

## Propofol Infusion Syndrome or Probable Overinterpretation Syndrome?

*To the Editor:*—It was with great interest that we read the article by Cravens *et al.*<sup>1</sup> on the incidence of propofol infusion syndrome. This is obviously an important question with significant clinical relevance. However, with all of the inherent limitations of a retrospective study as recognized by the authors, we find the interpretation and conclusion of the authors (“this study provides evidence that even in a non-critically ill population, prolonged high-dose propofol infusion is associated with otherwise unexplained metabolic acidosis in a significant number of patients”) to be inconsistent with the limited data presented.

To begin, their definition of metabolic acidosis is problematic, because it merely represents the upper limit of the reference range for base excess. We understand that the definition of metabolic acidosis might be tricky, particularly if bicarbonate and chloride are unknown. However, the definition should meet the generally accepted criterion, and base excess should be lower than, and not equal to,  $-2$  mEq/l.<sup>2</sup> As it were, 2 of 13 patients with “propofol infusion syndrome” really had a normal base excess ( $= -2$ ), and 4 patients had a base excess of  $-2$ , which is nearly normal (fig. 1 in the article).

Of the cohort of 301 patients, only 55 patients had arterial blood gases drawn at various stages because of concern with their respiratory status. The authors argue that this may underestimate, and not overestimate, the incidence of “propofol infusion syndrome.” We respectfully disagree. A more appropriate interpretation is that the incidence remains unknown, because the factors that predispose these individuals to respiratory depression may also have resulted in the metabolic acidosis. Without a control group, the influence of this built-in bias simply cannot be assessed.

Another problem relates to the variability of blood sampling timing and the lack of baseline data. The authors’ figure 1 shows that one patient had base excess of  $-6$  at a very low rate of propofol infusion. Without baseline blood gases and knowledge of the total dose of propofol infused, the authors cannot consider this patient to have propofol infusion syndrome. Moreover, because in all patients the timing of blood sampling is not reported and baseline blood gases are not available, the data in figure 1 are essentially uninterpretable, and one wonders why the plot was made at all. Similarly, the data displayed in their table 2 regarding duration of propofol infusion is not meaningful because the crucial time is the duration of infusion (and amount of propofol given) at the time of blood gas sampling, not the total duration of the infusion for the procedure. About the only fact we can be certain of is that the authors overestimate the duration of propofol infusion before the development of this mild metabolic acidosis, which may not have any relation to the propofol infusion.

Propofol infusion syndrome is diagnosed in cases of unexplained severe metabolic, usually lactic, acidosis and is associated with high-dose<sup>3-5</sup> or long-duration propofol infusion,<sup>6,7</sup> usually both.<sup>8,9</sup> We are surprised that Cravens *et al.* titled their work as “Incidence of Propofol Infusion Syndrome during . . .” because the study did not include any

patient who developed frank propofol infusion syndrome. Finally, to conclude that “this study provides evidence that even in a non-critically ill population, prolonged high-dose propofol infusion is associated with otherwise unexplained metabolic acidosis in a significant number of patients” is a stretch of one’s imagination. Not only was the duration of propofol infusion before the development of metabolic acidosis unknown, the dose of propofol given was a sedative dose and could hardly qualify as high dose by any clinical standard.

To be fair, as the authors indicated, it is difficult to draw definitive conclusions from a retrospective study. However, they should be valid if not definitive. We performed a similar retrospective chart review, comparing lactate, bicarbonate, chloride, arterial carbon dioxide tension, pH, and other parameters in patients receiving high-dose propofol anesthesia ( $n = 50$ ) and volatile anesthesia ( $n = 100$ ) over time in long-duration spine surgeries, and we observed that lactate levels are significantly lower during propofol infusion anesthesia.<sup>10</sup> The manuscript is currently in preparation. We do fully agree with Cravens *et al.* on one aspect: A larger prospective study is warranted to look for early signs of propofol infusion syndrome and its incidence.

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### References

1. Cravens GT, Packer DL, Johnson ME: Incidence of propofol infusion syndrome during noninvasive radiofrequency ablation for atrial flutter or fibrillation. *ANESTHESIOLOGY* 2007; 106:1134-8
2. Gunnerson KJ, Saul M, He S, Kellum JA: Lactate *versus* non-lactate metabolic acidosis: A retrospective outcome evaluation of critically ill patients. *Crit Care* 2006; 10:R22
3. Burrow BK, Johnson ME, Packer DL: Metabolic acidosis associated with propofol in the absence of other causative factors. *ANESTHESIOLOGY* 2004; 101:239-41
4. Liolios A, Guerit JM, Scholtes JL, Raftopoulos C, Hantson P: Propofol infusion syndrome associated with short-term large-dose infusion during surgical anesthesia in an adult. *Anesth Analg* 2005; 100:1804-6
5. Salengros JC, Velghe-Lenelle CE, Bollens R, Engelman E, Barvais L: Lactic acidosis during propofol-remifentanyl anesthesia in an adult. *ANESTHESIOLOGY* 2004; 101:241-3
6. 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
7. Merz TM, Regli B, Rothen HU, Felleiter P: Propofol infusion syndrome: A fatal case at a low infusion rate. *Anesth Analg* 2006; 103:1050
8. Kang TM: Propofol infusion syndrome in critically ill patients. *Ann Pharmacother* 2002; 36:1453-6
9. Vasile B, Rasulo F, Candiani A, Latronico N: The pathophysiology of propofol infusion syndrome: A simple name for a complex syndrome. *Intensive Care Med* 2003; 29:1417-25
10. Tontisirin N, Rozet I, Vavilala MS, Lee LA, Lam AM: Lactate levels during long spine surgery: Comparison between propofol infusion and volatile anesthetics. *J Neurosurg Anesthesiol* 2006; 18:311

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## Propofol Infusion and Lactic Acidosis

*To the Editor:*—We read with interest the retrospective study from Cravens *et al.*<sup>1</sup> about propofol infusion syndrome. The authors reported a high incidence of slight metabolic acidosis during prolonged propofol infusion in patients who received a total dose of approximately 20 mg/kg.

The main cause of propofol infusion syndrome would be cumulative high-dose propofol, whereas low doses would be safe.<sup>2-5</sup> However, there is a lack of studies looking for acidosis related to propofol infusion, and prospective studies are needed to confirm the relation between high-dose propofol and acidosis and to guarantee the safety of low-dose propofol routinely used for sedation or anesthesia. Regarding the latter, our group recently performed a prospective randomized trial in 42 patients scheduled to undergo thoracotomy to evaluate the effects of almitrine and inhaled nitric oxide on oxygenation.<sup>6</sup> Arterial blood gases and lactic acid were determined in all patients: the former because arterial oxygen tension was the main variable, and the latter to discard lactic acidosis that could be an eventual complication of almitrine administration.<sup>7,8</sup> All of the patients in the study received intravenous anesthesia with propofol and remifentanyl.<sup>6</sup> The research protocol and the administration of propofol were strictly standardized. In all of the patients, anesthesia was induced with  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  propofol and maintained with  $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  propofol, so that all of the patients received an average dose of 6 mg/kg propofol.

Arterial pH and lactic acid concentrations did not significantly change during the study, remaining within the normal range in all patients (7.35–7.45 and 0.5–1.6 mm, respectively).<sup>6</sup>

These results suggest that our patients were not at risk of propofol infusion syndrome after receiving approximately a third of the dose administered by Cravens *et al.*<sup>1</sup>

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*In Reply:*—We appreciate the interest in our report<sup>1</sup> by Drs. Rozet and Lam and by Dr. Gallart *et al.*, and we welcome the opportunity to address the important issues raised in their letters. We agree with them that our results are limited by the retrospective study design and require a prospective study for confirmation, as we stated in our report.

