pandora's Box?*

IN this issue of ANESTHESIOLOGY, Whitehead *et al.*<sup>1</sup> bring experimental evidence suggesting that a high tidal volume ventilation can markedly reduce the release of inflammatory cytokines in response to intratracheal lipopolysaccharide. They attribute this paradoxical effect to a reduction of the alveolar macrophage population and hypothesize that injurious ventilation may increase susceptibility to infection, a detrimental effect that may participate in ventilator-induced lung injury.

Clinicians have long known some of the risks of mechanical ventilation. The classic and well-known manifestations of gross barotrauma (air leaks) and the adverse hemodynamic effects of high pressure/volume mechanical ventilation were described shortly after the generalization of mechanical ventilators in intensive care units. More recently, severe histologic distension of bronchoalveolar structures,<sup>2</sup> lung overinflation,<sup>3-6</sup> large air cysts, and extended bronchiectasis<sup>7,8</sup> have been reported in acute respiratory distress syndrome (ARDS) patients mechanically ventilated with high tidal volumes and pressures. One of the most important breakthroughs in the ventilatory management of such patients was the recognition of another iatrogenic potential of mechanical ventilation, which has been termed *ventilator-induced lung injury* (VILI). The concept was derived from animal studies that clearly showed that mechanical ventilation with high airway pressure and tidal volume rapidly caused a permeability-type pulmonary edema with diffuse alveolar damage and was accompanied by severe lung inflammation when protracted.<sup>9</sup> High lung volume rather than pressure was identified as responsible for these abnormalities, hence the term *volutrauma*.

In the 1970s, the recommendation was to deliver generous tidal volumes in the range of 15–20 ml/kg to patients with acute lung injury<sup>10,11</sup> to provide adequate carbon dioxide elimination and counterbalance the formation of atelectasis with ensuing development of lung regions with low ventilation/perfusion ratios.<sup>12</sup> In the following years, practices progressively moved toward a

reduction of tidal volume to values lower than 10 ml/kg,<sup>13</sup> and, interestingly, a decrease in ARDS mortality was simultaneously observed.<sup>14</sup> These progressive changes in ventilation modalities over time were supported by solid pathophysiologic foundations that form the concept of VILI. Definite proof of a causal relation between mortality and ventilatory strategy was given by the results of a multicenter randomized controlled trial that showed better survival in patients ventilated with a 6-ml/kg rather than a 12-ml/kg tidal volume.<sup>15</sup>

In addition to the permeability alterations and diffuse alveolar damage observed during VILI, the possibility that lung cell overstretching induced a biochemical reaction was soon investigated. Indeed, lung cell stretch elicits many responses, including opening of ion channels,<sup>16</sup> increased lipid trafficking in cell membranes,<sup>17</sup> and CXC chemokine release.<sup>18</sup> The release of many cytokines by lungs subjected *ex vivo* to injurious ventilatory modalities was also reported.<sup>19</sup> These findings led to the hypothesis that the multiple organ system dysfunction observed in many patients with ARDS was the result of uncontrolled production of inflammatory cytokines by the lungs and their systemic diffusion because of the alveolocapillary barrier alterations produced by injurious ventilation.<sup>20,21</sup> Should this hypothesis prove to be true, it would offer both an interesting explanation for the reduced mortality observed with lung-protective ventilation strategies during ARDS and an exciting avenue for the search for newer treatments for this deadly disease. Some authors strongly advocated the use of antiinflammatory therapies during mechanical ventilation of patients with ARDS to decrease the risk and severity of associated organ failure.<sup>20,22,23</sup> Given the high costs of such therapies and their potential for adverse effects,<sup>24</sup> their administration should be based on strong and concordant experimental and clinical data. This may not be the case for the time being.

Too many inconsistencies and contradictions exist that preclude making a straightforward link between cell responses to stress, VILI, organ failure, and their putative treatments.<sup>25</sup> Detailing these conceptual problems is beyond the scope of this editorial, but several aspects deserve mentioning. Pulmonary and systemic cytokine release was found highly variable during experimental VILI, even when experiments were performed under the same conditions and by the same team. For example, the concentration of tumor necrosis factor  $\alpha$  in bronchoalveolar lavage was found higher than 1,000 pg/ml after

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ventilating isolated nonperfused lungs with a high tidal volume<sup>19</sup> but 10 pg/ml under the same conditions at another institution.<sup>26</sup> Similarly, the level of interleukin 6 was more than 1,500 pg/ml in the perfusate (indicating the systemic release of lung borne cytokine) of isolated perfused mice lungs subjected to injurious high-volume ventilation,<sup>27</sup> whereas it was less than 100 pg/ml (a value lower than that observed during normal tidal volume ventilation in the former article) in a subsequent experiment conducted under the same conditions by the same team.<sup>28</sup>

