

Why Does Prophylactic Epidural Blood Patch Fail to Demonstrate Efficacy in Preventing Post-Dural Puncture Headache in Parturients after Dural Puncture?

To the Editor:— We read with interest the study by Scavone *et al.*¹ that demonstrates the absence of efficacy of a prophylactic epidural blood patch after inadvertent dural puncture. We suggest that two factors could have influenced the negative result of this trial. First, inadvertent dural puncture could have been overdiagnosed, namely when loss of resistance to saline was used to locate epidural space. This could explain the lower incidence of post-dural puncture headache and less frequent realization of therapeutic epidural blood patch reported in this study compared with others.^{2,3}

Second, 20 ml may not be the adequate blood volume to test a prophylactic epidural blood patch. This volume has tended to increase over time to 20 ml or more, 23 ± 5 ml in a study by Safat-Tisseront *et al.*³ The optimal blood volume may be the volume at which pain in the back, buttocks, or legs occurs, which was only achieved for seven patients in the study of Scavone *et al.* This higher volume may lead to either a larger patch over the dural tear or a significantly higher increase in lumbar and intracranial pressure, leading to reduced cerebral vasodilation.

Anesthesiology 2005; 103:900

In Reply:—We appreciate the comments of Dr. Pruszkowski *et al.* regarding our recently published article.¹ Although we did not standardize epidural placement technique, it is standard practice at our institution to use loss of resistance to air to identify the epidural space, and it is unlikely that many, if any, procedures were performed using the loss of resistance to saline technique. Therefore, we do not believe this contributed to an overdiagnosis of inadvertent dural puncture, as suggested. In fact, the loss of resistance to air technique may be associated with a higher rate of post-dural puncture headache than the loss of resistance to saline technique.² The rate of post-dural puncture headache in our study (56%) corresponds closely with that found in a meta-analysis of dural puncture with an epidural needle in obstetric patients: 52.1% (95% confidence interval, 51.4–52.8%).³

We agree with the authors that the optimal volume of blood for an epidural blood patch is not known. Although approximately 20 ml seems to be the standard dose, volume of blood was not associated with epidural blood patch success in the retrospective study cited by the authors.⁴ As noted, sacral pressure or pain was observed in only a small number of subjects who received a prophylactic epidural blood patch. This likely reflects the fact that the blood was, of necessity, injected through the 19-gauge, 88-cm epidural catheter at a much slower rate than is possible through a 17- or 18-gauge, 9-cm epidural needle, thus resulting in a smaller increase in epidural pressure during

Olivier Pruszkowski, M.D.,* Orlando Goncalves, M.D., Claude Lentschener, M.D., Alexandre Mignon, M.D., Ph.D. *Hôpital Cochin Maternité Port-Royal, Assistance Publique-Hôpitaux de Paris, Paris, France. olivier.prus@club-internet.fr

References

1. Scavone BM, Wong CA, Sullivan JT, Yaghmour E, Scherwani SS, McCarthy RJ: Efficacy of prophylactic epidural blood patch in preventing post dural puncture headache in parturients after inadvertent dural puncture. *ANESTHESIOLOGY* 2004; 101:1422-7
2. Safat-Tisseront V, Thormann F, Malassine P, Henry M, Riou B, Coriat P, Seebacher J: Effectiveness of epidural blood patch in the management of post-dural puncture headache. *ANESTHESIOLOGY* 2001; 95:334-9
3. Crawford JS: Experiences with epidural blood patch. *Anaesthesia* 1980; 35:513-5

(Accepted for publication June 7, 2005.)

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

the injection. Although it is possible that modifications of the technique could result in a higher rate of efficacy of prophylactic epidural blood patch, our study clearly demonstrated no difference in the incidence of post-dural puncture headache using the technique as it is commonly practiced.

Barbara M. Scavone, M.D.,* Cynthia A. Wong, M.D. *Northwestern University Feinberg School of Medicine, Chicago, Illinois. bimsdavone@aol.com

References

1. Scavone BM, Wong CA, Sullivan JT, Yaghmour E, Scherwani SS, McCarthy RJ: Efficacy of a prophylactic epidural blood patch in preventing post dural puncture headache in parturients after inadvertent dural puncture. *ANESTHESIOLOGY* 2004; 101:1422-7
2. Aida S, Taga K, Yamakura T, Endoh H, Shimoji K: Headache after attempted epidural block. *ANESTHESIOLOGY* 1998; 88:76-81
3. Choi PT, Galinski SE, Takeuchi L, Lucas S, Tamayo C, Jadad AR: PDPH is a common complication of neuraxial blockade in parturients: A meta-analysis of obstetrical studies. *Can J Anaesth* 2003; 50:460-9
4. Safat-Tisseront V, Thormann F, Malassine P, Henry M, Riou B, Coriat P, Seebacher J: Effectiveness of epidural blood patch in the management of post-dural puncture headache. *ANESTHESIOLOGY* 2001; 95:334-9

(Accepted for publication June 7, 2005.)

Anesthesiology 2005; 103:900-1

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Iliac Crest Bone Harvest: Should We Really Use Continuous Infusion of Ropivacaine?

To the Editor:—We read with interest the article by Blumenthal *et al.*¹ about effectiveness of continuous ropivacaine infusion at the iliac crest donor site. This study seems to confirm the results of Brull *et al.*² obtained with continuous bupivacaine infusion. However, several

points deserve some comments from the authors before their conclusions can be accepted.

First, the primary goal and the calculation of the number of patients needed for the study deserve clarification. Was this study built to

demonstrate a reduction in pain scores at rest, at movement, or both, and if so, at 24 h or 48 h or both? This is of importance because it has direct impact on the accuracy of the calculation of the number of patients needed to test the null hypothesis and because the use of multiple statistical comparisons dramatically increases the α risk.

Second, the chronic analgesic therapy of the patients at 3 months is not reported. Because of the highly significant difference in the pain at the iliac crest during motion between the two groups, it would be important to determine whether analgesic therapy was accurately administered in the two groups at that time. Otherwise, this would represent a possible confounding factor contributing to artificially exacerbate the difference in pain scores between groups at 3 months.

Third, the authors make a case that higher patient satisfaction and lower pain score during motion 3 months after surgery are present in the ropivacaine group. Although these data are potentially very interesting, maybe more interesting than the primary goal itself (postoperative short-term reduction in pain scores), they correspond only to a secondary endpoint. Therefore, we think it is premature to state, as the

Anesthesiology 2005; 103:901

In Reply:—We thank Dr. Geoffroy *et al.* for their interest in our study and the opportunity to clarify the points mentioned by these authors: We clearly disagree with the assessment that our study¹ is a simple repetition of the study of Brull *et al.*² Besides many methodologic differences (historic control group, different operations within the study group, close proximity of the operation site to the iliac crest, and others), the major difference is the application of repeated bupivacaine boluses in the study of Brull *et al.* compared with a continuous infusion of ropivacaine in ours. The number of patients in our study was calculated to demonstrate reduced pain intensity at rest during the first 48 h postoperatively. This was clearly stated in our article. Because pain was assessed every 8 h from t0 to t48, a Bonferroni correction for multiple comparisons was performed to avoid an increase of a type I risk error. This point was also clearly stated in the article.

Regarding the question of pain therapy after discharge, it should read “3 months” instead of “3 weeks” (page 393, fifth line of the second column). We apologize for having produced confusion with this. We

Anesthesiology 2005; 103:901–2

Off-pump Coronary Artery Bypass: Randomized Trials, Real-world Experience, Clinical Relevance, and Statistical Significance

To the Editor:—I read with great interest the editorial by Floyd and Fleisher¹ accompanying the article by Cheng *et al.*² in the January issue of *ANESTHESIOLOGY*. They have raised the issue of undertaking further studies recruiting high-risk patients with appropriate controls for important confounders, to compare the impact of off-pump coronary artery bypass (OPCAB) on graft patency and incidence of postoperative stroke, because in their opinion the meta-analysis of Cheng *et al.*² is underpowered to draw conclusions regarding these outcomes. This suggestion of Floyd and Fleisher does not come as a surprise because we are living in an era of evidence-based medicine where statistical significance and not clinical relevance is regarded as the final word.

Since its revival, OPCAB has been under the microscope of skeptics. It has always been the focus of scientific scrutiny, and current medical literature contains a staggering amount of research related to this technique. In fact, among modalities of myocardial revascularization, OPCAB is perhaps the most rigorously tested technique.³ Despite the fact that there is plenty of high-quality evidence from meta-analyses and systematic reviews^{2,4–7} in support of OPCAB, call for further trials,

authors did, that “the benefit of this technique is still present after 3 months.” To report data on the social consequences of persistent pain at the iliac crest at 3 months (e.g., ability to work, quality of daily life) would have strengthened the potential clinical impact of the current study.

Arnaud Geffroy, M.D.,* Fabrice Cook, M.D., Philippe Juvin, M.D., Ph.D., Jean Mantz, M.D., Ph.D. *Beaujon University Hospital, Clichy, France. arnaud.geffroy@bjn.aphp.fr.

References

1. Blumenthal S, Dullenkopf A, Rentsch K, Borgeat A: Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *ANESTHESIOLOGY* 2005; 102:392–7
2. Brull SJ, Lieponis JV, Murphy MJ, Garcia R, Silverman DG: Acute and long-term benefits of iliac crest donor site perfusion with local anesthetics. *Anesth Analg* 1992; 74:145–7

(Accepted for publication June 7, 2005.)