The other concerns of Drs. Rozet and Lam seem to derive from their criticism that “the study did not include any patient who developed frank propofol infusion syndrome.” Although it is true that none of our patients exhibited severe metabolic acidosis, the purpose of our study was not to detect fulminant propofol infusion syndrome, which is rare and unlikely to be detected in the size population we studied, but to determine whether we could detect “initially reversible and usually benign” metabolic acidosis in patients receiving propofol.<sup>1</sup> Drs. Rozet and Lam’s assertion that propofol infusion syndrome includes only “unexplained severe metabolic, usually lactic, acidosis and is associated with high-dose or long-duration propofol infusion, usually both,” implies that the mild syndrome either never occurs or never progresses to become severe and clinically evident. These assertions are incorrect (see references 12, 14–17, and 19 and the associated discussion in our article<sup>1</sup>) and highlight the need to address the question we posed in our study.

As Drs. Rozet and Lam suggest, defining metabolic acidosis for our study was challenging. They suggest that a definition of base excess (BE) of  $-3 \text{ mEq/l}$  or less would be more appropriate than BE of  $-2$  or

In conclusion, we did not observe lactic acidosis in patients receiving low-dose propofol. These results can be useful to support the safety of short-duration, low-dose propofol, strengthening the hypothesis that acidosis after propofol infusion would be related to cumulative high doses of the drug.

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### References

1. Cravens GT, Packer DL, Johnson ME: Incidence of propofol infusion syndrome during noninvasive radiofrequency ablation for atrial flutter or fibrillation. *ANESTHESIOLOGY* 2007; 106:1134–8
2. Wysowski DK, Pollock ML: Reports of death with use of propofol (Diprivan) for nonprocedural (long-term) sedation and literature review. *ANESTHESIOLOGY* 2006; 105:1047–51
3. Kam PC, Cardone D: Propofol infusion syndrome. *Anaesthesia* 2007; 62: 690–701
4. Ahlen K, Buckley CJ, Goodale DB, Pulsford AH: The “propofol infusion syndrome”: The facts, their interpretation and implications for patient care. *Eur J Anaesthesiol* 2006; 23:990–8
5. Crozier TA: The “propofol infusion syndrome”: myth or menace? *Eur J Anaesthesiol* 2006; 23:987–9
6. Silva-Costa-Gomes T, Gallart L, Valles J, Trillo L, Minguella J, Puig MM: Low-versus high-dose almitrine combined with nitric oxide to prevent hypoxia during open-chest one-lung ventilation. *Br J Anaesth* 2005; 95:410–6
7. B’chir A, Mebazaa A, Losser MR, Romieu M, Payen D: Intravenous almitrine bismesylate reversibly induces lactic acidosis and hepatic dysfunction in patients with acute lung injury. *ANESTHESIOLOGY* 1998; 89:823–30
8. Gallart L, Lu Q, Puybasset L, Umamaheswara Rao GS, Coriat P, Rouby JJ: Intravenous almitrine combined with inhaled nitric oxide for acute respiratory distress syndrome. The NO Almitrine Study Group. *Am J Respir Crit Care Med* 1998; 158:1770–7

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less, which we chose, to “meet the generally accepted criterion” given in their reference 2. However, that reference and others we are aware of refer to stratifying critically ill intensive care unit patients, with the acidotic population in their reference 2 having a mortality of 45%.<sup>2</sup> In contrast, we were trying to detect early metabolic acidosis in a relatively healthy population where no mortality was expected. As we noted in our report, “in three well-documented cases of the syndrome, the initial negative BE was  $-2$  to  $-3$ ,”<sup>1</sup> so we prospectively selected BE of  $-2$  or less before data abstraction. Furthermore, it is clear from inspecting our data (table 1 and fig. 1) that excluding the few patients with maximal negative BE of  $-2$  would cause only minor changes in the incidence of metabolic acidosis in our study population and would not change the statistical comparison with our comparator group.

Our original submission did contain data on time and propofol dose for each arterial blood gas sampling in all patients who had multiple arterial blood gases drawn. This was deleted in the interest of shortening the article, but did not appreciably affect our analysis.

We look forward to publication of the details of the retrospective study of Drs. Rozet and Lam. We congratulate them on the collection of more detailed parameters of acid–base status, including lactate and chloride, than were available to us in our study. It will be important for the report to include data on calculated BE as well as the other parameters listed, because it is the parameter most indicative of metabolic acidosis independent of ventilator adjustments.

We appreciate Dr. Gallart *et al.* making us aware of the article by their group where arterial blood gases and lactate levels were obtained during propofol anesthesia while studying almitrine and nitric oxide during one-lung ventilation.<sup>3</sup> Both in terms of total dose and time administered, their patients' propofol exposure was less than a third of ours, suggesting a possible lower threshold for propofol metabolic acidosis. However, their study, although well designed for the questions it was addressing, may be limited by variables besides propofol: Almitrine is known to affect metabolic acidosis, ventilation was adjusted after institution of one-lung ventilation while BE was not reported, and cardiac index decreased and then increased significantly during the study.

It is important to elucidate the mechanism and incidence of propofol infusion syndrome to better prevent and treat it. We appreciate the interest of Drs. Rozet and Lam and Dr. Gallart *et al.* in addressing this area of concern.

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## References

1. Cravens GT, Packer DL, Johnson ME: Incidence of propofol infusion syndrome during noninvasive radiofrequency ablation for atrial flutter or fibrillation. *ANESTHESIOLOGY* 2007; 106:1134-8
2. Gunnerson KJ, Saul M, He S, Kellum JA: Lactate *versus* non-lactate metabolic acidosis: A retrospective outcome evaluation of critically ill patients. *Crit Care* 2006; 10:R22
3. Silva-Costa-Gomes T, Gallart L, Valles J, Trillo L, Minguella J, Puig MM: Low-*versus* high-dose almitrine combined with nitric oxide to prevent hypoxia during open-chest one-lung ventilation. *Br J Anaesth* 2005; 95:410-6

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## The Future for B-type Natriuretic Peptide in Preoperative Assessment

*To the Editor:*—We congratulate Dr. Mahla *et al.*<sup>1</sup> on their recent work on using brain natriuretic peptide (BNP) to predict adverse cardiac outcomes after vascular surgery. We would like to comment on the editorial by Augoustides and Fleischer<sup>2</sup> on the possible future use of BNP in this regard.

It is obviously highly desirable to now move from using BNP to better predict risk to using it to better reduce risk. However, this next step requires careful thought because, unlike many other risk predictors, BNP is not a culprit itself but is rather a marker of other culprits. We feel that the next crucial step is to fully phenotype high-BNP/high-risk preoperative individuals to better target the “multimodal perioperative interventions” suggested by Augoustides and Fleischer.

This phenotyping step is crucial because BNP can be elevated by virtually any cardiac abnormality, many of which will be silent. BNP can be elevated by (silent) myocardial ischemia, valve disease, left ventricular dysfunction, left atrial dilatation, left ventricular hypertrophy, or even atrial fibrillation. Many of these may coexist in some individuals. The study of Mahla *et al.*<sup>1</sup> only excluded a few of these causes of elevated BNP (left ventricular systolic dysfunction, atrial fibrillation, and one form of valve disease). Therefore, many of the patients studied who had high BNP could harbor silent ischemia, left atrial dilatation, left ventricular hypertrophy, and subtle valve disease other than aortic stenosis. Surely a crucial step is for us to fully phenotype such high-BNP/high-risk individuals to get a full picture of the spectrum of their underlying cardiac abnormalities so that when we devise intervention trials to try to reduce their risk, the interventions will be targeted to the underlying cardiac abnormality, *i.e.*, “smarter” trials. This is because each of the different aforementioned cardiac abnormalities (if found) would best be treated in different ways, *e.g.*,  $\beta$  blockade, higher statin dose or angioplasty for silent ischemia, angiotensin receptor blocker, aldosterone blockade and ultralow blood pressure for left ventricular hypertrophy, ARB and anti-

coagulation for left atrial dilatation, and even valve repair or valvuloplasty in some valve disease cases. Surely we ought not to devise therapeutic interventions before we fully phenotype these individuals to better understand the source of their increased BNP/increased risk.