To their own surprise, Whitehead *et al.*<sup>1</sup> found that injurious ventilation can markedly reduce the release of inflammatory cytokines in response to intratracheal lipopolysaccharide challenge. This is different from the results of a recent experimental study showing that injurious ventilation promotes the release of inflammatory cytokines in rats with mesenteric ischemia-reperfusion (a two-hit lung injury).<sup>29</sup> It is also worth noting that the study by Whitehead *et al.*<sup>1</sup> also confirms the highly variable release of cytokines observed during experimental injurious ventilation. They found no increase in the chemokine macrophage inflammatory protein 2 (the rodent equivalent of interleukin 8) in the bronchoalveolar lavage fluid of preparations ventilated with an injurious modality (high tidal volume, zero end-expiratory pressure) as compared with those ventilated with a protective lung strategy (low tidal volume, positive end-expiratory pressure), whereas in a previous article, using the same experimental settings, they reported a marked increase in this mediator.<sup>19</sup> The authors ascribe this discrepancy to minor protocol changes.<sup>1</sup> Similarly, they report that most of cytokine release in their study was due to alveolar macrophages, whereas in an earlier work, they concluded that pulmonary epithelium was a major contributor of cytokine production during injurious ventilation and may play an important role in the pathogenesis of lung injury.<sup>30</sup>

These discrepancies are at the heart of the problem of the relation between mechanical ventilation and cytokine release and balance toward inflammation or antiinflammation. Whatever their origin, it is quite difficult to draw a comprehensive theory linking mechanical ventilation and systemic inflammation and organ failure and even more difficult to derive any therapeutic conclusion because, depending on the study, one may conclude that injurious ventilation does not affect cytokine balance<sup>26,31</sup> or promotes either inflammation<sup>19,23</sup> or antiinflammation, as in the study by Whitehead *et al.*<sup>1</sup> Clinical studies are as puzzling. One concluded that injurious ventilation orientates lung and systemic cytokine balance toward inflammation,<sup>32</sup> whereas another showed that this balance was oriented toward antiinflammation.<sup>33,34</sup>

What can clinicians conclude? Obviously, lung cells are challenged by multiple aggressions in critically ill patients (infection, hyperoxia, mechanical ventilation).

There is no doubt that their response to these potentially injurious stimuli involves a cascade of mediators, including cytokines, whose complexity is fantastic. However, the variability of the biochemical response observed in extraphysiologic experimental conditions (isolated nonperfused lungs as in the current study<sup>1</sup>) must be balanced against the well-defined and easy-to-evidence morphologic alterations observed in ARDS patients ventilated for prolonged periods of time with high pressure/volume mechanical ventilation.<sup>2-8</sup> In addition, VILI is certainly not solely the result of mechanical injury<sup>9</sup> and may be worsened by hyperoxia, lung infection, and malnutrition.<sup>2</sup> In the past decade, the prognosis of ARDS markedly improved because of a comprehensive physiologic approach of the effects of positive-pressure mechanical ventilation,<sup>35</sup> and it may further improve as a result of the considerable amount of basic research on cytokines and VILI, including that presented in the article by Whitehead *et al.*<sup>1</sup> However, we should remain modest before drawing definitive theoretical and, more importantly, therapeutic conclusions, and avoid playing the sorcerer's apprentice. Some exciting hypotheses turned out to be catastrophic for the patients.<sup>36</sup>

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## References

- Whitehead TC, Zhang H, Mullen B, Slutsky AS: Effect of mechanical ventilation on cytokine response to intratracheal lipopolysaccharide. *ANESTHESIOLOGY* 2004; 101:000-000
- Rouby JJ, Lherm T, Martin de Lassale E, Poète P, Bodin L, Finet JF, Callard P, Viars P: Histologic aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure. *Intensive Care Med* 1993; 19:383-9
- Rouby JJ, Puybasset L, Nieszkowska A, Lu Q: Acute respiratory distress syndrome: Lessons from computed tomography of the whole lung. *Crit Care Med* 2003; 31:S285-95
- Lim CM, Soon Lee S, Seoung Lee J, Koh Y, Sun Shim T, Do Lee S, Sung Kim W, Kim DS, Dong Kim W: Morphometric effects of the recruitment maneuver on saline-lavaged canine lungs: A computed tomographic analysis. *ANESTHESIOLOGY* 2003; 99:71-80
- Rouby JJ: Lung overinflation: The hidden face of alveolar recruitment. *ANESTHESIOLOGY* 2003; 99:2-4
- Rouby JJ, Lu Q, Goldstein I: Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; 165:1182-6
- Tobin MJ: Advances in mechanical ventilation. *N Engl J Med* 2001; 344:1986-96
- Treggiari MM, Romand JA, Martin JB, Suter PM: Air cysts and bronchiectasis prevail in nondependent areas in severe acute respiratory distress syndrome: A computed tomographic study of ventilator-associated changes. *Crit Care Med* 2002; 30:1747-52
- Dreyfuss D, Saumon G: Ventilator-induced lung injury: Lessons from experimental studies. *Am J Respir Crit Care Med* 1998; 157:294-323
- Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB: Ventilation with end-expiratory pressure in acute lung disease. *J Clin Invest* 1972; 51:2315-23
- Suter PM, Fairley B, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975; 292:284-9
- Bendixen HH: Rational ventilator modes for respiratory failure. *Crit Care Med* 1974; 2:225-7
- Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ: Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. *JAMA* 2002; 287:345-55
- Milberg JA, Davis DR, Steinberg KP, Hudson LD: Improved survival of

patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA* 1995; 273:306-9

15. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301-8

16. Parker JC, Ivey CL, Tucker JA: Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. *J Appl Physiol* 1998; 84: 1113-8