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

agree with Geffroy *et al.* that it would have been a wonderful way to strengthen our study to include data on the social consequences of persistent or relieved pain at the iliac crest at 3 months. However, these questions were not part of our original study protocol, and thus we did not include retrospective data in our prospective investigation.

Stephan Blumenthal, M.D., Alain Borgeat, M.D.* *Balgrist University Hospital, Zurich, Switzerland. alain.borgeat@balgrist.ch

References

1. Blumenthal S, Dullenkopf A, Rentsch K, Borgeat A: Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *ANESTHESIOLOGY* 2005; 102:392–7
2. Brull SJ, Lieponis JV, Murphy MJ, Garcia R, Silverman DG: Acute and long-term benefits of iliac crest donor site perfusion with local anesthetics. *Anesth Analg* 1992; 74:145–7

(Accepted for publication June 7, 2005.)

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

none of which can ever be large enough to conclusively prove the superiority of OPCAB, seems nothing more than naivety. Instead, it will be much more appropriate to regularly update existing meta-analyses, incorporating outcomes of newly published trials as well as longer-term outcomes of trials already published, according to the concept of cumulative meta-analysis, which was coined by Lau *et al.*⁸ Thereby, the statistical power will increase further, and statistical significance for superiority of OPCAB can be conclusively shown. Moreover, a reanalysis of pooled raw trial data in general will result in more precise effect estimates⁹ and will provide an opportunity to study the difference in effect between OPCAB and conventional myocardial revascularization more thoroughly, including the influence of preoperative risk factors. To make such pooled reanalysis of raw trial data a success, however, investigators must collaborate and share their raw trial data.

At the same time, it is extremely important to realize that clinical trials are conducted under controlled conditions with strict inclusion and exclusion criteria, and their results may not be translated into “real-world” clinical practice where indications of use of OPCAB are

more liberal. Interestingly, real-world clinical experience suggests that a more challenging patient category might benefit most from OPCAB and that OPCAB surgery can be safely performed in high-risk patients with multivessel coronary artery disease.¹⁰ In fact, the real-world results of OPCAB are comparable with those of randomized trials and justify the use of OPCAB in unselected patients, with significant economic as well as clinical benefits.³

To cut things short, it is extremely important to understand that there is abundant clinically relevant, though not necessarily statistically significant, scientific evidence to validate the midterm safety and efficacy of OPCAB. Instead of demanding further trials, it will perhaps be more prudent to accept that the place of OPCAB in the treatment of coronary artery disease is irrefutable and let time decide whether it has statistically significant superiority over conventional on-pump myocardial revascularization for all outcomes in the long term.

Shahzad G. Raja, M.R.C.S., Royal Hospital for Sick Children, Yorkhill NHS Trust, Glasgow, United Kingdom.
drrajashahzad@hotmail.com

References

1. Floyd T, Fleisher LA: Off-pump coronary artery bypass and the hypothesis from which it grew: Is it yet to be tested? What are the downsides of the lingering questions? *ANESTHESIOLOGY* 2005; 102:3-5

2. Cheng DC, Bainbridge D, Martin JE, Novick RJ: The Evidence-based Perioperative Clinical Outcomes Research Group. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *ANESTHESIOLOGY* 2005; 102:188-203

3. Raja SG: Safety of off-pump coronary artery surgery: No more skepticism please! (letter). *Eur J Cardiothorac Surg* 2004; 26:1229

4. Parolari A, Alamanni F, Cannata A, Naliato M, Bonati L, Rubini P, Veglia F, Tremoli E, Biglioli P: Off-pump versus on-pump coronary artery bypass: Meta-analysis of currently available randomized trials. *Ann Thorac Surg* 2003; 76:37-40

5. Reston JT, Tregear SJ, Turkelson CM: Meta-analysis of short-term and mid-term outcomes following off-pump coronary artery bypass grafting. *Ann Thorac Surg* 2003; 76:1510-5

6. van der Heijden GJ, Nathoe HM, Jansen EW, Grobbee DE: Meta-analysis on the effect of off-pump coronary bypass surgery. *Eur J Cardiothorac Surg* 2004; 26:81-4

7. Raja SG, Dreyfus GD: Off-pump coronary artery bypass surgery: To do or not to do? Current best available evidence. *J Cardiothorac Vasc Anesth* 2004; 18:486-505

8. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC: Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; 327:248-54

9. Stewart LA, Parmar MK: Meta-analysis of the literature or of individual patient data: Is there a difference? *Lancet* 1993; 341:418-22

10. Raja SG, Dreyfus GD: Will off-pump coronary artery surgery replace conventional coronary artery surgery? *J R Soc Med* 2004; 97:275-8

(Accepted for publication May 10, 2005.)

Anesthesiology 2005; 103:902

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Underreporting of Conversion from Off-pump Coronary Artery Bypass Surgery

To the Editor:—We read with interest the meta-analysis of Cheng *et al.*¹ recently published in *ANESTHESIOLOGY* and agree in considering it the best evidence on which to base future treatment decisions and research directions.²

With the aim of adding a piece of evidence, we reviewed all of the 37 randomized controlled trials included in the meta-analysis, focusing on the reported incidence of conversion from off-pump (OP) to standard cardiopulmonary bypass (CPB) technique. This is a common event during OP surgery and is caused by either deep intramural vessels (elective) or hemodynamic instability (urgent).

We were surprised to note that only 13 of 37 studies (35.1%) of the meta-analysis stated that they adopted the intention-to-treat analysis, whereas 18 of 37 studies avoided citing this important point, 4 studies affirmed that the patients who crossed over from OP to CPB were excluded from the analysis, and 2 studies considered the converted patients in the CPB group. Only 1 study reported the outcome of the converted patients.

Conversion from OP to standard CPB technique is a common but underreported event, with poor outcome and increased perioperative mortality. An extensive Medline search evidenced only five studies focusing on conversion from OP to CPB, with a cumulative incidence of conversion of 4.85% (202 of 4,163 patients) and a range from 3.7 to 13.3%. Mortality in these patients is 25 in 202 (12.3%). These data are

consistent with our experience (Landoni *et al.*, unpublished data, Vita-Salute University of Milan, IRCCS San Raffaele Hospital, Milan, Italy, June 2001–July 2003) of a conversion rate of 37 in 450 (8.2%), with 2 in 37 deaths (5.4%).

We suggest that conversion from OP to standard CPB is underreported in literature and recommend that outcome of converted patients should be reported in future randomized controlled studies.

Alberto Zangrillo, M.D., Franco Annalisa, M.D., Giuseppe Crescenzi, M.D., Federico Pappalardo, M.D., Filippo Boroli, M.D., Ornella Sottocorna, M.D., Giovanni Landoni, M.D.* Vita-Salute University of Milan, IRCCS San Raffaele Hospital, Milan, Italy.
landoni.giovanni@hsr.it

References

1. Cheng DC, Bainbridge D, Martin JE, Novick RJ: Evidence-based Perioperative Clinical Outcomes Research Group. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *ANESTHESIOLOGY* 2005; 102:188-203

2. Floyd T, Fleisher LA: Off-pump coronary artery bypass and the hypothesis from which it grew: Is it yet to be tested? What are the downsides of the lingering questions? *ANESTHESIOLOGY* 2005; 102:3-5

(Accepted for publication May 10, 2005.)

Anesthesiology 2005; 3:902-3

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—We agree with Dr. Raja that more trials of the same type of patients prevalent in this meta-analysis to continue the chase after

The above Letters were sent to the authors of the Editorial View. The authors did not feel that a response was required. —Michael M. Todd, Editor-in-Chief
David C. Warltier, M.D., Ph.D., served as Handling Editor for this exchange.

be questioned. Examination of the confidence intervals reveals that clinically relevant differences have been largely ruled out in the patient populations studied. However, this futility in further research should not be considered to extend to other understudied outcomes. Even in this generally younger and lower-risk patient population, there has been inadequate study of the long-term durability of the grafts (*i.e.*, need for reintervention, myocardial infarction, and survival at 1 yr and beyond). In addition, the need for further study in higher-risk groups should not be understated, because few high-risk patients have been included in randomized trials.¹ The wide confidence intervals around most endpoints reported at 1–3 yr in our meta-analysis suggest that the difference in off-pump and on-pump surgery may be harmful, no different, or beneficial. Until randomized studies adequately explore this, equipoise will remain. Formal exploration of the expected payoff of further research in this area could be quantified through Bayesian estimation of the “expected value of perfect information.”² This calculation would be laudable to best focus our limited research dollars and time.

We agree that meta-analysis of individual patient data would be valuable to provide further information, especially to determine whether certain patient risk factors at baseline are associated with differences in outcomes with off-pump *versus* on-pump coronary artery bypass surgery. It is hoped that clinical trial investigators would share their individual patient-level data with meta-analysts attempting the formidable task of individual patient data to maximize the information we can glean from existing randomized trials. Meta-analysts conducting studies of individual patient data would also benefit from further trials of outcomes and patient groups not currently adequately represented in existing randomized trials (long-term outcomes, high-risk subgroups). As suggested by Lau *et al.*,³ we plan to prospectively update our meta-analysis with the release of each randomized trial of off-pump *versus* on-pump coronary bypass surgery in the hopes that, over time, further unanswered questions will be addressed.