Phenotyping high-BNP preoperative individuals could produce another benefit. This is because experience in other settings suggests that an obvious cause for the high BNP may not be found in every case. Therefore, phenotyping high-BNP individuals may enable us to even better target our interventions because we could then target our interventions to those who fail two high-risk screening tests rather than just one, *i.e.*, therapies could be targeted not just to those who failed a BNP test but to those who failed a BNP test and a search for silent cardiac abnormalities.

That is, high BNP patients may need to be phenotyped not only because the information will be necessary for us to move forward to “smarter” trials, but also because it may be more cost effective ultimately to target whatever therapies are devised toward those who fail two screening tests (BNP and phenotyping) rather than just one (BNP).

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## References

1. Mahla E, Baumann A, Rehak P, Watzinger N, Vicenzi MN, Maier R, Tiesenhäuser K, Metzler H, Toller W: N-terminal pro-brain natriuretic peptide identified patients at high risk for adverse cardiac outcome after vascular surgery. *ANESTHESIOLOGY* 2007; 106:1088-95
2. Augoustides J, Fleisher LA: Advancing perioperative prediction of cardiac risk after vascular surgery: Does postoperative N-terminal pro-brain natriuretic peptide do the trick? *ANESTHESIOLOGY* 2007; 106:1080-2

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*In Reply:*—We thank Dr. Struthers *et al.* for their valuable comments on our recent editorial<sup>1</sup> about the value of brain natriuretic peptide (BNP) in the perioperative prediction of cardiac risk after vascular surgery. The editorial discussed the implications of the recent article by Dr. Mahla *et al.*<sup>2</sup>

In their letter, Dr. Struthers *et al.* emphasize that an elevated BNP is a marker of diverse cardiac phenotype. These include disorders of the atrium (*e.g.*, fibrillation, distention), the ventricle (*e.g.*, hypertrophy, ischemia, dysfunction), and/or a cardiac valve (*e.g.*, aortic stenosis). They further suggest that perioperative trials designed to reduce car-



diac risk in the setting of increased BNP be calibrated to the specific etiologic cardiac phenotype.

This principle for trial design based on BNP makes excellent sense because perioperative intervention (mechanical and/or pharmacologic) will depend on the cardiac phenotypic profile. Mechanical interventions include valve repair/replacement for aortic stenosis and/or angioplasty with possible stenting for coronary syndromes. Pharmacologic interventions include anticoagulation and statins for coronary syndromes as well as angiotensin blockade for left ventricular hypertrophy. Mixed intervention will blend appropriate mechanical and pharmacologic therapies as in the aforementioned examples for coronary syndromes.

This type of clinical trial is already being implemented in the care of patients with cardiac disease. In the perioperative setting, an increase in BNP after coronary artery bypass surgery can trigger refinement of biventricular pacing for optimal ventricular synchronization and consequent significant increase in ejection fraction.<sup>3</sup> In the ambulatory setting, the trend in BNP over time can assess the outcome of pharmacologic intervention in patients with stable ischemic cardiomyopathy.<sup>4</sup>

As Dr. Struthers *et al.* also point out, the combination of BNP and cardiac phenotype will not only stratify cardiac risk, but can also target intervention in patients with no overt cardiac disease. These interventions would aim to reduce future adverse cardiac events.

Again, this type of intervention is already being explored in the therapy of cardiac disease. As an example, angiotensin blockade with valsartan has recently been shown to significantly improve the overall cardiovascular profile in adults with asymptomatic cardiovascular abnormalities.<sup>5</sup> Furthermore, increased BNP significantly predicted future cardiovascular mortality and morbidity in low-risk patients with stable coronary artery disease and preserved ventricular function (a patient cohort with silent cardiac abnormalities).<sup>6</sup>

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*In Reply:*—We thank Dr. Struthers *et al.* for their interest in our article<sup>1</sup> and their suggestions for future research based both on high preoperative levels of brain natriuretic peptide (BNP) and the specifics of underlying cardiac pathology.

We are well aware that fully phenotyping, *i.e.*, identification of the underlying cardiac disease and targeted therapy, comprises current and future possibilities for primary and secondary prevention in the individual cardiac patient, as recently highlighted by Drs. Struthers and Lang.<sup>2</sup>

Preoperative phenotyping, however, is often limited by timely constrictions due to concomitant and disabling illness that necessitates a rapid surgical intervention. Furthermore, surgical illness and the specifics of the perioperative period (obesity, immobilization, opioids, anemia, catecholamine surges, and hypercoagulability) may both obscure and aggravate the underlying cardiac disease. In addition, recent trials in patients with stable coronary artery disease demonstrated that knowledge of functional coronary artery stenoses and subsequent prophylactic revascularization did not improve cardiac outcome when compared with optimized conventional therapy.<sup>3,4</sup>

For many years, anesthesiologists have been relying on clinical risk indices to define perioperative cardiac risk.<sup>5</sup> Recently BNP, though being an “unspecific” marker of cardiac damage, outperformed risk indices<sup>6</sup> and stress testing.<sup>7</sup> In the future, determination of BNP might therefore complement anesthesiologic risk assessment by identifying high-risk/high-BNP patients and define the best time (preoperative, early postoperative, or after surgical rehabilitation) for further cardiac evaluation and targeted therapy. However, because of the lack of well-established cutoffs of BNP,<sup>2</sup> influence of various patient-specific factors,<sup>8</sup> and perioperative undulation of BNP, “high” values will have

In summary, Dr. Struthers *et al.* are to be congratulated for further refining the predictive value of perioperative BNP with the role of the associated cardiac phenotype whether symptomatic or not. We anticipate that future trials in this area will be of higher quality and impact as a result.

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## References

1. Augoustides J, Fleisher LA: Advancing perioperative prediction of cardiac risk after vascular surgery: Does postoperative N-terminal pro-brain natriuretic peptide do the trick? *ANESTHESIOLOGY* 2007; 106:1080-2
2. Mahla E, Baumann A, Rehak P, Watzinger N, Vicenzi MN, Maier R, Tiesenhausen K, Metzler H, Toller W: N-terminal pro-brain natriuretic peptide identifies patients at high risk for adverse outcome after vascular surgery. *ANESTHESIOLOGY* 2007; 106:1088-95
3. Raab S, Oertel F, Weimann T, Danoy V, Beyer M: Brain natriuretic peptide: A reliable parameter for the effectiveness of cardiac resynchronization therapy after coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg* 2006; 4:439-43
4. Di Napoli P, Di Giovanni P, Gaeta MA, D'Apollito G, Barsotti A: Beneficial effects of trimetazidine treatment on exercise tolerance and B-type natriuretic peptide and troponin T plasma levels in patients with stable ischemic cardiomyopathy. *Am Heart J* 2007; 154:602.e1-5
5. Duprez DA, Florea ND, Jones K, Cohn JN: Beneficial effects of valsartan in asymptomatic individuals with vascular or cardiac abnormalities: The DETECTIV Pilot Study. *J Am Coll Cardiol* 2007; 50:835-9
6. Omland T, Sabatine MS, Jablonski KA, Rice MM, Hsia J, Wergeland R, Landaas S, Rouleau JL, Domanski MJ, Hall C, Pfeffer MA, Braunwald E, PEACE Investigators: Prognostic value of B-type natriuretic peptide in patients with stable coronary artery disease: The PEACE Trial. *J Am Coll Cardiol* 2007; 50:205-14

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to be defined and validated in future studies in different surgical settings.