17. Vlahakis NE, Schroeder MA, Pagano RE, Hubmayr RD: Deformation-induced lipid trafficking in alveolar epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2001; 280:L938-46

18. Pugin J, Dunn I, Jolliet P, Tassaux D, Magnenat J, Nicod L, Chevrolet J: Activation of human macrophages by mechanical ventilation in vitro. *Am J Physiol* 1998; 275:L1040-50

19. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997; 99:944-52

20. Slutsky AS, Tremblay LN: Multiple system organ failure: Is mechanical ventilation a contributing factor? *Am J Respir Crit Care Med* 1998; 157:1721-5

21. Dreyfuss D, Saumon G: From ventilator-induced lung injury to multiple organ dysfunction? (editorial). *Intensive Care Med* 1998; 24:102-4

22. Dos Santos CC, Slutsky AS: Invited review: mechanisms of ventilator-induced lung injury: A perspective. *J Appl Physiol* 2000; 89:1645-55

23. Slutsky AS: Basic science in ventilator-induced lung injury: Implications for the bedside. *Am J Respir Crit Care Med* 2001; 163:599-600

24. Fisher CJ Jr, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, Abraham E, Schein RM, Benjamin E: Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med* 1996; 334:1697-702

25. Dreyfuss D, Ricard JD, Saumon G: On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury. *Am J Respir Crit Care Med* 2003; 167:1467-71

26. Ricard JD, Dreyfuss D, Saumon G: Production of inflammatory cytokines in

ventilator-induced lung injury: A reappraisal. *Am J Respir Crit Care Med* 2001; 163:1176-80

27. von Bethmann AN, Brasch F, Nüsing R, Vogt K, Volk HD, Müller K, Wendel A, Uhlig S: Hyperventilation induces release of cytokines from perfused mouse lung. *Am J Respir Crit Care Med* 1998; 157:263-72

28. Uhlig U, Fehrenbach H, Lachmann RA, Goldmann T, Lachmann B, Vollmer E, Uhlig S: Phosphoinositide 3-OH kinase inhibition prevents ventilation-induced lung cell activation. *Am J Respir Crit Care Med* 2004; 169:201-8

29. Bouadma L, Schortgen F, Ricard J, Martet G, Dreyfuss D, Saumon G: Ventilation strategy affects cytokine release after mesenteric ischemia-reperfusion in rats. *Crit Care Med* 2004; (in press)

30. Tremblay LN, Miatto D, Hamid Q, Govindarajan A, Slutsky AS: Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor- $\alpha$  and interleukin-6 messenger RNA. *Crit Care Med* 2002; 30:1693-700

31. Verbrugge SJ, Uhlig S, Neggers SJ, Martin C, Held HD, Haitsma JJ, Lachmann B: Different ventilation strategies affect lung function but do not increase tumor necrosis factor- $\alpha$  and prostacyclin production in lavaged rat lungs *in vivo*. *ANESTHESIOLOGY* 1999; 91:1834-43

32. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1999; 282:54-61

33. Stuber F, Wrigge H, Schroeder S, Wetegrove S, Zinserling J, Hoeft A, Putensen C: Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. *Intensive Care Med* 2002; 28:834-41

34. Pugin J: Is the ventilator responsible for lung and systemic inflammation? *Intensive Care Med* 2002; 28:817-9

35. Dreyfuss D, Saumon G: Evidence-based medicine or fuzzy logic: What is best for ARDS management? *Intensive Care Med* 2002; 28:230-4

36. Freeman BD, Danner RL, Banks SM, Natanson C: Safeguarding patients in clinical trials with high mortality rates. *Am J Respir Crit Care Med* 2001; 164: 190-2

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## For Outpatients, Does Regional Anesthesia Truly Shorten the Hospital Stay, and How Should We Define Postanesthesia Care Unit Bypass Eligibility?

IN this issue of *ANESTHESIOLOGY*, Hadzic *et al.*<sup>1</sup> report on hand surgery outpatients randomly assigned to receive general anesthesia (GA) or infraclavicular nerve block. The specific aim was to compare discharge times (a 97-min difference favoring infraclavicular); the secondary aim was to compare bypass of the postanesthesia care unit (PACU; 76% infraclavicular *vs.* 24% GA). This study promotes the use of regional anesthesia (RA) to shorten the outpatient stay.

Based on these findings, two questions are raised: (1) What is the recent evidence indicating that RA use will reduce discharge times, and (2) what criteria should be used to delineate the PACU bypass milestone?

In clinical practice, many orthopedic procedures have

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use predicted postoperative fentanyl use (in women), and (3) cumulative fentanyl dose predicted postoperative nausea and vomiting. Our group's work has shown that each postoperative nursing intervention is associated with a 27- to 45-min delay in discharge,<sup>3</sup> a notion corroborated by Kitz *et al.*,<sup>6</sup> who showed that postoperative administration of controlled analgesics is more costly than the administration of noncontrolled analgesics. These studies refute the intuitive notion that simply administering more intraoperative opioids *via* conventional bolus methods will prevent discharge time increases. To my knowledge, advanced opioid dosing techniques (*e.g.*, target-controlled infusions) have not been compared with RA techniques with respect to analgesic outcome differences.