We thank Landoni *et al.* for putting further perspective on the very important issue of patients converted from off-pump coronary artery bypass to cardiopulmonary bypass. We agree that the reporting of conversions was far from complete in the randomized trials, and this warrants further investigation, perhaps by contacting the authors. Future investigators should take care to report conversions and appropriately analyze these patients by intention to treat. Most importantly, the reasons for and the outcomes of converted patients should be reported separately so that future systematic reviews can gather sufficient power to analyze the magnitude and breadth of risks of converted

patients. Because outcomes were not reported explicitly for converted patients in any of the randomized trials, we performed sensitivity analyses by worst-case scenario for those trials that had reported conversions.¹ The conclusions were generally robust even during worst-case scenarios, except for the endpoints of mortality, stroke, and myocardial infarction. This is concerning; previous retrospective analyses have suggested that patients converted from off-pump to on-pump surgery have increased risk of mortality and complications compared with nonconverted patients.⁴ Because conversion cannot be predicted at the time of deciding surgery technique but may be more likely in patients who have higher baseline risk, the tantamount question is whether converted patients do worse than they would have had they undergone planned conventional coronary artery bypass surgery from the outset. This underscores the importance of analysis by intention to treat, because the risk of conversion should be attributed to the overall risk of off-pump bypass surgery.

Davy C. Cheng, M.D., M.Sc., F.R.C.P.C.,* Daniel Bainbridge, M.D., F.R.C.P.C., Janet E. Martin, Pharm.D., Richard J. Novick, M.D., M.Sc., F.R.C.S.C. *London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada. davy.cheng@lhsc.on.ca

References

1. Cheng DC, Bainbridge D, Martin JE, Novick RJ: Evidence-based Perioperative Clinical Outcomes Research Group. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *ANESTHESIOLOGY* 2005; 102:188–203
2. Claxton K, Neumann PJ, Araki S, Weinstein MC: Bayesian value-of-information analysis: An application to a policy model of Alzheimer's disease. *Int J Technol Assess Health Care* 2001; 17:38–55
3. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC: Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; 327:248–54
4. Soltoski P, Salerno T, Levinsky L, Schmid S, Hasnain S, Diesfeld T, Huang C, Akhter M, Alnowaiser O, Bergsland J: Conversion to cardiopulmonary bypass in off-pump coronary artery bypass grafting: Its effect on outcome. *J Card Surg* 1998; 13:328–34

(Accepted for publication May 10, 2005.)

The above letters were sent to the authors of the Editorial View. The authors did not feel that a response was required.—Michael M. Todd, Editor-in Chief.

David C. Warltier, M.D., Ph.D., served as Handling Editor for this exchange.

Is the Activated Clotting Time Dangerous?

To the Editor:—Avidan *et al.*¹ present a novel method of treating heparin resistance in patients about to undergo cardiopulmonary bypass (CPB). Implicit but undocumented is the premise that patients with heparin resistance, defined as failure of the activated clotting time (ACT) to increase above the institutional protocol after a standard dose of heparin, are in danger of insufficient anticoagulation to tolerate CPB safely.

The issue is more than academic. If patients with heparin resistance are indeed endangered by a low ACT, correcting the low ACT is lifesaving. If patients with heparin resistance are not endangered by the low ACT, intervention presents risk without benefit.

A heparin dose of 300 U/kg is considered the minimum dose required for safe CPB, although one study reported routine use of 150 U/kg without ill effect.² On the other hand, the Society of Cardiovascular Anesthesiologists survey³ quoted by Avidan *et al.*¹ revealed a wide range of institutional ACT protocols. Some institutions omit ACT measurements entirely.⁴

No prospective study indicates that any protocol is safer or more dangerous than others when administering conventional doses of heparin.

Commonly used target ACTs have little substance to corroborate them. Young *et al.*⁵ proposed their recommended 400 s on the basis of nine monkeys whose CPB circuits were primed with monkey blood and then five children who did fine with ACTs above 400 s. Bull *et al.*⁶ recommended 480 s on the basis on a computer simulation with no patient data; their report contained no rationale for selecting 480 s as an optimal target.

Several studies demonstrate the lack of correlation between bad outcome and uncorrected low heparinized ACTs before or during CPB.^{2,4,7}

The value of the study by Avidan *et al.*¹ is that it presents an alternative treatment for heparin resistance. The use of recombinant human antithrombin will allow clinicians to increase the heparinized ACT without danger of additional heparin or blood transfusion. In-

stead, the patient endures the lesser risk of anaphylactic reaction and the cost of the drug. The alternative not discussed by Avidan *et al.* is to ensure that the heparin went intravascular (a heparin level will suffice) and then ignore the ACT. This last alternative has no documented risks.

If Avidan *et al.* are aware of studies more recent than the antiquated studies quoted here that might invalidate this conclusion, it would be educational to discuss them.

Heparin resistance is a disease carried in ACT tubes. Once assured that the standard dose of heparin went intravascular, we may spare patients the dreaded consequences of treating heparin resistance (delay of CPB, more heparin, blood products, recombinant antithrombin) if we manage them without the ACT.

Samuel Metz, M.D., Oregon Anesthesiology Group, Providence Milwaukie Hospital, Portland, Oregon. samuel.metz@comcast.net

References

1. Avidan MS, Levy JH, Scholz J, Delphin E, Rosseel PMJ, Howie MB, Gratz I, Bush CR, Skubas N, Aldea GS, Licina M, Bonfiglio LJ, Kajdasz DK, Ott E, Despotis GJ: A phase III, double-blind, placebo-controlled, multicenter study on the effi-

Anesthesiology 2005; 103:904

In Reply:—We thank Dr. Metz for his interest in our study and for his thought-provoking letter. We agree with the comments about the limitations of the activated clotting time (ACT) test and the lack of evidence supporting any particular approach linked to any particular target ACT number. However, the limitations of the ACT do not undermine the importance of heparin resistance (or decreased sensitivity to heparin), an entirely different problem. Dr. Metz suggests that “The alternative [treatment for heparin resistance] not discussed by Avidan *et al.* is to ensure that the heparin went intravascular . . . and then ignore the ACT.” This is potentially a risky approach, because with severe heparin resistance, there may be an apparent adequate blood heparin concentration without sufficient anticoagulant effect.

We cannot agree with the sentiment that “Heparin resistance is a disease carried in ACT tubes.” This statement implies that the diagnosis of heparin resistance owes its existence entirely to a flawed point of care coagulation test. Of course it is likely that, following the unreliability of the ACT, some false diagnoses of heparin resistance will be made, but to attribute all diagnoses of heparin resistance to the unreliability of the ACT is disingenuous. Heparin depends on the presence of antithrombin for its anticoagulant efficacy. Antithrombin deficiency and antithrombin abnormalities are important and very real causes of heparin resistance.^{1–3} In many of the patients in our study, we demonstrated low blood antithrombin concentrations both at baseline and during cardiopulmonary bypass.⁴ We can therefore state confidently that the diagnosis of heparin resistance in our patients rests on a more solid foundation than a potentially unreliable ACT number.

We do, however, agree that monitoring heparin concentration may

cacy of recombinant human antithrombin in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass. *ANESTHESIOLOGY* 2005; 102:276–84

2. Dauchot PJ, Berinza-Moettus L, Rabinovitch P, Ankeny JL: Activated coagulation and activated partial thromboplastin times in assessment and reversal of heparin induced anticoagulation for cardiopulmonary bypass. *Anesth Analg* 1983; 62:710–9

3. Despotis GJ, Gravlee G, Filos K, Levy J: Anticoagulation monitoring during cardiac surgery: A review of current and emerging techniques. *ANESTHESIOLOGY* 1999; 91:1122–51

4. Metz S, Keats AS: Low activated coagulation time during cardiopulmonary bypass does not increase postoperative bleeding. *Ann Thorac Surg* 1990; 49:440–4

5. Young JA, Kisker CT, Doty DB: Adequate anticoagulation during cardiopulmonary bypass determined by activated clotting time and the appearance of fibrin monomer. *Ann Thorac Surg* 1978; 26:231–40

6. Bull BS, Korpman RA, Huse WM, Briggs BD: Heparin therapy during extracorporeal circulation. *J Thorac Cardiovasc Surg* 1975; 69:675–84

7. Culliford AT, Gitel SN, Starr N, Thomas ST, Baumann FG, Wessler S, Spencer FC: Lack of correlation between activated clotting time and plasma heparin during cardiopulmonary bypass. *Ann Surg* 1981; 193:105–11

(Accepted for publication June 21, 2005.)

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

be more effective than monitoring the ACT in guiding anticoagulation for cardiopulmonary bypass. Of course, clinicians would have to agree on the appropriate heparin concentration for all patients. This would vary according to each physician’s bias and of course each individual’s sensitivity to heparin.