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## References

1. Mahla E, Baumann A, Rehak P, Watzinger N, Vicenzi MN, Maier R, Tiesenhausen K, Metzler H, Toller W: N-terminal pro-brain natriuretic peptide identifies patients at high risk for adverse outcome after vascular surgery. *ANESTHESIOLOGY* 2007; 106:1088-95
2. Struthers A, Lang C: The potential to improve primary prevention in the future by using BNP/N-BNP as an indicator of silent “pancardiac” target organ damage: BNP/N-BNP could become for the heart what microalbuminuria is for the kidney. *Eur Heart J* 2007; 28:1678-82
3. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG: Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004; 351:2795-804
4. Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrun M, de Jaegere P, Maat A, van Sambeek MR, Kertai MD, Boersma E: A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: The DECREASE-V Pilot Study. *J Am Coll Cardiol* 2007; 49:1763-9
5. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gusberg RJ, Leppo JA: ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2002; 39:542-53
6. Dernelis JM, Panaretou MP: Assessment of cardiac risk before noncardiac surgery: Brain natriuretic peptide in 1590 patients. *Heart* 2006; 92:1645-50

7. Feringa HH, Schouten O, Dunkelgrun M, Bax JJ, Boersma E, Elhendy A, de Jonge R, Karagiannis SE, Vidakovic R, Poldermans D: Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. *Heart* 2007; 93:226-31

8. Maisel A: The coming of age of natriuretic peptides: The emperor does have clothes! *J Am Coll Cardiol* 2006; 47:61-4

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## A Critique of Intradiscal Administration for Treatment of Radiculopathy

*To the Editor:*—The recent article by Cohen *et al.*<sup>1</sup> uses intradiscal administration of the anti-tumor necrosis factor (TNF) biologic etanercept for the treatment of two subsets of patients with chronic disc-related pain. The rationale for the selection of an anti-TNF biologic for these patients, including the 42% of the study subjects with chronic lumbosacral radiculopathy, has a substantial scientific basis, which includes both basic science and clinical evidence that excess TNF- $\alpha$  is centrally involved in the pathogenesis of disc-related pain.<sup>2-5</sup> In the case of lumbosacral radiculopathy, the anatomical site of inflammation and neuronal dysfunction is well delineated by the clinical presentation establishing dysfunction of a particular nerve root.

In addition, there is a reasonable scientific basis to study delivery of etanercept, which is anatomically targeted to the nerve root in those patients with clinically defined chronic radiculopathy. This scientific basis is supported not only by the evidence cited above implicating TNF- $\alpha$  in the initiation, amplification, and maintenance of disc-related pain, but also by the long history of the use of anatomically targeted delivery of corticosteroids for the treatment of sciatica.<sup>6</sup> But it should be pointed out that each of these studies, and established medical practice, involves the use of perispinal *extradiscal* administration of antiinflammatories, rather than *intradiscal* administration, as used by the study authors.

It is therefore puzzling that Cohen *et al.* chose to include patients with lumbosacral radiculopathy in a study of minute doses of etanercept delivered into the intervertebral disc, where the anti-TNF biologic would be surrounded by a thick, fibrous capsule, the annulus fibrosus. It seems reasonable that the annulus fibrosus, in view of its structure, might impede delivery of etanercept to the nerve root, the expected primary site of TNF- $\alpha$ -mediated pathology.

The intradiscal design of the study of Cohen *et al.* is all the more puzzling in view of the published work of my colleagues and me, some of which is cited in the article of Cohen *et al.*<sup>2,3</sup> The use of etanercept for disc-related pain was first described in 1999.<sup>7</sup> Since that time, my colleagues and I have successfully treated a large number of patients with severe and intractable disc-related pain using perispinal *extradiscal* etanercept, a method designed to deliver etanercept in therapeutic concentration to the site of neuronal pathology, including the nerve root.<sup>2,3,8-12</sup>

To the credit of the authors, they point out that the low doses of etanercept studied, ranging from 0.1 to 1.5 mg, may have contributed to the lack of therapeutic effect in their study. The *intradiscal* doses they used ranged from 0.4% to 6% of the *extradiscal* etanercept dose in our studies.<sup>2,3,8</sup> Although it is certainly reasonable to be cautious in choosing the appropriate dose, selection of a subtherapeutic dose may doom a study to failure. In the case of etanercept for neuropathic pain, there is basic science evidence that high local concentrations of etanercept may be necessary for an optimal therapeutic effect, a rationale

supporting targeted extradiscal etanercept.<sup>13,14</sup> In their discussion, the authors hypothesize whether systemic delivery may be superior. One would argue, based on the above, that it was the subtherapeutic doses of etanercept selected, along with the choice of intradiscal rather than extradiscal perispinal administration, that resulted in the lack of efficacy observed.

It seems that Cohen *et al.* may not disagree with the above analysis, because they presently are conducting a trial of perispinal extradiscal etanercept, delivered epidurally, for treatment of sciatica\* at doses ranging from 2 to 6 mg. The concept of epidural etanercept for treatment of sciatica has been previously described,<sup>9-11</sup> but we currently are uncertain whether this more invasive delivery method will be as efficacious as larger doses of etanercept injected superficial to the ligamentum flavum.<sup>2,3,8,12</sup> We look forward to the results of this clinical trial.

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### References

- Cohen SP, Wenzell D, Hurley RW, Kurihara C, Buckenmaier CC III, Griffith S, Larkin TM, Dahl E, Morlando BJ: A double-blind, placebo-controlled, dose-response pilot study evaluating intradiscal etanercept in patients with chronic idiopathic low back pain or lumbosacral radiculopathy. *ANESTHESIOLOGY* 2007; 107:99-105
- Tobinick EL, Britschgi-Davoodifar S: Perispinal TNF-alpha inhibition for discogenic pain. *Swiss Med Wkly* 2003; 133:170-7
- Tobinick E, Davoodifar S: Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: A study of clinical observations in 143 patients. *Curr Med Res Opin* 2004; 20:1075-85
- Sommer C, Schafers M: Mechanisms of neuropathic pain: The role of cytokines. *Drug Discovery Today Dis Mech* 2004; 1:441-8
- Aoki Y, Takahashi K, Ohtori S, Moriya H: Neuropathology of discogenic low back pain: A review. *Internet J Spine Surg* 2005; 2 (1)
- Arden NK, Price C, Reading I, Stubbing J, Hazelgrove J, Dunne C, Michel M, Rogers P, Cooper C: A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: The WEST study. *Rheumatology (Oxford)* 2005; 44:1399-406
- Tobinick E, Tobinick A, inventors; TACT IP, LLC, assignee: Tumor necrosis factor antagonists for the treatment of neurological disorders. US patent 6,015,557. January 18, 2000
- Tobinick EL: Targeted etanercept for discogenic neck pain: Uncontrolled, open-label results in two adults. *Clin Ther* 2003; 25:1211-8
- Tobinick E, inventor; TACT IP, LLC, assignee: Cytokine antagonists for the treatment of localized disorders. US patent 6,419,944. July 16, 2002
- Tobinick E, inventor; TACT IP, LLC, assignee: Cytokine antagonists for treatment of localized disorders. US patent 6,537,549. March 25, 2003
- Tobinick E, inventor; TACT IP, LLC, assignee: Cytokine antagonists for neurological and neuropsychiatric disorders. US patent 6,982,089. January 3, 2006
- Tobinick E: Spinal delivery of p38: TNF-alpha inhibitors. *PLoS Med* 2006; 3:e511
- Sommer C, Schafers M, Marziniak M, Toyka KV: Etanercept reduces hyperalgesia in experimental painful neuropathy. *J Peripher Nerv Syst* 2001; 6:67-72
- Wacnik PW, Eikmeier LJ, Simone DA, Wilcox GL, Beitz AJ: Nociceptive characteristics of tumor necrosis factor-alpha in naive and tumor-bearing mice. *Neuroscience* 2005; 132:479-91

\* Listed at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Accessed July 20, 2007.