Recently developed target-controlled infusion technologies<sup>7</sup> could in theory obviate the need for RA techniques to produce an ideal analgesic recovery profile after invasive outpatient orthopedic surgery. This may be especially true if target-controlled opioid dosing was associated with lower rates of postoperative nausea and/or vomiting (PONV) and other opioid-related side effects. However, limited evidence available shows high incidences of PONV after both target-controlled remifentanyl (27% nausea, 10% vomiting)<sup>8</sup> and alfentanil (30% nausea) infusions.<sup>9</sup> The alfentanil target-controlled study group was compared to patients receiving conventional perioperative morphine boluses, and both treatment groups had a postoperative nausea rate of 30%.<sup>9</sup> Separating the therapeutic index of opioid analgesia and the

"toxic index" of opioid-induced PONV (and other undesirable side effects for outpatients) may prove to be a daunting task. If the following scenarios were to occur, a significant clinical advance would be made, perhaps obviating the pressing need for labor-intensive RA analgesic procedures in complex orthopedic outpatient procedures: (1) a synthetic parenteral opioid that does not produce PONV in therapeutic analgesic doses; (2) appropriate supporting technology for a target-controlled infusion with this opioid; and (3) a reliable oral opioid with low diversion potential (*i.e.*, low street value) that produces therapeutic analgesic levels free from nausea/vomiting, somnolence, respiratory depression, pruritus, urinary retention, and constipation. The scenario described above does not even account for the PONV risk associated with volatile agent use when compared with the use of total intravenous propofol GA.

Opioids are not the sole analgesic option for outpatient surgery; multimodal analgesia is an important concept. Pavlin *et al.*<sup>5</sup> showed that intraoperative parenteral ketorolac predicted (1) lower use/consumption of perioperative fentanyl, (2) less PONV, and (3) faster discharge time. Whether parecoxib<sup>10,11</sup> has a similar impact as does ketorolac in reducing PONV and providing faster discharge time remains to be seen. In either case, there is likely a procedural pain threshold above which it seems unlikely that nonsteroidal antiinflammatory drugs would be sufficient, rendering nerve blocks potentially valuable in reducing discharge times and avoiding un-

**Table 1. Proposal for Standardized PACU Bypass/Discharge Criteria and Scoring System for Outpatients**

Movement	Scores:
Purposeful movement of (at least) one lower and one upper extremity <sup>18</sup>	2
Purposeful movement of at least one upper extremity (but neither lower extremity) <sup>18</sup>	1
No purposeful movement <sup>15,18,21,22</sup>	0
	Movement score:
Blood pressure (sitting position assessment required after a supine assessment) <sup>18</sup>	Scores:
Within 20% of preoperative baseline, <sup>15</sup> without orthostatic changes <sup>18</sup>	2
Between 20–40% of preoperative baseline, <sup>15</sup> without orthostatic changes <sup>18</sup>	1
Less than 40% of preoperative baseline, <sup>15</sup> and/or orthostatic changes <sup>18</sup>	0
	BP score:
Level of consciousness	Scores:
Awake, <sup>15,18,21,22</sup> follows commands, <sup>18</sup> easily aroused when called <sup>15</sup>	2
Arousable to stimuli, exhibits protective reflexes, <sup>15</sup> with or without following commands	1
Obtunded or persistently somnolent; <sup>15,18,21,22</sup> with or without protective reflexes	0
	LOC score:
Respiratory effort	Scores:
Coughs and deep-breathes freely, <sup>21,22</sup> and/or on command <sup>15,18</sup>	2
Only able to cough involuntarily, but not on command; <sup>18</sup> maintains airway without support <sup>15</sup>	1
Tachypnea, dyspnea, or apnea, <sup>18</sup> and/or requiring airway maintenance <sup>15</sup>	0
	Respiratory score:
Oxygen saturation	Scores:
≥ preoperative reading minus 1%, without supplemental oxygen <sup>15</sup>	2
≥ preoperative reading minus 1%, with supplemental oxygen <sup>15</sup>	1
< preoperative reading minus 1%, with or without supplemental oxygen <sup>15</sup>	0
	Saturation score:
	Total score:

Parameters below should be assessed only for patients who do not require any parenteral interventions for pain, nausea, vomiting, pruritis, shivering, or hypotension/orthostasis.<sup>18</sup> Patient pain scores should not exceed 2–3 (out of 10) at the time of PACU bypass or PACU discharge.<sup>1</sup>

PACU = postanesthesia care unit.

planned admissions. These “procedural pain thresholds” require further research.