Michael S. Avidan, M.B.B.Ch., D.A., F.C.A.(SA),* George J. Despotis, M.D. *Washington University School of Medicine, St. Louis, Missouri. avidanm@msnotes.wustl.edu

References

1. Bauters A, Zawadzki C, Bura A, Thery C, Watel A, Subtil D, Aiach M, Emmerich J, Jude B: Homozygous variant of antithrombin with lack of affinity for heparin: Management of severe thrombotic complications associated with intrauterine fetal demise. *Blood Coagul Fibrinolysis* 1996; 7:705–10

2. Nielsen LE, Bell WR, Borkon AM, Neill CA: Extensive thrombus formation with heparin resistance during extracorporeal circulation: A new presentation of familial antithrombin III deficiency. *Arch Intern Med* 1987; 147:149–52

3. Chasse JF, Esnard F, Guitton JD, Mouray H, Perigois F, Fauconneau G, Gauthier F: An abnormal plasma antithrombin with no apparent affinity for heparin. *Thromb Res* 1984; 34:297–302

4. Avidan MS, Levy JH, Scholz J, Delphin E, Rosseel PMJ, Howie MB, Gratz I, Bush CR, Skubas N, Aldea GS, Licina M, Bonfiglio LJ, Kajdasz DK, Ott E, Despotis GJ: A phase III, double-blind, placebo-controlled, multicenter study on the efficacy of recombinant human antithrombin in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass. *ANESTHESIOLOGY* 2005; 102:276–84

(Accepted for publication June 21, 2005.)

Anesthesiology 2005; 103:904–5

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

The “Anesthetic Cascade”: Fact or Fiction?

To the Editor:—In a recent issue of *ANESTHESIOLOGY*, John and Prichep¹ outlined a neurophysiologic theory of anesthesia. According to this theory, loss of awareness and amnesia are produced in six steps. In steps 1 and 2, depression of the brainstem reticular activation system causes diminution of availability of acetylcholine, resulting in decreased reactivity of the limbic system and block of memory storage. In steps 3 and 4, further depression of the reticular activation system

results in closure of thalamic gates, thereby blocking reverberations in the thalamocortical system. Finally, in steps 5 and 6, parietal-frontal transactions are blocked, prefrontal cortex is depressed, and unconsciousness occurs.

After this sequence of events, brainstem cholinergic neurons should be significantly depressed at subhypnotic and hypnotic anesthetic concentrations (steps 1 and 2), leading to decreased cholinergic acti-

vation of the thalamocortical system. However, studies on the effects of anesthetics on neurons in brainstem cholinergic nuclei report a moderate (approximately 20%) decrease in activity at anesthetic concentrations twofold higher than those producing sedation and amnesia.² Furthermore, blockers of brain acetylcholine receptors should be potent hypnotics, if decreased cholinergic activation of the thalamocortical system is a central mechanism of anesthetic action. However, this is clearly not the case. Clinically used hypnotics such as propofol and etomidate do not induce unconsciousness *via* blocking acetylcholine receptors.³ Taken together, the authors' statement that anesthetic-induced sedation and amnesia are causally related to a decreased concentration of acetylcholine in the brain is not backed by experimental evidence.

In steps 3 and 4, it is assumed that further depression of the reticular activation system is resulting in closure of thalamic gates. Unlike most other anesthetics, etomidate and ketamine do not attenuate thalamic information transfer in the somatosensory system when applied at hypnotic concentrations.^{4,5} Obviously, depression of thalamic gating is not a necessary requirement for producing unconsciousness, as assumed by an "anesthetic cascade." In addition, it is difficult to follow John and Prichep's implicit assumption that different anesthetic agents produce unconsciousness *via* the same neurophysiologic mechanism. This issue clearly needs careful elucidation.

In the last step of the model, it is proposed that prefrontal cortex is depressed to reduce awareness: The anesthetic cascade explains unconsciousness by a bottom-up approach: The starting point is in the brainstem. At higher concentrations, the prefrontal cortex gets involved. However, experimental data available so far seem to be better explained by a top-down approach. There is considerable evidence that cortical neurons are more sensitive to anesthetic treatment compared with neurons in the brainstem.^{3,6}

How might anesthetic agents work? Ion channels, highly sensitive to general anesthetics, exist in almost all parts of the central nervous system, including the neocortex, hippocampus, amygdala, thalamus, and spinal cord.^{7,8} There is increasing evidence that the anesthetic, sedative, and hypnotic properties of anesthetic agents are mediated by molecular targets located in diverse neural networks. For example, studies in knockout mice showed that a specific γ -aminobutyric acid type A receptor subtype, most prominently expressed in the hippocampus, is involved in learning and memory.⁹ This receptor is significantly modulated by very small concentrations of isoflurane.¹⁰ Therefore, molecular targets located in hippocampal pyramidal cells most probably contribute to the anesthetic properties of isoflurane.

What about anesthetic-induced sedation? Benzodiazepines and intravenous anesthetics produce sedation *via* γ -aminobutyric acid receptors, present in the cerebral cortex in high densities.^{11,12} There is a linear relation between the reduction in metabolic blood flow that occurs during propofol-induced hypnosis and the known regional benzodiazepine binding sites, suggesting that cortical γ -aminobutyric acid receptors mediate anesthetic-induced depression of cortical networks in humans.¹³ A similar conclusion has been drawn from animal studies. Recent investigations showed that neocortex is a major substrate of sedative and hypnotic concentrations of volatile anesthetics.⁶ The presence or absence of brainstem cholinergic nuclei had no influence on the depressive effects of volatile anesthetics on spontaneous firing of cortical neurons. Similarly, anesthetic-induced alterations of rhythmic brain activity, in particular attenuation of γ oscillations or induction of θ/δ oscillations have been observed in isolated cortical circuits, in the absence of subcortical structures.^{14,15} All of these data indicate that sedation, and in part hypnosis, are largely mediated by molecular targets located in the cerebral cortex.

With the above arguments, I do not intend to state that brainstem cholinergic nuclei and sleep pathways are irrelevant in the context of anesthesia. They probably come into play. Instead, my criticism addresses the theoretical concept: John and Prichep's theory is a unitary theory of anesthetic action. The authors do not assume that a single ion channel causes amnesia and hypnosis, but they assume that a single neural substrate does it. Approximately 10 yr ago, Kendig,¹⁶ Eger *et al.*,¹⁷ and Kissing¹⁸ proposed a different theory. They argued that anesthetics pro-

duce different aspects of anesthesia at different sites in the central nervous system by different molecular targets. That is, anesthesia is composed of elementary components, largely independent on each other. This "old" idea is in line with many recent findings. For example, the sedative and hypnotic actions of intravenous anesthetics can be distinguished by the subtype of γ -aminobutyric acid receptor that is involved.^{19,20} For example, amnesia and sedation are distinct components of anesthetic action that can be separated experimentally.²¹ All of these observations argue against a unitary brain mechanism producing the diverse aspects of anesthetic action in the central nervous system. They argue against something like an anesthetic cascade as well.

Bernd Antkowiak, Ph.D., University of Tuebingen, Tuebingen, Germany. bernd.antkowiak@uni-tuebingen.de

References

1. John ER, Prichep LS: The anesthetic cascade: A theory of how anesthesia suppresses consciousness. *ANESTHESIOLOGY* 2005; 102:447-71
2. Ogawa T, Shingu K, Shibata M, Osawa M, Mori K: The divergent actions of volatile anaesthetics on background neuronal activity and reactive capability in the central nervous system. *Can J Anesth* 1992; 39:862-72
3. Rudolph U, Antkowiak B: Molecular and neuronal substrates for general anaesthetics. *Nature Rev Neurosci* 2004; 5:709-20
4. Angel A, Arnott RH: The effect of etomidate on sensory transmission in the dorsal column pathway in the urethane-anaesthetized rat. *Eur J Neurosci* 1999; 11:2497-505
5. Schubert A, Licina M, Lineberry PJ: The effect of ketamine on human somatosensory evoked potentials and its modification by nitrous oxide. *ANESTHESIOLOGY* 1990; 72:33-9
6. Hentschke H, Schwarz C, Antkowiak B: Neocortex is the major target of sedative concentrations of volatile anaesthetics: strong depression of firing rates and increase of GABA_A receptor-mediated inhibition. *Eur J Neurosci* 2005; 21:93-102
7. Campagna JA, Miller KW, Forman SA: Mechanisms of actions of inhaled anesthetics. *N Engl J Med* 2003; 348:2110-24
8. Urban BW: Current assessment of targets and theories of anaesthesia. *Br J Anaesth* 2002; 89:165-83
9. Collinson N, Kuenzi FM, Jarolimek W, Maubach KA, Cothliff R, Sur C, Smith A, Otu FM, Howell O, Atack JR, McKernan RM, Seabrook GR, Dawson GR, Whiting PJ, Rosahl TW: Enhanced learning and memory and altered GABAergic synaptic transmission in mice lacking the alpha 5 subunit of the GABA_A receptor. *J Neurosci* 2002; 22:5572-80
10. Caraiscos VB, Newell JG, You T, Elliott EM, Rosahl TW, Wafford KA, MacDonald JF, Orser BA: Selective enhancement of tonic GABAergic inhibition in murine hippocampal neurons by low concentrations of the volatile anesthetic isoflurane. *J Neurosci* 2004; 24:8454-8
11. Rudolph U, Crestani F, Benke D, Brunig I, Benson JA, Fritschy JM, Martin JR, Bluethmann H, Mohler H: Benzodiazepine actions mediated by specific gamma-aminobutyric acid(A) receptor subtypes. *Nature* 1999; 401:796-800
12. Möhler H, Fritschy JM, Rudolph U: A new benzodiazepine pharmacology. *J Pharmacol Exp Ther* 2002; 300:2-8
13. Alkire MT, Haier RJ: Correlating in vivo anaesthetic effects with ex vivo receptor density data supports a GABAergic mechanism of action for propofol, but not for isoflurane. *Br J Anaesth* 2001; 86:618-26
14. Dickinson R, Awaiz S, Whittington MA, Lieb WR, Franks NP: The effects of general anaesthetics on carbachol-evoked gamma oscillations in the rat hippocampus in vitro. *Neuropharmacology* 2003; 44:864-72
15. Drexler B, Roether CL, Jurd R, Rudolph U, Antkowiak B: Opposing actions of etomidate on cortical theta oscillations are mediated by different γ -aminobutyric acid type A receptor subtypes. *ANESTHESIOLOGY* 2005; 102:346-52
16. Kendig JJ: Spinal cord as a site of anesthetic action. *ANESTHESIOLOGY* 1993; 79:1161-2
17. Eger II, El Koblun, DD, Harris RA, Kendig JJ, Pohorille A, Halsey MJ, Trudell JR: Hypothesis: Inhaled anesthetics produce immobility and amnesia by different mechanisms at different sites. *Anesth Analg* 1997; 84:915-8
18. Kissin I: A concept for assessing interactions of general anesthetics. *Anesth Analg* 1997; 85:204-10
19. Jurd R, Arras M, Lambert S, Drexler B, Siegart R, Crestani F, Zaugg M, Vogt KE, Ledermann B, Antkowiak B, Rudolph U: General anesthetic actions in vivo strongly attenuated by a point mutation in the GABA(A) receptor beta 3 subunit. *FASEB J* 2003; 17:250-2
20. Reynolds DS, Rosahl TW, Cirone J, O'Meara, GF, Haythornthwaite A, Newman RJ, Myers J, Sur C, Howell O, Rutter AR, Atack J, Macaulay AJ, Hadingham KL, Hutson PH, Bellelli D, Lambert JJ, Dawson GR, McKernan R, Whiting PJ, Wafford KA: Sedation and anesthesia mediated by distinct GABA(A) receptor isoforms. *J Neurosci* 2003; 23:8608-17
21. Veselis RA, Reinsel RA, Feshchenko VA: Drug-induced amnesia is a separate phenomenon from sedation: Electrophysiologic evidence. *ANESTHESIOLOGY* 2001; 95:896-907