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*In Reply:*—We are grateful to Dr. Tobinick for his clinical work evaluating etanercept for spinal pain, and his astute and prescient comments regarding our past and future endeavors.<sup>1</sup> First, we would like to point out that intradiscal tumor necrosis factor- $\alpha$  administration to relieve radicular pain is not quite analogous to the intradiscal injection of corticosteroid, which has been shown in previous studies to be no more effective than placebo for this condition.<sup>2,3</sup> Although inflammatory cytokines released from a degenerative disc might be the source of a painful, chemically irritated nerve root,<sup>4–6</sup> the disc itself is not the primary site of inflammation. Therefore, it is not surprising that intradiscal steroids are ineffective for lumbosacral radiculopathy. For predominantly axial low back pain presumed secondary to internal disc disruption, there is no scientific basis to suppose that the epidural injection of tumor necrosis factor- $\alpha$  inhibitors might be effective.

In contrast, the “mechanistic-based treatment of pain” paradigm advocates identifying the principal pain generator (*i.e.*, high concentrations of tumor necrosis factor  $\alpha$  expelled from a degenerated disc) and treating it with target-specific medications (*i.e.*, tumor necrosis factor- $\alpha$  inhibitors).<sup>7</sup> In this context, injecting etanercept intradiscally can be viewed as a logical extension of this theory.

Second and perhaps more importantly, Dr. Tobinick seems to have overlooked the possibility that our intradiscal study was never intended to be the decisive word on the subject. Rather, our main objectives in undertaking this endeavor were to establish safety (hence our low, logarithmically increasing doses) in this setting and to determine dose ranges for the more definitive and auspicious epidural study he alluded to. The risk:benefit ratio is considerably higher for the epidural administration of etanercept in radiculopathy, a condition for which effective treatments are available, than it is for refractory low back pain patients already scheduled to undergo discography in a last-ditch effort to determine eligibility for either experimental intradiscal procedures or spine surgery. In addition, we have previously demonstrated that a significant portion of intradiscal injectate extravasates into the epidural space in patients with degenerative disc

disease.<sup>8</sup> This suggests that the poor response of our patients may better reflect their long duration of pain (inflammatory cytokines play a more prominent role in acute pain than chronic pain) and multiple previous treatment failures, rather than the intradiscal route of administration.

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## References

1. Cohen SP, Wenzell D, Hurley RW, Kurihara C, Buckenmaier CC III, Griffith S, Larkin TM, Dahl E, Morlando BJ: A double-blind, placebo-controlled, dose-response pilot study evaluating intradiscal etanercept in patients with chronic discogenic low back pain or lumbosacral radiculopathy. *ANESTHESIOLOGY* 2007; 107:99–105
2. Khot A, Bowditch M, Powell J, Sharp D: The use of intradiscal steroid therapy for lumbar spinal discogenic pain: A randomized controlled trial. *Spine* 2004; 29:833–6
3. Simmons JW, McMillin JN, Emery SF, Kimmich SJ: Intradiscal steroids: A prospective double-blind clinical trial. *Spine* 1992; 17 (suppl):S172–5
4. Ozakay AC, Cavanaugh JM, Asik I, DeLeo JA, Weinstein JA: Dorsal root sensitivity to interleukin-1 beta, interleukin-6 and tumor necrosis factor in rats. *Eur Spine J* 2002; 11:467–75
5. Olmarker K, Larsson K: Tumor necrosis factor (alpha) and nucleus-pulposus-induced nerve root injury. *Spine* 1998; 23:2538–44
6. Igarashi T, Kikuchi S, Shubayev V, Myers RR: Exogenous tumor necrosis factor-alpha mimics nucleus pulposus-induced neuropathology. *Spine* 2000; 25: 2975–80
7. Woolf CJ, American College of Physicians, American Physiological Society: Pain: Moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004; 140:441–51
8. Cohen SP, Oberfell R, Larkin T, Fant G, Stojanovic M: Does needle insertion site affect discography results? A retrospective analysis. *Spine* 2002; 27:2279–83

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## Perioperative Protective Ventilatory Strategies in Patients without Acute Lung Injuries

*To the Editor:*—We enjoyed reading the recent editorial and review article about optimal tidal volume ( $V_T$ ) in patients without acute lung injury.<sup>1,2</sup> Overstretching healthy lungs with “traditional”  $V_T$  in the range of 10–15 ml/kg predicted body weight has been shown to trigger inflammatory and procoagulant alveolar responses. Furthermore, synergism rather than additivity between ventilator-induced alveolar stress and other injurious pulmonary factors (sepsis, ischemia-reperfusion, hypoxia-reoxygenation, major trauma and surgery) has been incriminated in damaging the alveolocapillary barrier. Ultimately, a multiple hit concept has emerged to explain the pathophysiologic mechanisms of acute lung injury.

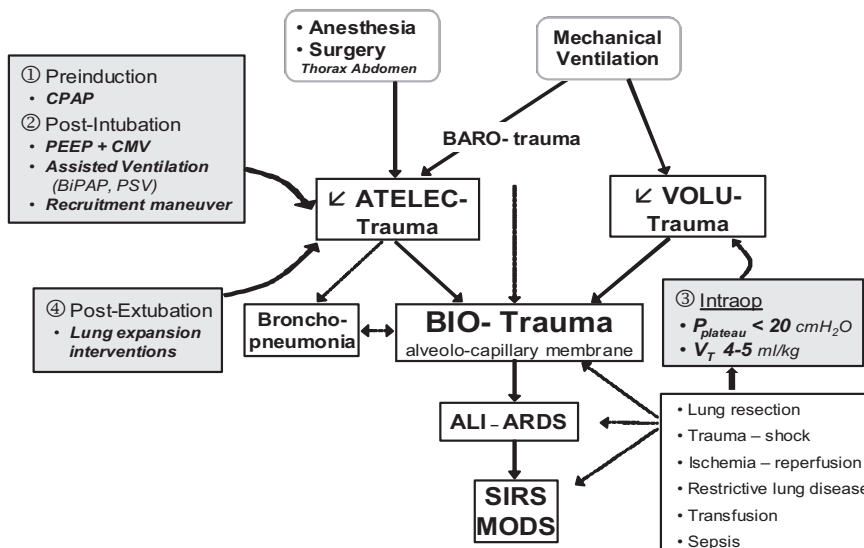
We fully agree that protective ventilatory strategies ( $V_T$  of 6 ml/kg predicted body weight, inspiratory plateau pressure <20 cm H<sub>2</sub>O, positive end-expiratory pressure [PEEP] levels >5 cm H<sub>2</sub>O) currently applied in the intensive care unit should also be adopted to manage surgical patients with “vulnerable” lungs (*e.g.*, ongoing inflammatory/infectious disease, lung resection, major trauma and surgery). Unfortunately, in the majority of surgical patients with “healthy” lungs and

no acute lung injury risk factors, the proposed ventilatory guidelines ( $V_T$  <10 ml/kg predicted body weight, inspiratory plateau pressure <20 cm H<sub>2</sub>O, PEEP  $\geq$  5 cm H<sub>2</sub>O) will little influence the incidence and severity of postoperative respiratory complications. Indeed, in this large population group, postoperative atelectasis is the commonest problem and the major cause of hypoxemia and nosocomial pneumonia. Accordingly, preventing atelectasis should be considered as an important objective in perioperative management.<sup>3</sup>

After anesthesia induction in the supine position, functional residual capacity is markedly reduced (approximately 0.7–1.3 l), and atelectasis develops in the dependent part of the lungs as a result of the loss of inspiratory muscle tone, cephalad diaphragm displacement, intrathoracic shift of blood volume, and oxygen resorption.<sup>4</sup> Starting from a lower functional residual capacity, the inspiratory-expiratory cycles are completed on a lesser compliant part of the pressure-volume curve, and the repetitive opening-closing of small airways and unstable alveoli initiate proinflammatory responses. Accordingly, the mechanical breath ( $V_T$ ) is delivered to a nonhomogenous lung with a continuum ranging from variable degree of alveolar collapse (dependent areas) to a variable degree of overdistension (nondependent areas) that translates into ventilation-perfusion mismatch with impaired oxygenation.

