

Anesthesiology 2008; 109:353

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Intraoperative Hypothermia and Blood Loss: Are Antifibrinolytic Exposure and Variations in Anesthetic Technique Possible Confounders?

To the Editor:—I read with great interest the excellent article by Dr. Rajagopalan *et al.*¹ detailing their meta-analysis to investigate the relation between mild perioperative hypothermia, blood loss, and transfusion. Their analysis demonstrated that mild hypothermia increases blood loss by approximately 16% and increases the risk for transfusion by approximately 22%.

My first question to the authors is whether perioperative antifibrinolytic exposure has confounded the results of the meta-analysis. For example, tranexamic acid was used in the one cardiac study that did not show increased blood loss or transfusion due to hypothermia.² Was antifibrinolytic therapy a major confounder across studies included in the meta-analysis? Does antifibrinolytic exposure explain the studies that documented no increased bleeding or transfusion risk due to mild hypothermia?

My second question to the authors is whether these negative studies are confounded by hemostatic variations in anesthetic technique, such as induced hypotension and/or regional anesthesia.^{3,4}

I congratulate Dr. Rajagopalan *et al.* on their excellent article that has further highlighted the importance of perioperative euthermia. I look forward to their comments.

John G. T. Augoustides, M.D., F.A.S.E., Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. yiandoc@hotmail.com

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(Accepted for publication April 22, 2008.)

Anesthesiology 2008; 109:353

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In Reply:—Dr. Augoustides asks whether antifibrinolytic use confounded our conclusion that even mild hypothermia significantly increases blood loss and transfusion requirement.¹ Among the studies included in our meta-analysis and as specified in the original publications, antifibrinolytic therapy was used in but one. Specifically, Nathan *et al.*² gave a 1-g bolus of tranexamic acid after induction, followed by 2 mg · kg⁻¹ · h⁻¹ intraoperatively. Because identical doses were used in the normothermic and hypothermic groups, antifibrinolytic use was not a confounding factor.

Similarly, all studies included in our meta-analysis were prospective trials in which thermal management was randomized. Analysis was based on group assignment rather than actual core temperature. Clinical management, whether with regional or general anesthesia, was thus comparable in the randomized groups within each study—again, as specified in the original publications. Induced hypotension was used in only one study, and again, management was comparable in the hypothermic and normothermic groups.³ Consequently, anesthetic management was not a confounding factor either.

Suman Rajagopalan, M.D., Daniel I. Sessler, M.D.* *The Cleveland Clinic, Cleveland, Ohio. ds@or.org

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(Accepted for publication April 22, 2008.)

Anesthesiology 2008; 109:353–4

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Monitoring of the Sublingual Microcirculation in Cardiac Surgery Using Two-dimensional Imaging

To the Editor:—With great interest, we read the article by Bauer *et al.*¹ on sublingual microvascular perfusion in 47 patients who underwent hypothermic cardiopulmonary bypass surgery. The authors report a 10% decrease in functional capillary density during cardiopulmonary bypass without changes in microvascular diameter or erythrocyte velocity. These results are partly in contrast with our recent findings in a comparable setting.²

Although both studies evaluated the sublingual microcirculation by a two-dimensional imaging technique, several differences do exist, of

which the imaging technique itself and the subsequent way of analysis are most important. To understand the different results more comprehensively, we would like to comment on several aspects of the study by Bauer *et al.*

First, we used side-stream dark-field imaging, a novel technology based on the orthogonal polarization spectral imaging technique used by the authors. Side-stream dark-field imaging differs from orthogonal polarization spectral technology in terms of magnification and capillary contrast. These differences between the two-dimensional imaging

techniques hinder comparison of results obtained by orthogonal polarization spectral *versus* side-stream dark-field imaging and may explain the differential results. Second, the authors used software to measure microvascular diameter, erythrocyte velocity, and functional capillary density. In our study, a semiquantitative analysis technique was used. Although software can be helpful in decreasing the burden of a time-consuming semiquantitative analysis, we have to look critically at the numbers produced by the software. For example, we would like to learn from the authors whether it was possible to measure erythrocyte velocity in each investigated capillary and venule. Using Microscan Analysis Software (MicroVisionMedical, Inc., Amsterdam, The Netherlands), we experienced that it was impossible to measure high erythrocyte velocities that do exist in a substantial number of capillaries. This problem is probably due to a limited video frame rate: 25 frames/s for phase alternating line standard. Finally, several issues remain unclear after reading the authors' article. The inclusion criteria used by the authors are not exactly mentioned. Did the authors investigate consecutive, low-risk patients? What was the estimated risk of surgery for the patient population (logistic European System for Cardiac Operative Risk Evaluation [EuroSCORE])? What were the incidences of postoperative morbidity and mortality? We think it might be interesting to investigate a possible relation between intraoperative hypoperfusion of the microcirculation and postoperative outcome. This might be studied in a subgroup of patients with impaired functional capillary density during cardiopulmonary bypass. In addition to this, we wonder why the authors did not separate venules from capillaries, using a cutoff of 20 μm .