(Accepted for publication June 21, 2005.)

Thalamocortical Connection and Anesthesia

To the Editor:—We read with much interest the recent Special Article by John *et al.*¹ They reviewed in detail recent progress in the mechanism of how anesthetics suppress consciousness, and they proposed their hypothesis to explain the effects of anesthetics that cause loss of consciousness. We have two questions.

First, they write that depression of the ascending reticular activating system leads to block of thalamo-cortico-thalamo-cortical reverberations and perception (γ decrease) in their hypothesis of step 4. Actually, a number of recent articles have suggested that γ waves generated by the neocortex and thalamus may be responsible for perception and consciousness.² However, as to the thalamo-cortico-thalamo-cortical reverberations, it would not be blocked even at the surgical level of anesthesia. At the surgical level of anesthesia, the spindle wave, whose rhythm is generated by thalamic reticular nuclei and thalamo-cortico-thalamo-cortical reverberations,^{3,4} becomes dominant in isoflurane, sevoflurane, or propofol anesthesia. We previously reported that quadratic phase coupling was significantly increased during isoflurane or sevoflurane anesthesia,⁵ and that was caused by some specific rhythm source that dominates both hemispheres.⁶ In this point of view, we think that blocking of thalamo-cortico-thalamo-cortical reverberations would not always be included in the “anesthetic cascade.”

Second, they showed changes of the power spectrum at several stages of anesthesia. In their data, δ power at loss of consciousness was much greater than that at just before recovery of consciousness and even greater than that at maintenance of anesthesia. This would be quite strange, because the physiologic state just after loss of consciousness would be the same as that just before recovery of consciousness. Large δ waves are often observed transiently when intravenous anesthetic, such as propofol or thiopental, is administered as a bolus. But such electroencephalographic change is not observed when the concentration of anesthetic is gradually increased. We speculate the emergence of large δ waves are caused by inhomogeneous distribution of anesthetic in the brain and would not reflect the level of consciousness

adequately. Actually, a large δ wave is sometimes observed when intense noxious stimuli is added under a certain level of anesthesia, which is known as the “paradoxical arousal” phenomenon.⁷ In such a situation, we could not estimate the level of consciousness from the electroencephalogram. Finally, we should take the speed of drug administration into account to investigate the relation between level of consciousness and electroencephalographic changes.

Satoshi Hagihira, M.D., Ph.D.,* Masaki Takashina, M.D., Takahiko Mori, M.D., Takashi Mashimo, M.D., Ph.D. *Osaka University Graduate School of Medicine, Osaka, Japan. hagihira@masui.med.osaka-u.ac.jp

References

1. John ER, Pritchep L: The anesthetic cascade: A theory of how anesthesia suppress consciousness. *ANESTHESIOLOGY* 2005; 102:447–71
2. Gottesmann C: Neurophysiological support of consciousness during waking and sleep. *Prog Neurobiol* 1999; 59:469–508
3. Steriade M, Nunez A, Amzica F: Intracellular analysis of relations between the slow (<1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *J Neurosci* 1993; 13:3266–83
4. Steriade M, Contreras D, Dossi RC, Nunez A: The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: Scenario of sleep rhythm generation in interacting thalamic and neocortical networks. *J Neurosci* 1993; 13:3284–99
5. Hagihira S, Takashina M, Mori T, Mashimo T, Yoshiya I: Changes of electroencephalographic bicoherence during isoflurane anesthesia combined with epidural anesthesia. *ANESTHESIOLOGY* 2002; 97:1409–15
6. Hagihira S, Takashina M, Mori T, Mashimo T: Bispectral analysis really gives us more information than power spectral-based analysis. *Br J Anaesth* 2004; 92:772–3
7. Bischoff P, Kochs E, Droese D, Meyer-Moldenhauer WH, Schulte am EschJ: Topographic-quantitative EEG-analysis of the paradoxical arousal reaction: EEG changes during urologic surgery using isoflurane/N2O anesthesia. *Anaesthesist* 1993; 42:142–8

(Accepted for publication June 21, 2005.)

In Reply:—We appreciate Professor Antkowiak’s thoughtful disagreement with the mechanism we propose for how anesthesia suppresses consciousness.¹ Professor Antkowiak concludes that “the anesthetic cascade” explains anesthesia by a bottom-up process, criticizes assumptions we did not make, and provides examples of anesthetic effects at various brain levels to rebut what he perceives as our unitary theory of anesthetic action. We contend that consciousness is produced by a resonance binding together a phase-locked ensemble of oscillations linking spatially dispersed thalamocortical loops. Anesthetic agents act by blocking this resonance, which is constructed by a neurophysiologic process engaging brainstem, thalamic, limbic, and cortical regions. To describe this as a bottom-up unitary process is a misperception.

Professor Antkowiak asserts that the “statement that anesthetic-induced sedation and amnesia are causally related to a decreased concentration of acetylcholine in the brain is not backed by experimental evidence”; however, we made no such assertion in our article. Rather, we summarized previous work suggesting: (1) that cholinergic influences from the ascending reticular activating system diminish hyperpolarizing influences of γ -aminobutyric acid-mediated reticular nucleus neurons and facilitate throughput to the cortex; (2) that a circulating flow of activation between the ascending reticular activating system, the intralaminar nuclei, and the cortex may be necessary for the state of consciousness; (3) that

acetylcholine receptors are probably irrelevant to how inhaled anesthetics achieve immobility; (4) that interconnections by gap junctions are critically dependent on cholinergic action; and (5) that common regional effects of halothane and isoflurane were a significant reduction of regional cerebral glucose metabolic rate utilization in the cuneus, thalamus, midbrain reticular formation, dorsolateral prefrontal cortex, medial frontal gyrus, inferior temporal gyrus, cerebellum, and occipital cortex. This and other evidence was interpreted to indicate that loss of consciousness may be due to four possible mechanisms or a combination thereof: (1) direct hyperpolarizing effects on thalamic and cortical cell membrane potentials;² (2) suppression of midbrain/pontine areas involved with regulating arousal, removing excitatory inputs to the TC-CT loops by inhibiting glutamatergic and cholinergic neurotransmission;³ (3) depression of cortical activity; or (4) complex γ -aminobutyric acid-mediated inhibitory effects in the limbic system.

Our article further reviewed physiologic evidence that perception depended on the coincidence at the cortical level between exogenous, sensory specific input of information about the environment and endogenous, nonsensory specific readout from a representational system encoding memories of the relevant past. We proposed a detailed mechanism whereby exogenous and endogenous fragments of percepts are linked by pyramidal neurons serving as coincidence detec-

tors, resulting in spatially extensive γ oscillations. Coherent cortico-thalamic discharge of dispersed synchronized populations of cortical pyramidal neurons, and the resulting back-propagation from those neurons whose thalamocortical exogenous and endogenous projections resulted in coincidence detection, may bind these fragments together into a unified resonating system, which is the perceptual content of consciousness. We proposed that just as the functions of binding dispersed elements of sensation into a unified perception provide the framework for integrating multiple simultaneous processes into a unified conscious experience, so might a paradigm of unbinding provide a framework for understanding the actions that underlie anesthesia. We reviewed evidence that supports the concept of cognitive unbinding as a final common mechanism for anesthesia, occurring at many different levels ranging from convergence at the cellular level to interruption of synchronization within an ensemble assembling dispersed fragments of information within a system to binding the state of many systems into conscious awareness, and reversing the elements of brain interactions that produce cognitive binding.