After numerous failed attempts to acquire a Reply from the Editorial authors to this Letter, it is being published without the benefit of their response.—James C. Eisenach, M.D., Editor-in-Chief.





**Fig. 1.** Perioperative multimodal lung-protective approach. ALI = acute lung injury; ARDS = adult respiratory distress syndrome; BiPAP = bilevel positive airway pressure; CMV = controlled mechanical ventilation; CPAP = continuous positive airway pressure; Intraop = intraoperative; MODS = multiple organ dysfunction syndrome; PEEP = positive end-expiratory pressure; PSV = pressure-support ventilation; SIRS = systemic inflammatory response syndrome;  $V_T$  = tidal volume.

Besides limiting alveolar trauma with low  $V_T$ , attenuating the loss of functional residual capacity and preventing the formation of atelectasis should be attempted by a stepwise approach (fig. 1): (1) application of continuous positive airway pressure and PEEP during the induction of anesthesia<sup>5,6</sup>; (2) titration of low to moderate PEEP levels according to physiologic indices (lower inflection point of the pressure-volume curve, oxygenation indices, hemodynamics) and/or lung imaging techniques (e.g., electrical thoracic impedance<sup>7</sup>); (3) intraoperative lung recruitment maneuvers (manual inflation up to the vital capacity, “ramp” PEEP elevation up to 20 cm H<sub>2</sub>O)<sup>8</sup>; (4) use of inspiratory oxygen concentration less than 80%; and (5) postoperative lung expansion strategies, including postural changes, early mobilization, and deep breathing exercises, as well as noninvasive ventilatory support.

Whenever possible, partial ventilatory modes (assist-controlled, pressure-support, bilevel positive airway pressure) through facial or laryngeal masks should be considered to avoid tracheal (re)intubation, to reduce the duration of mechanical ventilation, and to promote active displacement of the dependent part of the diaphragm. Intraoperatively, bilevel positive airway pressure ventilation has been shown to improve oxygenation indices by decreasing ventilation-perfusion mismatch.<sup>9</sup> Likewise, reversal of atelectasis and hypoxemia after major thoracic and abdominal surgery has been successfully achieved with noninvasive ventilatory techniques that resulted in a reduced need for reintubation and a lower incidence of pneumonia and sepsis.<sup>10</sup>

To date, further randomized controlled trials are needed to question whether a multimodal lung approach effectively prevents the formation of lung atelectasis and reduces the incidence of other pulmonary complications (pneumonia, respiratory failure, hypoxemia necessitating oxygen therapy) after various types of surgical procedures.

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## References

- Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? *ANESTHESIOLOGY* 2007; 106:1226-31
- Putensen C, Wrigge H: Tidal volumes in patients with normal lungs: One for all or the less, the better? *ANESTHESIOLOGY* 2007; 106:1085-7
- Turrentine FE, Wang H, Simpson VB, Jones RS: Surgical risk factors, morbidity, and mortality in elderly patients. *J Am Coll Surg* 2006; 203:865-77
- Hedensternia G, Edmark L: The effects of anesthesia and muscle paralysis on the respiratory system. *Intensive Care Med* 2005; 31:1327-35
- Rusca M, Proietti S, Schnyder P, Frascarolo P, Hedenstierna G, Spahn DR, Magnusson L: Prevention of atelectasis formation during induction of general anesthesia. *Anesth Analg* 2003; 97:1835-9
- von Ungern-Sternberg BS, Regli A, Schibler A, Hammer J, Frei FJ, Erb TO: The impact of positive end-expiratory pressure on functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen. *Anesth Analg* 2007; 104:1364-8
- Erlundsson K, Odenstedt H, Lundin S, Stenqvist O: Positive end-expiratory pressure optimization using electric impedance tomography in morbidly obese patients during laparoscopic gastric bypass surgery. *Acta Anaesthesiol Scand* 2006; 50:833-9
- Whalen FX, Gajic O, Thompson GB, Kendrick ML, Que FL, Williams BA, Joyner MJ, Hubmayr RD, Warner DO, Sprung J: The effects of the alveolar recruitment maneuver and positive end-expiratory pressure on arterial oxygenation during laparoscopic bariatric surgery. *Anesth Analg* 2006; 102:298-305
- Yu G, Yang K, Baker AB, Young I: The effect of bi-level positive airway pressure mechanical ventilation on gas exchange during general anaesthesia. *Br J Anaesth* 2006; 96:522-32
- Squadrone V, Coia M, Cerutti E, Schellino MM, Biolino P, Occella P, Belloni G, Vilianis G, Fiore G, Cavallo F, Ranieri VM, Piedmont Intensive Care Units Network (PICUN): Continuous positive airway pressure for treatment of postoperative hypoxemia: A randomized controlled trial. *JAMA* 2005; 293:589-95

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**In Reply:**—We thank Dr. Licker *et al.* for their comments on our article about optimal ventilator strategies in patients without acute lung injury.<sup>1</sup> Indeed, overstretching lungs with conventional and abnormally high tidal volumes during surgery has been shown to trigger procoagulant and proinflammatory alveolar responses in patients with healthy lungs, while not being particularly useful to prevent intraoperative atelectasis.<sup>2,3</sup> When we consider the concept of “multiple hits” to explain the pathophysiologic mechanisms of acute lung injury, a protective ventilatory strategy (using “normally sized” tidal

volume to prevent lung stretch) is certainly indicated in the management of surgical patients with lungs at risk for lung injury (e.g., with systemic inflammatory response syndrome, major trauma, major surgery). In this context, we would like to stress that the terminology chosen for a strategy aiming at prevention of overstretching the lungs (conventional *vs.* low tidal volumes) is wrong and may be even misleading. Instead of “lower” tidal volumes, we should use the term “normal” or “normally sized” tidal volumes. It is like traffic speeding: traffic speeding during rush hours is very dangerous—but traffic

speeding is always dangerous, even when there are not so many other cars on the road; therefore, regulations mandate that we never drive faster than the speed limit. The size of a normal tidal volume is approximately 6 ml/kg for all mammals<sup>4</sup>—we should always consider use of normally sized tidal volumes rather than (very) high tidal volumes.

We agree that ventilation with normal tidal volumes as proposed in our review may not prevent the development of postoperative atelectasis. Although limited evidence supports the use of higher positive end-expiratory pressure, intraoperative recruitment maneuvers, lower oxygen fraction, and postoperative noninvasive ventilation,<sup>5</sup> a multimodal lung-protective approach has not been tested.

Although postoperative pulmonary complications are common and associated with significant morbidity, few studies investigated the influence of intraoperative ventilator and nonventilator management (e.g., fluid balance, transfusions). Indeed, randomized controlled trials are needed to answer whether a multimodal lung-protective approach effectively prevents the formation of atelectasis and reduces the incidence of acute lung injury and other pulmonary complications after various types of surgical procedures.