Two recent retrospective studies of outpatient anesthesia for hand surgery showed RA patients to have faster discharge times. In one, intravenous regional (Bier) block patients had faster discharge times than did GA and axillary block patients (by 32 and 48 min, respectively)<sup>12</sup>; in another, wrist block patients for carpal tunnel release were discharged sooner *versus* Bier block and GA patients (by 23 and 65 min, respectively).<sup>13</sup> The GA groups in both studies used simple bolus dosing of opioids, as did the current study by Hadzic *et al.*<sup>1</sup>

Discharge time improvements shown by the aforementioned hand surgery studies have not yet translated to other outpatient orthopedic procedures. While calling for potential change in their institution’s discharge processes, Collins *et al.*<sup>14</sup> reported a 7-min improvement in hospital discharge time when an RA program was developed for outpatient foot surgery. In another randomized trial (n = 60, knee arthroscopy patients), Jankowski *et al.*<sup>15</sup> provided spinal, psoas-compartment lumbar plexus block, or GA and found no differences in discharge times, but these authors required voiding in all patients, a requirement which may no longer be necessary in low-risk patients undergoing regional/neuraxial techniques.<sup>16</sup>

It is difficult to generalize meaningful hospital staffing/cost-saving benefits if RA techniques were used as opposed to GA-only techniques (*via* PACU bypass or same-day discharge time reductions or both). Generally speaking, if the conversion from GA to RA techniques encompassed only 25–100 cases/yr, it seems highly unlikely that the duration-of-stay benefits would translate to meaningful reductions in hospital expenditures (for staffing *etc.*). However, if 500–3,000+ cases/yr were converted from GA to RA and the results (PACU bypass, reduced duration of stay) by Hadzic *et al.*<sup>1</sup> were able to be generalized to all cases/case categories subject to the anesthesia process transformation, it seems more likely that actual cost savings would be tenable.<sup>17–20</sup> The threshold is unknown for the proportion of outpatients requiring GA-to-RA conversions to produce meaningful hospital cost advantages.

Our group studied 1,432 consecutive outpatients undergoing anterior cruciate ligament reconstruction and more invasive knee procedures.<sup>17–20</sup> In our institution, these procedures were associated with a 17% unplanned admission rate when GA was used (without nerve blocks); GA was used 90% of the time (and nerve blocks none of the time) before July 1996. Nerve blocks evolved as the centerpiece of analgesia during the next 2 yr, leading to routine same-day discharge of complex knee surgery patients by 1998, when all of these patients were previously admitted.<sup>4</sup>

In addition to achieving routine same-day discharge after invasive outpatient orthopedic surgery (associated with the routine use of nerve blocks), we designed a

PACU bypass score to address specific needs of RA patients. Our scoring system was modeled after the 10-point modified Aldrete score,<sup>21</sup> with special provisions forbidding the bypass of patients with any pain, PONV, shivering, pruritus, orthostatic symptoms, or hypotension. We believed it was inefficient to use a PACU nurse (trained in critical care nursing) for the treatment of postoperative patients who met the stated criteria. Similarly, we did not want to create “loopholes” in which patients were inappropriately transferred from the PACU, because patients can have pain or PONV without reflecting adversely on the Aldrete score.

Hadzic *et al.*<sup>1</sup> used the modified Aldrete score of 9 or greater for PACU bypass (if following these criteria to the letter, nerve block patients could never achieve a score of 10 because these patients cannot move their blocked upper extremity). Meanwhile, Jankowski *et al.*<sup>15</sup> used a Mayo Modified Discharge Scoring System score of 8 or greater to qualify for PACU bypass; these criteria were based largely on the same modified Aldrete score criteria. Thankfully, Hadzic *et al.*<sup>1</sup> did not bypass patients who had pain scores higher than 3 (out of 10); this is a loophole in both the Aldrete and the Mayo criteria (because pain is not evaluated in either of these). Other than our group’s criteria<sup>17–20</sup> and the Mayo criteria, the only other reported criteria are those by White and Song,<sup>22</sup> which were not designed for patients undergoing RA. The White-Song criteria allow PACU bypass for patients with (1) transient vomiting or retching or (2) moderate to severe pain controlled with intravenous analgesics, if all other parameter scores are perfect. The White-Song criteria do not address shivering or pruritus.<sup>18</sup> Table 1 lists my suggestion for merging clinically useful PACU bypass quality indicators.

In conclusion, Hadzic *et al.*<sup>1</sup> demonstrate the possibility of routinely using RA for peripheral orthopedic surgery in an effort to minimize same-day discharge times. Much work is required, especially *via* randomized controlled trials, to determine whether discharge time savings are found whenever RA is used or whether emerging pharmacology and technology (*e.g.*, target-controlled opioid infusions) may obviate the need for routine RA procedures in invasive outpatient orthopedic surgery. Standardizing PACU bypass criteria is an important step to render discharge time studies comparable, because nursing qualifications and staffing ratios in the PACU *versus* phase II may be an important covariate in the study of discharge times. PACU bypass criteria should prohibit undue increases in phase II labor intensity by discharging (or bypassing) a patient without fully addressing common labor intensive symptoms (PONV and pain) that are not in the forefront of critical care symptomatology (as are airway management and hemodynamics).