We proposed that the neurophysiologic effects that produce amnesia and loss of awareness due to the action of anesthetics occur in six steps: step 1: depression of the brainstem reduces the influences of the ascending reticular activating system on the thalamus and cortex; step 2: depression of mesolimbic-dorsolateral prefrontal cortex interactions leads to blockade of memory storage; step 3: further depression of the ascending reticular activating system releases its inhibition of nucleus reticularis of the thalamus, resulting in closure of thalamic gates (especially in the diffuse projection system) by hyperpolarizing γ -aminobutyric acid-mediated inhibitory action of n. reticularis (θ increase), thereby blocking step 4: thalamo-cortical-thalamo-cortical reverberations and perception (γ decrease), so that step 5: parietal-frontal transactions are uncoupled (γ coherence decreases), blocking cognition, and step 6: prefrontal cortex is depressed to reduce awareness (increase of frontal δ and θ).

Steps 1-6 are arranged in a sequence that corresponds to their sequential activation and thus constitute a "cascade." These steps are different stages of a process. The process can be initiated at any stage and ripple through the system. Our article pointed out very explicitly, "Although one may consider these six steps as a hierarchical sequence, it must be kept in mind that reciprocal pathways interconnect all of the neuroanatomical structures engaged in this cascade. There are many ways that amnesia and blockade of awareness can be accomplished." We then enumerated many ways in which disruption may occur at any level in the process. Effects initiated at any level of the system rapidly propagate both upward and downward through the brain to modulate other parts of this interactive network. There is no unique neuroanatomical structure at which action is both necessary and sufficient for an agent to accomplish modulation of the level of awareness, because this depends on the integrity of the system as a whole.

We have no disagreement with the evidence that Professor Antkowiak presents, but in spite of the provocative title of his critique, we do not find it relevant to our central proposal: Anesthetics act by disrupting resonance among oscillations binding together processes at many levels of the brain.

Professor Hagihira *et al.* state that blocking of T-C-T-C reverberations is not always included in the anesthetic cascade. They infer this based on their observation that peak bicoherence (pBIC) values, measured from the electroencephalogram recorded from a single electrode derivation (FP1-A1) in the frequency range from $2 < f < 15$ Hz, increased

in two regions: pBIC-high appeared in the 7- to 14-Hz frequency range, which is the frequency range of the spindle wave, and pBIC-low appeared around 4 Hz, the frequency of the δ wave (conventionally called θ). They cite evidence by other workers that indicates that spindle waves arise from thalamo-cortico-thalamic circuits and the δ rhythm is the intrinsic rhythm of thalamocortical neurons. On this basis, they assume that nonlinear modulation among the spindle waves and the δ waves in the thalamus account for their observations.

Inferences drawn from measures of bicoherence in low frequency ranges are not relevant to the discussion. Our theory proposes that anesthetic action disrupts resonance among phase-locked thalamocortical and corticocortical oscillations in the γ frequency range (around 40 Hz). We cite a body of evidence that such oscillations are generated by coincidence detection of congruent inputs to apical dendrites in layer 1 and basal dendrites in layer 4 of cortical pyramidal neurons. We also cite our own evidence based on direct computations of interactions among all 19 electrodes in the 10/20 system, not only on inferences drawn from only one lead. We found that cortical-cortical coherence of all electroencephalographic frequency bands including γ is disrupted on loss of consciousness, and such incoherence is sustained at surgical plane, but only in the γ band is coherence restored before return of consciousness. Finally, although we believe that blockade of thalamocortical reverberations plays a dominant role in the action of anesthetics, the cascade theory suggests that consciousness can be disrupted by actions at many levels.

Second, they point out that in our data, δ activity is greater at loss of consciousness than during maintenance or just before return of consciousness and argue that the physiologic state just after loss of consciousness would be the same as just before return of consciousness. They point out correctly that such large δ is seen when anesthesia is induced by bolus administration of intravenous anesthetic. Although this was the case in all of the cases reported in our study, our report documented the changes in θ rather than δ .

They are quite correct that speed of administration must be taken into account when investigating the correlation between level of consciousness and electroencephalographic changes. Contemporary quantitative electroencephalographic instruments widely used to monitor the depth of anesthesia, such as the Patient State Analyzer (PSA[®] monitor; Physiometrix, Inc., N. Billerica, MA) or Bispectral Index[®] monitor (Aspect Medical, Newton, MA), are based on multivariate algorithms that do not depend on any single measure, such as the presence or amplitude of δ activity.

E. Roy John, Ph.D.,* Leslie S. Prichep, Ph.D. *New York University School of Medicine, New York, New York, and Nathan S. Kline Psychiatric Research Institute, Orangeburg, New York. roy.john@med.nyu.edu

References

1. John ER, Prichep LS: The anesthetic cascade: A theory of how anesthesia suppresses consciousness. *ANESTHESIOLOGY* 2005; 102:447-71
2. Sugiyama K, Muteki T, Shimoji K: Halothane-induced hyperpolarization and depression of post-synaptic potentials of guinea pig thalamic neurons in vitro. *Brain Res* 1992; 576:97-103
3. Violet JM, Downie DL, Nakisa RC, Lieb WR, Franks NP: Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics. *ANESTHESIOLOGY* 1997; 86:866-74

(Accepted for publication June 21, 2005.)

What's Old in Obstetric Anesthesia?

To the Editor:—We read with interest the recent Special Article entitled "Gerard W. Ostheimer 'What's New in Obstetric Anesthesia' Lec-

ture."¹ As proponents of blood conservation, we were particularly interested in the obstetric hemorrhage section of the article. We found

it curious that the author stressed the use of interventional radiology, darbepoetin, Sengstaken-Blakemore esophageal balloon catheters, and recombinant factor VIIa in the management of obstetric hemorrhage. Advocacy for these techniques is supported by single case reports, whereas therapies such as cell salvage or intravenous iron are given little attention.

In the special article, it is reported that 2-3 units of blood can be obtained from cell salvage. In fact, much more can be returned to the patient when the users of the equipment have a sound understanding of the parameters that influence cell salvage efficiency. The safety of cell salvage has been questioned, but there are approximately 390 reports in the literature of cell salvage being used safely.²⁻⁴ All known components of amniotic fluid can be removed from shed blood to a concentration equivalent to what is circulating in the maternal circulation.⁵ A recent editorial in the *British Journal of Obstetrics and Gynaecology* argued that the time has come to accept cell salvage as a safe modality.⁶ It seems unreasonable to argue for the use of recombinant factor VIIa, a drug with a cost of approximately \$4,000/dose, based on a single case report and spurn a technology such as cell salvage, where the overwhelming body of evidence suggests safety.

The author argues for the use of darbepoetin, a long-acting form of erythropoietin, but no data exists to support its use in this setting. It is even questionable whether erythropoietin has a role in obstetrics because endogenous erythropoietin concentrations are increased to 2-4 times normal. In general, obstetric patients are iron deficient. Endogenous erythropoietin concentrations seem to be correlated with the degree of iron deficiency.⁷ We would argue that the appropriate method of increasing erythrocyte mass in obstetric patients is through the use of intravenous iron therapy alone. In the hematology practice of one of the authors of this letter (P. F.), pregnant Jehovah's Witnesses have been treated with intravenous iron or intravenous iron combined with erythropoietin. Intravenous iron resulted in a mean increase in hemoglobin of 2.36 g/dl (n = 32), whereas the combination of intravenous iron and exogenous erythropoietin resulted in a mean increase of 2.23 g/dl (n = 18). In the Special Article, the implication is made that erythropoietin may be a causative agent for preeclampsia. Based

on this caution, it seems that the most appropriate method of increasing erythrocyte mass is through iron supplementation.

We also question the role of interventional radiology. Intraarterial balloon catheters require a catheterization laboratory and an interventional radiologist. A significant percentage of obstetric hemorrhage occurs unexpectedly and at hours when interventional radiologists are typically not available. Many reports of this treatment modality record significant transfusion needs for patients with these catheters, raising the question as to how useful the catheters are.

Perhaps cell salvage and supplemental iron do not have the glamour of interventional radiology, darbepoetin, Sengstaken-Blakemore esophageal balloon catheters, and recombinant factor VIIa, but they seem to be far more effective and less costly than these newer techniques. So, we suggest that "What's old in obstetric anesthesia?" should be the answer when addressing obstetric hemorrhage.

Jonathan H. Waters, M.D.,* Patricia Ford, M.D. *University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania. watejh@upmc.edu

References

1. Tsen LC; Gerard W, Ostheimer "What's New in Obstetric Anesthesia" Lecture. *ANESTHESIOLOGY* 2005; 102:672-9
2. Rainaldi MP, Tazzari PL, Scagliarini G, Borghi B, Conte R: Blood salvage during caesarean section. *Br J Anaesthesia* 1998; 80:195-8
3. Grimes DA: A simplified device for intraoperative autotransfusion. *Obstet Gynecol* 1988; 72:947-50
4. Jackson SH, Lonser RE: Safety and effectiveness of intracasean blood salvage. (letter). *Transfusion* 1993; 33:181
5. Waters JH, Biscotti C, Potter P, Phillipson E: Amniotic fluid removal during cell-salvage in the caesarean section patient. *ANESTHESIOLOGY* 2000; 92:1531-6
6. Catling JS: Cell salvage in obstetrics: The time has come. *Br J Obstet Gynaecol* 2005; 112:131-2
7. Perewusnyk G, Huch R, Huch A, Breyman C: Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. *Br J Nutr* 2002; 88:3-10

(Accepted for publication July 7, 2005.)