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## References

1. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? *ANESTHESIOLOGY* 2007; 106:1226–31
2. Choi G, Wolthuis EK, Bresser P, Levi M, van der Poll T, Dzoljic M, Vroom MB, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. *ANESTHESIOLOGY* 2006; 105:689–95
3. Wolthuis EK, Choi G, Dessing MC, Bresser P, Lutter R, Dzoljic M, van der Poll T, Vroom MB, Hollmann M, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexistent lung injury. *ANESTHESIOLOGY* 2008; 108:46–54
4. Tenney SM, Remmers JE: Comparative quantitative morphology of the mammalian lung: Diffusing area. *Nature* 1963; 197:54–6
5. Whalen FX, Gajic O, Thompson GB, Kendrick ML, Que FL, Williams BA, Joyner MJ, Hubmayr RD, Warner DO, Sprung J: The effects of the alveolar recruitment maneuver and positive end-expiratory pressure on arterial oxygenation during laparoscopic bariatric surgery. *Anesth Analg* 2006; 102:298–305

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## Endotracheal Tube with End-tidal Carbon Dioxide Port

*To the Editor:*—I read with interest the brief report by Dr. Al-Nabhani *et al.*<sup>1</sup> on problems of monitoring end-tidal carbon dioxide in extremely low-birth-weight infants during perioperative period. For the monitoring of end-tidal carbon dioxide in neonates, I agree that it is necessary to sample alveolar gases to avoid the dilution of carbon dioxide by dead space created by ventilating devices such as the endotracheal tube adaptor, the Y-piece of the breathing circuit, and even the T-piece for carbon dioxide sampling, and it is necessary to insert a catheter into the endotracheal tube for sampling of alveolar gases.

For sampling of alveolar gases without using an endotracheal catheter, an endotracheal tube with end-tidal carbon dioxide monitoring port (Mallinckrodt Inc., St. Louis, MO) is available. As shown in figure 1, the lumen for end-tidal carbon dioxide sampling extends to near the distal end of endotracheal tube. The outside diameter of the 3.0-mm uncuffed tube with monitoring port is 4.5 mm, compared with 4.3 mm for a standard uncuffed tube. Although the endotracheal tube with monitoring port is slightly larger in size by 0.2 mm, the difference is negligible. I have never had any problems with endotracheal intubation. With use of this tube, one can avoid the insertion of the catheter into the endotracheal tube, and hence avoid related complications.

**Charles Her, M.D., F.C.C.P.,** New York Medical College, Valhalla, New York. charles6133@msn.com

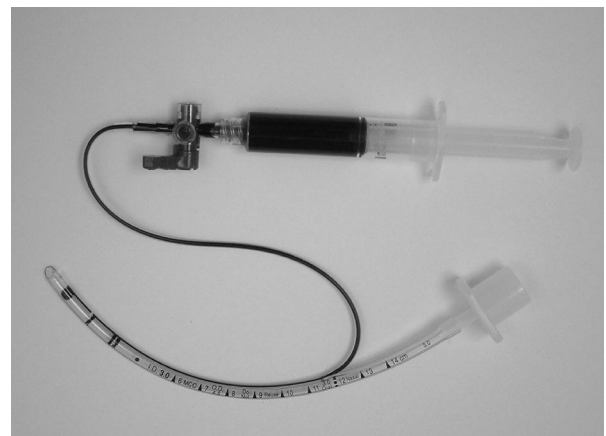
## Reference

1. Al-Nabhani D, Shivananda S, Holtby H, McNamara PJ: Hazardous course of an end-tidal carbon dioxide catheter in a premature infant. *ANESTHESIOLOGY* 2007; 107:180–1

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*In Reply:*—We are delighted that our report has stimulated some interesting discussion on the challenges of end-tidal carbon dioxide monitoring.<sup>1</sup> Dr. Her describes his experience with a new type of endotracheal tube, which has a built-in end-tidal carbon dioxide monitoring port (Mallinckrodt Inc., St. Louis, MO). We agree that the complication seen in our patient could have been avoided with this form of tube because dislodgement and distal migration are less likely. There are some other advantages that should be noted. Because the monitoring line does not



**Fig. 1.** A 3.0-mm uncuffed endotracheal tube with end-tidal carbon dioxide monitoring port. Methylene blue dye was injected into the end-tidal carbon dioxide monitoring port to visualize the separate lumen. The dye entered the main lumen of the endotracheal tube at the near distal end of tube.

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occupy the inner lumen, airway resistance is not increased. This is particularly relevant for very low-birth-weight infants, where 2.0- to 2.5-mm uncuffed endotracheal tubes are commonly used and airway resistance is most likely to be affected. This type of tube can be easily used with an appropriate end-tidal measuring system, provided the sample volume aspirated does not compromise the delivered tidal volume.

There are some limitations that need to be pointed out. The additional tubing may become entangled with other tubes (e.g., nasogastric



tube) or may be pulled on by an active patient, both potentiating an accidental extubation. If the tube is inadvertently cut (e.g., during tube suturing or taping) or the stopcock is left open to the atmosphere, a leak may occur, leading to ventilator autocycling and suboptimal tidal volume delivery. If used chronically for long-standing ventilated patients, the sampling line may become occluded by mucous or water secondary to circuit humidification. Finally, the current cost of the device may prohibit widespread use.

Although continuous end-tidal carbon dioxide is a close measure of arterial carbon dioxide partial pressure in patients with normal ventilation and perfusion, it does not guarantee appropriate tube position.<sup>2</sup> It is most useful for trending or screening patients for abnormal carbon dioxide values. This type of endotracheal tube may be useful for patients requiring short-term procedural intubation in the operating room or during high-risk neonatal transport, where the risk of endo-

tracheal tube migration/dislodgement is high. The reliability of this device needs careful prospective evaluation.

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## References

1. Al-Nabhani D, Shivananda S, Holtby H, McNamara PJ: Hazardous course of an end-tidal carbon dioxide catheter in a premature infant. *ANESTHESIOLOGY* 2007; 107:180-1
2. Noble JJ: Carbon-dioxide monitors: Exhaled gas (capnographs, capnometry, end-tidal CO<sub>2</sub> monitors). *Pediatr Emerg Care* 1993; 9:244-6

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## Limitations of Genetic Findings That Are Not in Hardy-Weinberg Equilibrium

*To the Editor:*—Zaugg *et al.*<sup>1</sup> report an association between the Arg389Gly (rs1801253) single nucleotide polymorphism of the  $\beta_1$ -adrenergic receptor and adverse cardiac outcomes occurring within 1 yr of spinal anesthesia in patients with clinically important coronary artery disease. Although quite interesting, this report may be flawed by an important statistical methodology error.

The reported genotypes of rs1801253 are not in Hardy-Weinberg equilibrium ( $P = 4.2 \times 10^{-7}$ ) and have a lower than expected number of heterozygotes. Publicly available genotyping demonstrates that the Arg389Gly genetic variant is generally found to be in Hardy-Weinberg equilibrium.\* The most frequent cause of reduced heterozygote expression is genotyping error caused by low amplification of one of the two alleles in the genotyping process. Examination of genotyping intensity plots will frequently, but not always, identify such errors. With such a markedly abnormal result, the authors would be advised to re genotype this single nucleotide polymorphism using another genotyping platform, preferably by an independent laboratory, to confirm their findings.

The reader is referred to an informative description of Hardy-Weinberg equilibrium in the same issue of *ANESTHESIOLOGY* for an explanation of this important quality control measure in genotyping studies.<sup>2</sup> Guidance for quality control and reporting the results of genotyping studies have recently been provided.<sup>3</sup> Specifically, measures to assess the quality of genotype data should include (1) excluding single nucleotide polymorphisms with low genotyping frequencies, (2) excluding single

nucleotide polymorphisms not in Hardy-Weinberg equilibrium, (3) performing genotyping on known study sample duplicates or publicly available samples to confirm accuracy of the genotyping methods, and (4) other methodologic and statistical techniques to ensure data quality. Accordingly, the association reported by Zaugg *et al.* should be regarded with considerable caution until confirmation in other cohorts.