To conclude, it is of interest to note that both studies reported

moderate changes in the sublingual microcirculation that probably reflect a complex pathophysiology during cardiopulmonary bypass. It is expected that novel bedside imaging technology will simplify further microcirculation research in patients based on studies that were performed previously in laboratory animals.^{3,4} We should focus on the questions of which individual stimuli are responsible for the reported changes and whether these changes are of clinical significance. Larger studies, perhaps in high-risk patients, would be helpful to draw stronger conclusions.

Corstiaan A. den Uil, M.D.,* Eva Klijn, M.D., Jasper J. Brugts, M.D., M.Sc., Wim K. Lagrand, M.D., Ph.D., Peter E. Spronk, M.D., Ph.D. *Erasmus Medical Center, Rotterdam, The Netherlands. c.denuil@erasmusmc.nl

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(Accepted for publication April 22, 2008.)

Anesthesiology 2008; 109:354–5

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In Reply:—We appreciate the interest of Dr. den Uil *et al.* in our article¹ and thank the authors for their comments. They refer to their publication² and point out some perceived differences between the studies.

Although the authors mention in their letter that our results are partly in contrast with their own findings using side-stream dark-field imaging during cardiac surgery, we suggest that both studies show rather similar alterations during cardiopulmonary bypass (CPB) for cardiac surgery. We found a transient 10% decrease of functional capillary density during CPB,¹ and den Uil *et al.* reported a reduction of microvascular perfusion index and an increased proportion of patients with impaired flow during CPB that normalizes within the first hours after surgery.²

The authors point out that difference in analysis routine exists: Dr. den Uil *et al.* used a semiquantitative analysis³ to calculate the microvascular flow index, whereas we assessed the microcirculatory parameters of erythrocyte velocity, vessel diameter, and functional capillary density using Cap-image (Dr. Zeintl GmbH, Heidelberg, Germany). We do agree that automatic software to analyze routines must be well selected; however, Cap-image software is extremely well validated and has been frequently used in animal models using intravital microscopy. In the current study, all parameters were analyzed manually: diameter by drawing a vertical straight line from one vessel wall to the other, erythrocyte velocity with the use of a line-shift diagram, and functional capillary density by marking all visual perfused capillaries in a selected video sequence. Moreover, we recently found a good correlation between functional capillary density analyzed with this technique and the procedure described by De Backer *et al.*⁵ giving a correlation coefficient of 0.868 (our unpublished data, May 2007 comparison study of the analysis procedures as used by De Backer *et al.* and our analysis routine). Using this Cap-image diameter and erythrocyte velocity could not be analyzed in all microvessels because in this two-dimensional optical method, not all vessels in one region of interest are in focus. It has been discussed by Lindert *et al.*⁴ that using orthogonal polarization spectral imaging with a European phase alternating line (PAL) video standard,

blood flow velocities can only be measured up to a maximum of approximately 1,000 $\mu\text{m}/\text{s}$, a fact that restricts its use in studies on arteriolar perfusion. In our experience, erythrocyte velocity in venules and capillaries (these are the type of vessels that can be mainly visualized with orthogonal polarization spectral imaging in sublingual tissue) is usually below 1,000 $\mu\text{m}/\text{s}$.

Regarding the patient selection and the inclusion criteria in our study, we indeed selected low-risk, elective patients and excluded any emergency or high-risk procedures. Therefore, postoperative morbidity and mortality were low; however, logistic European System of Cardiac Operative Risk Evaluation (EuroSCORE) was not assessed. We consider this reasonable to establish the normal range of microcirculatory changes during CPB in uncomplicated cases. Of course it would be most relevant to assess any possible relation between intraoperative microvascular hypoperfusion and postoperative outcome. However, it seems sensible to first characterize microcirculatory changes during uncomplicated operations. Although interesting, single case reports on patients with impaired microvascular perfusion during CPB and poor outcome do not substantially increase our knowledge regarding the role of optical methods in microcirculatory monitoring in cardiac surgery.

Finally, although De Backer *et al.* have defined a cutoff at 20 μm for the diameter of small and large microvessels, this will not enable a differentiation between venules and capillaries as suggested by Dr. den Uil *et al.*, because many smaller venules will certainly have diameters lower than 20 μm , especially taking into consideration that orthogonal polarization spectral imaging and the side-stream dark-field technique will contrast erythrocytes only, and this will underestimate vessel diameter by up to 5 μm .⁵

Further studies will have to show whether—as in septic patients—these optical methods are able to predict patients' outcome and can be influenced by therapeutic approaches.

Andreas Bauer, M.D., Frank Christ, M.D.* *Ludwig-Maximilian University Munich, Munich, Germany. frank.christ@med.uni-muenchen.de