Anesthesiology 2005; 103:908-9

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

In Reply:—

"Those who stare at the past have their backs turned to the future."

—Anonymous

I thank Drs. Waters and Ford for an additional opportunity to share the legacy of Gerard Ostheimer and highlight the purpose of the "What's New in Obstetric Anesthesia" lecture given in his honor at Annual Meeting of the Society for Obstetric Anesthesia and Perinatology. The lecture and accompanying articles in *ANESTHESIOLOGY*¹ and the *International Journal of Obstetric Anesthesia*² serve as a review of published literature from the preceding calendar year relevant to clinical care and research in the obstetric patient. Although the *ANESTHESIOLOGY* article provides a more focused look at a few subtopics, the overall premise is to feature new and novel concepts, techniques, and advances in understanding.

Recombinant factor VIIa, interventional radiology embolization, and Sengstaken-Blakemore esophageal balloon catheters in the management of obstetric hemorrhage are modalities that can be described as both new and novel; more importantly, each represents a potentially lifesaving intervention for which there is growing literature support. Of note, although Drs. Waters and Ford are advocates for the controversial use of cell salvage in the obstetric setting,^{3,4} I am not aware of any published reports where cell salvage has been able to successfully reverse clinical disseminated intravascular coagulation, as has been reported with recombinant factor VIIa,⁵⁻⁷ or stop postpartum hemorrhaging from specific uterine vessels, as witnessed with interventional radiology

procedures,^{8,9} and from diffuse intrauterine vessels, as observed with Sengstaken-Blakemore esophageal balloon catheters.^{10,11} Within the past 6 months, I have personally witnessed the successful reversal of disseminated intravascular coagulation with recombinant factor VIIa in two hemorrhaging obstetric patients and the avoidance of three gravid hysterectomies through the involvement of interventional radiology.

Drs. Waters and Ford misinterpret the level of support given to erythropoietin and darbepoetin, a hyperglycosylated analog, in obstetric patients. Indeed, the limited understanding of erythropoietin has been properly framed in the original article, and further investigations will be needed. Clearly, the induction of erythrocyte production through endogenous or exogenous erythropoietin during pregnancy is a complex riddle that will require robust analyses into the influences of iron, serum ferritin, transferrin, and hormones such as estradiol.¹²

It is interesting that all of the modalities cited above are finding increased validation in clinical practice. Although further investigations are necessary, even with cell-saver technologies, the introduction of new concepts and modalities for investigators and clinicians is vital to the practice of anesthesia. The value of many "old" modalities in the control of obstetric hemorrhage should be acknowledged; however, the most appropriate and specific interventions may not currently be known, and for these situations, an acceptance of what is "new and novel" may be the difference between life and death.

Lawrence C. Tsen, M.D., Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts. ltsen@zeus.bwh.harvard.edu

References

1. Tsen LC, Gerard W. Ostheimer "What's New in Obstetric Anesthesia" Lecture. *ANESTHESIOLOGY* 2005; 102:672-9
2. Tsen LC: What's new and novel in obstetric anesthesia? Contributions from the 2003 scientific literature. *Int J Obstet Anesth* 2005; 14:126-46
3. Weiskopf RB: Erythrocyte salvage during cesarean section. *ANESTHESIOLOGY* 2000; 92:1519-22
4. Camann W: Cell salvage during cesarean delivery: Is it safe and valuable? Maybe, maybe not! *Int J Obstet Anesth* 1999; 8:75-6
5. Tanchev S, Platikanov V, Karadimov D: Administration of recombinant factor VIIa for the management of massive bleeding due to uterine atonia in the post-placental period. *Acta Obstet Gynecol Scand* 2005; 84:402-3
6. Ahonen J, Jokela R: Recombinant factor VIIa for life-threatening postpartum haemorrhage. *Br J Anaesth* 2005; 94:592-5
7. Lim Y, Loo CC, Chia V, Fun W: Recombinant factor VIIa after amniotic fluid embolism and disseminated intravascular coagulopathy. *Int J Gynaecol Obstet* 2004; 87:178-9

8. Chung JW, Jeong HJ, Joh JH, Park JS, Jun JK, Kim SH: Percutaneous transcatheter angiographic embolization in the management of obstetric hemorrhage. *J Reprod Med* 2003; 48:268-76

9. Hansch E, Chitkara U, McAlpine J, El-Sayed Y, Dake MD, Razavi MK: Pelvic arterial embolization for control of obstetric hemorrhage: A five-year experience. *Am J Obstet Gynecol* 1999; 180:1454-60

10. Ferrazzani S, Guariglia L, Caruso A: Therapy and prevention of obstetric hemorrhage by tamponade using a balloon catheter [in Italian]. *Minerva Ginecol* 2004; 56:481-4

11. Japaraj RP, Raman S: Sengstaken-Blakemore tube to control massive postpartum haemorrhage. *Med J Malaysia* 2003; 58:604-7

12. Horiguchi H, Oguma E, Kayama F: The effects of iron deficiency on estradiol-induced suppression of erythropoietin induction in rats: Implications of pregnancy-related anemia. *Blood* 2005; 106:76-4

(Accepted for publication July 7, 2005.)

Anesthesiology 2005; 103:909

© 2005 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Acquired Carnitine Deficiency: A Clinical Model for Propofol Infusion Syndrome?

To the Editor:—Propofol toxicity, known as *propofol infusion syndrome*, has been described in both critically ill children¹ and adults² undergoing long-term high-dose propofol infusion. Although the exact mechanisms are not clearly defined, recent reports suggest its association with impaired fatty acid oxidation and mitochondrial respiratory dysfunction.³ Because propofol is dissolved in a lipid vehicle (0.1g/ml lipid consisting of mainly long-chain fatty acids), lipid infusion alone might yield similar derangement of fatty acid oxidation and share the common features of propofol infusion syndrome. Particularly when combined with the presence of carnitine deficiency, lipid overload may disturb fatty acid oxidation because carnitine is an essential cofactor in the transport of long-chain fatty acids into mitochondria.

We recently encountered a 34-yr-old woman said to be "allergic to fat emulsion" who was undergoing hepatectomy for hepatocellular carcinoma. Her medical record revealed that infusion of fat emulsion was temporally associated on two occasions with acute symptoms of a Reye-like syndrome. She underwent excision of a choledochal cyst as a child, which subsequently required pancreatoduodenectomy and partial gastrectomy. At 19 yr of age, she was hospitalized for persistent vomiting and poor oral intake for nutritional support. A few hours after administration of 200 ml fat, she became agitated and disoriented and finally lost consciousness. Before this, she had received no medication. No abnormalities were noted in the cerebrospinal fluid, in urinary toxicology screening, or on computed tomography of the brain. The next day, she had development of metabolic acidosis and hepatomegaly. Liver biopsy revealed microvesicular fatty accumulation, which led to a provisional diagnosis of Reye-like syndrome. She underwent hemofiltration, which resulted in rapid recovery from neurologic and hepatic dysfunction and acidemia. At follow-up examination, the patient made a full recovery, and inherited metabolic disorders resembling Reye syndrome were ruled out. Ten years later, she was rehospitalized for nutritional support. Again, she became acutely confused and hallucinated during fat emulsion administration. Hemofiltration quickly normalized her clinical and laboratory findings. The abnormal acylcarnitine profiles in her urine specimen during this episode made us suspect that she had an underlying acquired carnitine deficiency due to poor oral intake during these two episodes.

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

These observations of very similar clinical scenarios on different occasions led to the hypothesis that acute fat burden in the setting of inadequate delivery of carbohydrate and acquired carnitine deficiency may impair fatty acid oxidation, leading to the conditions similar to those seen in mitochondrial β oxidation defects. In this regard, lipid infusion alone may cause impaired β oxidation and, if severe enough, may lead to clinical conditions mimicking propofol infusion syndrome. Like our patient, clinical signs of acute impaired β oxidation often begin with acute neurologic symptoms. These early signs may be masked by the sedative effect of propofol, and severe signs of cellular hypoxia from mitochondrial respiratory dysfunction may manifest as a propofol infusion syndrome (metabolic acidosis and multiple organ failure) in its late stage. Patients in the intensive care unit tend to have development of acquired carnitine deficiency from various etiologies, including impaired biosynthesis of carnitine due to cirrhosis or chronic renal failure, malabsorption syndrome, increased excretion from the urine due to renal tubular acidosis, and iatrogenic causes such as concomitant use of valproate.⁴ Early recognition of inadequate carbohydrate intake and risk factors of acquired carnitine deficiency as well as close monitoring of subclinical β oxidation impairment may prevent development of propofol infusion syndrome when a large amount of propofol infusion is used.

Shoichi Uezono, M.D.,* Yukako Hotta, M.D., Yuichi Takakuwa, M.D., Ph.D., Makoto Ozaki, M.D., Ph.D. *Jikei University, Tokyo, Japan. uezono@jikei.ac.jp

References

1. Bray RJ: Propofol infusion syndrome in children. *Paediatr Anaesth* 1998; 8:491-9
2. 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
3. Wolf A, Weir P, Segar P, Stone J, Shield J: Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet* 2001; 357:606-7
4. Evangeliou A, Vlassopoulos D: Carnitine metabolism and deficit—when supplementation is necessary? *Curr Pharm Biotechnol* 2003; 4:211-9

(Accepted for publication May 17, 2005.)