**Simon C. Body, M.B., Ch.B., M.P.H.,† Debra A. Schwinn, M.D.** †Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. body@zeus.bwh.harvard.edu

## References

1. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, Hersberger M, Kälin G, Furrer L, Hofer C, Blumenthal S, Müller A, Zollinger A, Spahn DR, Borgeat A: Adrenergic receptor genotype but not perioperative Bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: A double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *ANESTHESIOLOGY* 2007; 107:33-44
2. Lötsch J: Basic genetic statistics are necessary in studies of functional associations. *ANESTHESIOLOGY* 2007; 107:168-9
3. NCI-NH GRI Working Group on Replication in Association Studies, Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF, Freimer NB, Gerhard DS, Gunter C, Guttmacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, Roberts J, Rotimi C, Tucker MA, Vogan KJ, Wacholder S, Wijsman EM, Winn DM, Collins FS: Replicating genotype-phenotype associations. *Nature* 2007; 447:655-60

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\* [http://www.ncbi.nlm.nih.gov/SNP/snp\\_ref.cgi?rs=1801253](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=1801253). Accessed July 19, 2007.

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*In Reply:*—We thank Drs. Body and Schwinn for their critical remarks on our study.<sup>1</sup> To clarify, our double-blinded, placebo-controlled trial was primarily designed to test the hypothesis that the perioperative administration of bisoprolol would reduce the incidence of cardiovascular complications in patients with or at risk for coronary artery disease undergoing surgery with spinal nerve block. However, because single nucleotide polymorphisms of the  $\beta$ -adrenergic receptor genes may act as disease modifiers,<sup>2</sup> biologically important nonsynonymous coding variants of the  $\beta$ -adrenergic receptor were determined in our study population. This

analysis showed that carriers of at least one Gly allele of the  $\beta_1$ -adrenergic receptor polymorphism Arg389Gly experienced a higher number of adverse events than Arg homozygotes.<sup>1</sup> Drs. Body and Schwinn raised concerns with respect to genotyping errors based on the observed deviation from Hardy-Weinberg equilibrium for this particular polymorphism in our trial. Genotyping error is indeed one of the many possible sources of Hardy-Weinberg disequilibrium. To exclude this possibility in our trial, we have carefully re genotyped all patients for the Arg389Gly polymorphism using internal controls for wild-type, heterozygous, and mutant

genotypes for each amplification process. As reported in our publication, from the 189 patients, who consented to genotyping, 186 could be unequivocally identified and confirmed by re-genotyping by three independent individuals. In three patients (notably without a primary outcome), genotyping was not possible, and these patients were excluded from genotype-related outcome analysis. Our genotyping platform was further meticulously validated by bidirectional sequencing of DNA samples for the Arg389Gly polymorphism from 12 randomly selected patients of this particular study and from many other patients not related to this study. Bidirectional sequencing is regarded as the standard of genotyping and as by far more reliable than any other genotyping platform.

Although testing for Hardy-Weinberg equilibrium is used as some quality-control measure, particularly in case-control gene association studies, it cannot be used to detect genotyping error.<sup>3,4</sup> Genotyping errors are generally small and do not generate sufficient deviations from Hardy-Weinberg equilibrium to be detected. In the case of a reduced number of observed heterozygous patients, as may occur in the presence of poor amplification of one of the alleles, large sample sizes are necessary to detect deviations from Hardy-Weinberg equilibrium. For example, with the Gly389 allele of the Arg389Gly polymorphism with a reported allele frequency of 0.27 and an error rate of 0.05, more than 8,000 patients would be necessary to detect deviation from Hardy-Weinberg with a power of 0.80 at an  $\alpha$  level of 0.05. Increasing the error rate to 0.15 reduces the sample size to the still considerably high patient number of 944. Therefore, testing for Hardy-Weinberg equilibrium is an unreliable tool to identify genotyping errors. Conversely, the presence of Hardy-Weinberg equilibrium does not rule out that genotyping errors might have occurred. Hence, it seems unlikely that genotyping error is the source of the Hardy-Weinberg disequilibrium observed in our study. Because approximately 10% of all genotype-phenotype association studies show deviation from Hardy-Weinberg equilibrium, the results of our trial cannot be considered "abnormal."<sup>5</sup> Rather, as outlined in the discussion of our findings,<sup>1</sup> a selection bias (population stratification) may have occurred because of inclusion and exclusion criteria of this randomized trial. A mortality bias (different survival of marker genes) due to varying genetic

and environmental background (*e.g.*, response to cardiovascular medication) in this elderly study population at the end of life expectancy may have also caused this disequilibrium. Of note, Hardy-Weinberg disequilibrium that is caused by most interesting biologic phenomena typically results in excess homozygosity, as observed in our study.<sup>1</sup> However, we agree with Drs. Body and Schwinn that violation of Hardy-Weinberg equilibrium in our study population implies a selected rather than a random sample, invalidating direct comparisons with other populations. Therefore, we share their view that our results should be regarded with caution. Our findings should be confirmed in future prospective larger-scale clinical trials, specifically designed and adequately powered to detect genotype-specific differences in cardiovascular outcome in patients with or at risk of coronary artery disease.

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## References

1. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, Hersberger M, Kalin G, Furrer L, Hofer C, Blumenthal S, Muller A, Zollinger A, Spahn DR, Borgeat A: Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: A double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *ANESTHESIOLOGY* 2007; 107:33-44
2. Zaugg M, Schaub MC: Genetic modulation of adrenergic activity in the heart and vasculature: Implications for perioperative medicine. *ANESTHESIOLOGY* 2005; 102:429-46
3. Zou GY, Donner A: The merits of testing Hardy-Weinberg equilibrium in the analysis of unmatched case-control data: A cautionary note. *Ann Hum Genet* 2006; 70:923-33
4. Leal SM: Detection of genotyping errors and pseudo-SNPs *via* deviations from Hardy-Weinberg equilibrium. *Genet Epidemiol* 2005; 29:204-14
5. Trikalinos TA, Salanti G, Khoury MJ, Ioannidis JP: Impact of violations and deviations in Hardy-Weinberg equilibrium on postulated gene-disease associations. *Am J Epidemiol* 2006; 163:300-9

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## Newborns and Anesthetic Neurotoxicity

*To the Editor:*—We read with interest Dr. Anand's Editorial View, "Anesthetic Neurotoxicity in Newborns: Should We Change Clinical Practice?" but we are concerned that readers may misinterpret his indication regarding postnatal day 35 (P35) rhesus monkeys: "anesthetic neurotoxicity primarily results from apoptosis in rodents, . . . whereas infant monkeys at P5 (but not at P35) exhibit both excitotoxicity and apoptosis."<sup>1</sup> Although the report referenced by Dr. Anand in regard to P35 monkeys did not find a neurotoxic effect, it used one control and one experimental sample of  $n = 3$ .<sup>2</sup> For each indicator of neurotoxicity, the SDs bracketing the observed results were far greater than the observed difference between the control group and the anesthetized group, such that a confidence interval around each observed difference includes levels of neurotoxicity that cannot be dis-

missed. Accordingly, the neurotoxicity of anesthetics has not been established beyond age P5 in a primate model. Absence of evidence is (still) not evidence of absence.<sup>3</sup>

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## References

1. Anand KJ: Anesthetic neurotoxicity in newborns: Should we change clinical practice? *ANESTHESIOLOGY* 2007; 107:2-4
2. Slikker W, Zou X, Hotchkiss CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP, Paule MG, Wang C: Ketamine-induced neuronal cell death in the perinatal rhesus monkey. *Toxicol Sci* 2007; 98:145-58
3. Hartung J, Cottrell JE, Giffin JP: Absence of evidence is not evidence of absence. *ANESTHESIOLOGY* 1983; 58:298-300

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The above letter was sent to the authors of the referenced report. The authors did not feel that a response was required.—James C. Eisenach, M.D., Editor-in-Chief.