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## References

1. Hadzic A, Arliss J, Kerimoglu B, Karaca PE, Yufa M, Claudio R, Vloka JD, Rosenquist R, Santos AC, Thys DM: A comparison of infraclavicular nerve block versus general anesthesia for hand and wrist day-case surgeries. *ANESTHESIOLOGY* 2004; 101:000-000
2. White PF, Issioui T, Skrivaneck GD, Early JS, Wakefield C: The use of a continuous popliteal sciatic nerve block after surgery involving the foot and ankle: Does it improve the quality of recovery? *Anesth Analg* 2003; 97:1303-9
3. Williams BA, Kentor ML: Making an ambulatory surgery center suitable for regional anaesthesia. *Best Pract Res Clin Anaesthesiol* 2002; 16:175-94
4. Pavlin DJ, Rapp SE, Polissar NL, Malmgren JA, Koerschgen M, Keyes H: Factors affecting discharge time in adult outpatients. *Anesth Analg* 1998; 87:816-26
5. Pavlin DJ, Chen C, Penaloza DA, Polissar NL, Buckley FP: Pain as a factor complicating recovery and discharge after ambulatory surgery. *Anesth Analg* 2002; 95:627-34
6. Kitz DS, McCartney M, Kissick JF, Townsend RJ: Examining nursing personnel costs: Controlled versus noncontrolled oral analgesic agents. *J Nurs Adm* 1989; 19:10-4
7. Egan TD: Target-controlled drug delivery: Progress toward an intravenous "vaporizer" and automated anesthetic administration. *ANESTHESIOLOGY* 2003; 99: 1214-9
8. Schraag S, Kenny GN, Mohl U, Georgieff M: Patient-maintained remifentanyl target-controlled infusion for the transition to early postoperative analgesia. *Br J Anaesth* 1998; 81:365-8
9. Irwin MG, Jones RD, Visram AR, Kenny GN: Patient-controlled alfentanil: Target-controlled infusion for postoperative analgesia. *Anaesthesia* 1996; 51: 427-30
10. Malan TP Jr, Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC: Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. *ANESTHESIOLOGY* 2003; 98:950-6
11. Joshi GP, Viscusi ER, Gan TJ, Minkowitz H, Cippolle M, Schuller R, Cheung RY, Fort JG: Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral COX-2 specific inhibitor. *Anesth Analg* 2004; 98:336-42
12. Chan VW, Peng PW, Kaszas Z, Middleton WJ, Muni R, Anastakis DG, Graham BA: A comparative study of general anesthesia, intravenous regional anesthesia, and axillary block for outpatient hand surgery: Clinical outcome and cost analysis. *Anesth Analg* 2001; 93:1181-4
13. Gebhard RE, Al-Samsam T, Greger J, Khan A, Chelly JE: Distal nerve blocks at the wrist for outpatient carpal tunnel surgery offer intraoperative cardiovascular stability and reduce discharge time. *Anesth Analg* 2002; 95:351-5
14. Collins L, Halwani A, Vaghadia H: Impact of a regional anesthesia analgesia program for outpatient foot surgery. *Can J Anaesth* 1999; 46:840-5
15. Jankowski CJ, Hebl JR, Stuart MJ, Rock MG, Pagnano MW, Beighley CM, Schroeder DR, Horlocker TT: A comparison of psoas compartment block and spinal and general anesthesia for outpatient knee arthroscopy. *Anesth Analg* 2003; 97:1003-9
16. Mulroy MF, Salinas FV, Larkin KL, Polissar NL: Ambulatory surgery patients may be discharged before voiding after short-acting spinal and epidural anesthesia. *ANESTHESIOLOGY* 2002; 97:315-9
17. Williams BA, Kentor ML, Williams JP, Figallo CM, Sigl JC, Anders JW, Bear TC, Tullock WC, Bennett CH, Harner CD, Fu FH: Process analysis in outpatient knee surgery: Effects of regional and general anesthesia on anesthesia-controlled time. *ANESTHESIOLOGY* 2000; 93:529-38
18. Williams BA, Kentor ML, Williams JP, Vogt MT, DaPos SV, Harner CD, Fu FH: PACU bypass after outpatient knee surgery is associated with fewer unplanned hospital admissions but more phase II nursing interventions. *ANESTHESIOLOGY* 2002; 97:981-8
19. Williams BA, Kentor ML, Vogt MT, Williams JP, Chelly JE, Valalik S, Harner CD, Fu FH: Femoral-sciatic nerve blocks for complex outpatient knee surgery are associated with less postoperative pain before same-day discharge: A review of 1200 consecutive cases from the period 1996-1999. *ANESTHESIOLOGY* 2003; 98: 1206-13
20. Williams BA, Kentor ML, Vogt MT, Vogt WB, Coley KC, Williams JP, Roberts MS, Chelly JE, Harner CD, Fu FH: The economics of nerve block pain management after anterior cruciate ligament reconstruction: Significant hospital cost savings via associated PACU bypass and same-day discharge. *ANESTHESIOLOGY* 2004; 100:697-706
21. Aldrete JA: The post-anesthesia recovery score revisited. *J Clin Anesth* 1995; 7:89-91
22. White PF, Song D: New criteria for fast-tracking after outpatient anesthesia: A comparison with the modified Aldrete's scoring system. *Anesth Analg* 1999; 88:1069-72