Rheumatoid Arthritis: A Significant but Often Underestimated Risk Factor for Perioperative Cardiac Morbidity

To the Editor:—Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology. Patients with RA are recognized to have a reduced life expectancy when compared with the general population. Cardiovascular death is a leading cause of mortality in patients with RA; it is responsible for approximately half of the deaths observed in RA cohorts.¹ Identification of high-risk patients is often difficult because of the frequent absence of traditional cardiac risk factors.^{2,3} We report the case of a patient with long-standing RA who had development of an acute myocardial infarction (MI) in the early postoperative period after multilevel cervical stabilization surgery. We outline the possible etiology of coronary artery disease (CAD) in patients with RA and highlight this important but often overlooked risk factor for perioperative MI.

A 56-yr-old woman was referred for surgical management of two-level cervical spondylosis. She had a background history of severe long-standing RA, requiring regular use of nonsteroidal antiinflammatory agents and oral morphine sulfate. The patient was not a smoker and had no personal or family history of ischemic heart disease. Preoperative anesthetic assessment did not reveal any symptoms or signs of cardiovascular disease. An electrocardiogram showed normal sinus rhythm, with no evidence of myocardial ischemia. Anesthesia was induced and maintained using sevoflurane in an air-oxygen mixture. In addition to routine monitoring of the electrocardiogram, non-invasive blood pressure, and oxygen saturation, peripheral arterial and central venous catheters were inserted for invasive hemodynamic monitoring. The surgical procedure was uneventful, and the patient remained hemodynamically stable throughout. Postoperatively, she was transferred to the intensive care unit for continued ventilation and invasive monitoring. Three hours after surgery, she had development of a sinus tachycardia of 150 beats/min, which was successfully treated with intravenous metoprolol. Twelve hours after surgery, the patient's trachea was extubation uneventfully. On the second postoperative day, 33 h after surgery, her condition deteriorated abruptly, with acute onset of tachycardia, dyspnea, and oxygen desaturation. At this time, an electrocardiogram revealed atrial fibrillation with ST-segment elevation in both inferior and anterior chest leads. Acute MI was confirmed by an increased troponin concentration of 0.27 $\mu\text{g/l}$ (reference range $\leq 0.01 \mu\text{g/l}$) and transthoracic echocardiogram, which showed inferior and apical hypokinesia. After a thorough discussion of benefit versus risk of therapy, systemic thrombolysis was administered. There were no complications associated with the thrombolytic therapy. The patient subsequently made an uneventful recovery, without any further cardiac or neurologic complications. A coronary angiogram performed 10 weeks later did not reveal significant coronary artery stenosis. At 6 months' follow-up, the patient remains well and continues β -blockade therapy.

Rheumatoid arthritis is a chronic inflammatory disease of unknown etiology, associated with long-term disability and a requirement for frequent anesthesia for orthopedic operative interventions. Patients with RA have a reduced life expectancy associated with extraarticular systemic comorbidities.^{3,4} Several recent large epidemiologic studies have found significantly increased cardiovascular mortality in RA patients as compared with age- and sex-matched controls.^{2,5} Women who had a history of RA of longer than 10 yr were found to be at significantly increased risk of fatal and nonfatal MI.^{6,7} The major independent risk factors for CAD include cigarette smoking, hypertension, diabetes, increased serum cholesterol, family history of CAD, and advanced age.⁸

However, it is being increasingly recognized that traditional risk factors for CAD do not wholly explain the high incidence of cardiovascular events in patients with RA.⁹ Standard clinical assessment may underestimate the prevalence of comorbid CAD in RA.¹⁰ Assessment of traditional risk factors was negative in this patient.

Although frequently due to coronary atherosclerosis, MI occurring in RA may arise due to coronary artery vasculitis with associated thrombosis, in the absence of coronary atheroma.^{11,12} There is accumulating evidence of accelerated atherogenesis occurring in systemic inflammatory diseases such as RA and systemic lupus erythematosus,^{13,14} raising the possibility that RA and atherosclerosis share common pathogenic mechanisms. Preliminary evidence suggests that inflammatory mediators such as C-reactive protein, interleukins, and tumor necrosis factor play a major role in this process.^{13,15,16} Coronary angiography performed in our patient 10 weeks postoperatively did not show evidence of significant coronary atheroma, raising the possibility of coronary arteritis being a significant factor in the etiology of MI in this case.

In addition to inflammatory mechanisms, drug therapy may increase susceptibility to development of atherosclerosis in patients with RA. Corticosteroids have a recognized atherogenic effect.¹⁷ Homocysteine, a novel factor recently associated with atherothrombosis, is increased in patients with RA.¹⁸ Long-term use of methotrexate induces increased homocysteine concentrations, possibly further increasing the risk of atherosclerosis.¹⁹ It has been suggested that "novel cardiovascular risk factors," including increased homocysteine concentrations, and inflammatory markers, such as C-reactive protein, may be more reliable indicators of increased risk of cardiovascular morbidity in RA than traditional cardiac risk factors.¹

In summary, we report an acute MI occurring in the early postoperative period, after uneventful anesthesia, in a patient with long-standing RA and no other traditional risk factors for cardiac disease. The high prevalence of coexisting CAD in patients with long-standing RA, coupled with the lack of consistent association with traditional cardiac risk factors, and the frequent occurrence of silent disease highlight the importance of maintaining a high index of suspicion for increased risk of perioperative myocardial ischemia in these patients. Anesthetic management of patients with long-standing RA should therefore include careful preoperative evaluation for CAD, appropriate intraoperative hemodynamic monitoring and risk-reducing strategies, and vigilant cardiac monitoring in the early postoperative period.

Eilish M. Galvin, F.C.A.R.C.S.I.,* Dermot O' Donnell, F.C.A.R.C.S.I., Irene E. Leonard, F.F.A.R.C.S.I. *Beaumont Hospital, Dublin, Ireland. eilishgalvin@hotmail.com

References

1. Goodson N: Coronary artery disease and rheumatoid arthritis. *Curr Opin Rheumatol* 2002; 14:115-20
2. del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A: High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44:2737-45
3. Allebeck P: Increased mortality in rheumatoid arthritis. *Scand J Rheumatol* 1982; 11:81-6
4. Mutru O, Laakso M, Isomaki H, Koota K: Ten year mortality and causes of death in patients with rheumatoid arthritis. *BMJ (Clin Res Ed)* 1985; 290:1797-9.
5. Watson DJ, Rhodes T, Guess HA: All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. *J Rheumatol* 2003; 30:1196-202
6. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE,

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

- Stampfer MJ, Curhan GC: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003; 107:1303-7
7. Myllykangas-Luosujarvi R, Aho K, Kautiainen H, Isomaki H: Cardiovascular mortality in women with rheumatoid arthritis. *J Rheumatol* 1995; 22:1065-7
8. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97:1837-47
9. Bacon PA, Stevens RJ, Carruthers DM, Young SP, Kitas GD: Accelerated atherogenesis in autoimmune rheumatic diseases. *Autoimmun Rev* 2002; 1:338-47
10. McEntegart A, Capell HA, Creran D, Rumley A, Woodward M, Lowe GD: Cardiovascular risk factors including thrombotic variables in a population with rheumatoid arthritis. *Rheumatology (Oxford)* 2001; 40:640-4
11. Takayanagi M, Haraoka H, Kikuchi H, Hirohata S: Myocardial infarction caused by rheumatoid vasculitis: Histological evidence of the involvement of T-lymphocytes. *Rheumatol Int* 2003; 23:315-8
12. Parry G, Goudevenos J, Williams DO: Coronary thrombosis postpartum in a young woman with Still's disease. *Clin Cardiol* 1992; 15:305-7
13. Bacon PA, Raza K, Banks MJ, Townend J, Kitas GD: The role of endothelial cell dysfunction in the cardiovascular mortality of RA. *Int Rev Immunol* 2002; 21:1-17
14. Fischer LM, Schlienger RG, Matter C, Jick H, Meier CR: Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myocardial infarction. *Am J Cardiol* 2004; 93:198-200
15. Manzi S, Wasko MC: Inflammation-mediated rheumatic diseases and atherosclerosis. *Ann Rheum Dis* 2000; 59:321-5
16. Lagrand WK, Visser CA, Hermans WT, Niessen HW, Verheugt FW, Wolbink GJ, Hack CE: C-reactive protein as a cardiovascular risk factor: More than an epiphenomenon? *Circulation* 1999; 100:96-102
17. Stern MP, Kolterman OG, Fries JF, McDevitt HO, Reaven GM: Adrenocortical steroid treatment of rheumatic diseases: Effects on lipid metabolism. *Arch Intern Med* 1973; 132:97-101
18. Roubenoff R, Dellaripa P, Nadeau MR, Abad LW, Muldoon BA, Selhub J, Rosenberg IH: Abnormal homocysteine metabolism in rheumatoid arthritis. *Arthritis Rheum* 1997; 40:718-22
19. Haagsma CJ, Blom HJ, van Riel PLCM: Influence of sulphasalazine, methotrexate, and the combination of both on plasma homocysteine concentrations in patients with rheumatoid arthritis. *Ann Rheumatic Dis* 1999; 58:79-84

(Accepted for publication May 23, 2005.)