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## Two Reports of Propofol Anesthesia Associated with Metabolic Acidosis in Adults

CURRENT anesthetics are remarkably safe, with few patients experiencing obvious side effects. Nevertheless, it is essential that clinicians remain alert to the possibility of new anesthetic-related side effects and to previously described side effects occurring in novel circumstances. The current issue of *ANESTHESIOLOGY* contains two provocative case reports that suggest that continuous propofol infusion during anesthesia in adult patients may result in metabolic acidosis.<sup>1,2</sup> The novelty of the two reports is the apparent occurrence of "propofol infusion syndrome" during anesthesia in adults; previous anecdotal

reports have described severe, sporadic, occasionally fatal metabolic acidosis during continuous infusion of propofol for sedation of critically ill children<sup>3-5</sup> and adults.<sup>6,7</sup> Although the mechanism by which propofol produces sporadic lactic acidosis is unclear, evidence implicates poisoning of the electron transport chain<sup>8</sup> and impaired oxidation of long-chain fatty acids.<sup>9</sup>

However, no previous reports have associated lactic acidosis with propofol infusion for surgical anesthesia in adults. Therefore, the current reports prompt the question of whether the authors have correctly interpreted their observations. The answer to that question hinges on the differential diagnosis of intraoperative metabolic acidosis.

In anesthetized patients, the differential diagnosis of newly developed metabolic acidosis is rarely challenging. Most commonly, intraoperative metabolic acidosis represents lactic acidosis resulting from an obvious cause, *e.g.*, lower body reperfusion after release of an aortic cross clamp or severe hemorrhagic shock. More recently, infusion of relatively large volumes of 0.9% saline has been associated with the development of hyperchloremic metabolic acidosis.<sup>10-14</sup> However, in

This Editorial View accompanies the following two articles: Burow BK, Johnson ME, Packer DL: Metabolic acidosis associated with propofol in the absence of other causative factors. *ANESTHESIOLOGY* 2004; 101:239-41; and Salengros J-C, Velghe-Lenelle C-E, Bollens R, Engelman E, Barvais L: Lactic acidosis during propofol-remifentanyl anesthesia in an adult. *ANESTHESIOLOGY* 2004; 101:241-3.

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cases where intraoperative metabolic acidosis is unanticipated, what diagnostic approach is both reasonable and cost effective?

During anesthesia, the differential diagnosis of metabolic acidosis begins with direct measurements of pH and arterial carbon dioxide tension ( $P_{aCO_2}$ ) and calculation of serum bicarbonate concentration ( $[HCO_3^-]$ ) and other derived variables, such as base excess. However, deviations of pH,  $P_{aCO_2}$ ,  $[HCO_3^-]$ , and base excess from normal values do not provide etiologic information. If the etiology is not obvious, further data are required.

The first critical differential diagnostic point is to distinguish between hyperchloremic metabolic acidosis and metabolic acidosis associated with excessive generation of organic acids, such as lactate and ketones. Three commonly used tools are the anion gap, the strong ion difference, and individual measurements of the anions of organic acids. The anion gap is within the normal range in hyperchloremic metabolic acidosis but usually is increased in lactic acidosis as in several other pathologic states. Intraoperative calculation of the anion gap often requires a specific request for a serum  $[Cl^-]$ , which many "stat" laboratories do not include in an electrolyte panel. Use of the strong ion difference, as part of the Fencl-Stewart approach, also requires measurement of electrolytes, including serum  $[Cl^-]$ , and at least a serum albumin concentration, which together would provide sufficient data to apply the recently proposed, simplified modification of the Fencl-Stewart approach.<sup>15</sup> In addition to calculation of the anion gap or the strong ion difference, quantification of the anions of organic acids, such as serum lactate or serum ketones, may be indicated.

Applying either approach to the two case reports in this issue of ANESTHESIOLOGY produces suggestive but not definitive information. Burow *et al.*<sup>1</sup> describe a 31-yr-old woman receiving a continuous propofol infusion for sedation during radiofrequency ablation for chronic atrial fibrillation. Propofol sedation was initiated at  $25 \mu g \cdot kg^{-1} \cdot min^{-1}$  and titrated to between 50 and  $125 \mu g \cdot kg^{-1} \cdot min^{-1}$  based on patient responsiveness. No more than 3 l saline solution, 0.9%, was infused during 395 min of propofol sedation. Intermittently obtained arterial blood gas measurements showed a steady decline in pH,  $[HCO_3^-]$ , and base excess without evidence of hypoperfusion, hypoxemia, or hypercapnia. Because no data were obtained to quantify the anion gap, the strong ion gap, or the anions of organic acids, hyperchloremic acidosis cannot be excluded. However, after the propofol infusion was discontinued, accompanied by the administration of 15 mEq sodium bicarbonate and mild mechanical hyperventilation, pH returned toward normal values.

Salengros *et al.*<sup>2</sup> describe a 64-yr-old man receiving a total intravenous anesthetic (propofol, remifentanyl, and mivacurium) for a radical prostatectomy for adenocarcinoma. During the third hour of the case, the patient's

heart rate increased. At that time, pH,  $P_{aCO_2}$ ,  $[HCO_3^-]$ , and serum lactate were normal. During the remaining 2 h of the case, pH and  $[HCO_3^-]$  progressively declined, and serum lactate increased. Intravenous fluid therapy consisted of 1 l saline, 0.9%, and 1 l hydroxyethyl starch, 6%. Hemodynamic variables other than tachycardia remained acceptable, and no other metabolic derangements were evident by laboratory analysis. The surgical procedure ended shortly after the second arterial blood gas measurement showed a worsening metabolic acidosis. The patient was transferred to the intensive care unit, and his acid-base status returned to baseline over the next several hours.

These two provocative cases are interesting because they describe the development of reversible metabolic acidosis associated with propofol anesthesia as the most likely explanation. The acidosis described by Burow *et al.*<sup>1</sup> could have resulted from saline infusion, although this is unlikely, given the time course and volume of infusion. In addition, the acidemia resolved despite continued infusion of saline. This report would be more convincing had electrolyte data been obtained or had lactate been measured. The report by Salengros *et al.*<sup>2</sup> is more convincing because measurement of serum lactate confirms the diagnosis of lactic acidosis. Hypoperfusion seems to be an unlikely explanation because blood pressure was well maintained, although abrupt onset of tachycardia was noted. Diabetic ketoacidosis was excluded, and hyperchloremic metabolic acidosis is also unlikely, given the volume and time course of fluid infusion. Cytopathic hypoxia secondary to sepsis is unlikely because, of the diagnostic criteria for sepsis or systemic inflammatory response syndrome as defined by the 1992 American College of Chest Physicians/Society of Critical Care Medicine consensus conference,<sup>16</sup> only tachycardia was present. Before infusion, the propofol had not been drawn into syringes and stored for an extended interval, which has been associated with sepsis.<sup>17</sup> Therefore, these two reports are most consistent with the possibility that occasionally, in adults, propofol in sufficiently high concentrations may itself produce a type of cytopathic hypoxia by impairing the electron transport chain or fatty acid oxidation.

What should anesthesiologists conclude on the basis of these two case reports? Unexpected tachycardia occurring during propofol anesthesia should prompt laboratory evaluation for possible lactic acidosis. The most cost-effective approach would be to request an arterial blood gas measurement and an immediate serum lactate measurement. Given the suspicion of lactic acidosis, documentation of an increased anion gap or strong ion difference would necessitate additional studies and further delay treatment. "Propofol infusion syndrome" will likely be identified in additional anesthetized patients.

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## References

1. Burow BK, Johnson ME, Packer DL: Metabolic acidosis associated with propofol in the absence of other causative factors. *ANESTHESIOLOGY* 2004; 101:000-000
2. Salengros J-C, Velghe-Lenelle C-E, Bollens R, Engelman E, Barvais L: Lactic acidosis during propofol-remifentanyl anesthesia in an adult. *ANESTHESIOLOGY* 2004; 101:000-000
3. Bray RJ: Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; 8:491-9
4. Cray SH, Robinson BH, Cox PN: Lactic acidemia and bradyarrhythmia in a child sedated with propofol. *Crit Care Med* 1998; 26:2087-92
5. Hanna JP, Ramundo ML: Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. *Neurology* 1998; 50:301-3
6. Perrier ND, Baerga-Varela Y, Murray MJ: Death related to propofol use in an adult patient. *Crit Care Med* 2000; 28:3071-4
7. Cremer OL, Moons KG, Bouman EA, Kruijswijk JE, de Smet AM, Kalkman CJ: Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357:117-8
8. Schenkman KA, Yan S: Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. *Crit Care Med* 2000; 28:172-7
9. Wolf A, Weir P, Segar P, Stone J, Shield J: Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet* 2001; 357:606-7
10. McFarlane C, Lee A: A comparison of plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. *Anaesthesia* 1994; 49:779-81
11. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *ANESTHESIOLOGY* 1999; 90:1265-70
12. Waters JH, Bernstein CA: Dilutional acidosis following hetastarch or albumin in healthy volunteers. *ANESTHESIOLOGY* 2000; 93:1184-7
13. Rehm M, Finsterer U: Treating intraoperative hyperchloremic acidosis with sodium bicarbonate or tris-hydroxymethyl aminomethane: a randomized prospective study. *Anesth Analg* 2003; 96:1201-8
14. Liskaser FJ, Bellomo R, Hayhoe M, Story D, Poustie S, Smith B, Letis A, Bennett M: Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass associated acidosis. *ANESTHESIOLOGY* 2000; 93:1170-3
15. Story DA, Morimatsu H, Bellomo R: Strong ions, weak acids and base excess: A simplified FencI-Stewart approach to clinical acid-base disorders. *Br J Anaesth* 2004; 92:54-60
16. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250-6
17. Bennett SN, McNeil MM, Bland LA, Arduino MJ, Villarino ME, Perrotta DM, Burwen DR, Welbel SF, Pegues DA, Sroud L, Zeitz PS, Jarvis WR: Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med* 1995; 333:147-54