Cracking Open the Door on Perioperative Visual Loss

RARE events are nearly impossible to study. There often simply are not enough of them to consolidate into meaningful case series, and information from these scarce occurrences is not sufficient to allow anything except very minimal analyses. Therefore, we are typically left with only conjecture on etiologies that may have prompted the rare events. That conjecture causes all sorts of problems, with "experts" claiming their own versions of potential etiologies and, sad to say, chastising colleagues in medicolegal cases for not providing the experts' theoretical standards of care that would have avoided the rare events. This rare event scenario has been particularly true during the past decade for blindness that develops after spine fusion surgery. Fortunately, in this issue of ANESTHESIOLOGY, The Postoperative Visual Loss Study Group provide us with a novel application of several methodologies that allows them to detect important risk factors for ischemic optic neuropathy (ION) in spine fusion patients and to speculate on potential etiologies of this devastating perioperative complication.

"Until now, there have been no data to support speculation on etiologies of [ischemic optic neuropathy] in this setting."

The authors have taken events in the American Society of Anesthesiologists' Postoperative Visual Loss Registry and used them as cases in a large 1:4 case-control study. In this study, controls were obtained from 17 medical centers that perform large volumes of spine fusion surgery. The blending of a case series (registry) and a multicenter case-control methodology is unique, allowing the authors to develop analyses for risk factors associated with perioperative ION and this type of surgery. The authors were careful in the construction of their methodology. For example, they matched out only one variable: cases and controls had to share the same year of surgery to avoid potential changes in practice over time influencing the outcomes. Their study design did, however, require similar criteria for inclusion; thus, all patients were adults, had anesthetic for longer than or equal to 4 h, and were placed in prone positions for at least a portion of their procedures. These inclusion criteria prevented analyses of several important questions (*e.g.*, odd ratios for prone *vs.* other positions such as lateral or supine in spine fusion surgery) or limited the power of analyses for others (*e.g.*, odd ratios for the full range of anesthetic durations).

While the authors found six risk factors associated with ION in the registry population, half of these strongly support their speculation that acute venous congestion of the optic canal is a potential etiology of ION in this setting. The use of a Wilson surgical bed frame, with its increased curvature resulting in the head being lower than the heart; obesity, with its potential elevation of intra-abdominal pressure in prone-positioned patients; and long anesthetic durations can all contribute to increased venous congestion in the optic canal and potentially reduce optic nerve perfusion pressure. Unfortunately, the study's retrospective methodology did not allow the authors to consider how patient tilt (*e.g.*, head down *vs.* other positions) may have played a role.

The authors also found that increased estimated blood loss, male gender, and lower percent of colloid administration were independently associated with the development of ION after spinal fusion surgery. They offer insights as to how these may or may not be clinically important. Their speculation on why 69% of the blindness cases occurred in men, when there were similar proportions of men and women in the controls who underwent spine fusion surgeries, is partic-

Image: © istockphoto.com.

Accepted for publication October 3, 2011. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2012; 116:1–2

◆ This Editorial View accompanies the following article: The Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. ANESTHESIOLOGY 2012; 116:15–24.

ularly interesting. They note that there is evidence estrogen may provide a neuroprotective effect.

A factor in perioperative neuropathies not studied extensively, but one that the authors tangentially mention in this blindness report, is systemic inflammation. A number of perioperative events trigger significant systemic inflammation and immunosuppression (*e.g.*, venous congestion,[2] blood transfusions,[3] inhaled anesthetics[4]). Until recently, no one linked perioperative neuropathies, including ION, to systemic inflammation. In 2010, however, Staff *et al.*[5] reported on 33 patients with prolonged postoperative ulnar neuropathy. Sural nerve biopsies in 21 of these patients demonstrated epineuronal inflammation. Intensive immunotherapy in 17 of these 21 patients resulted in significant resolution of neurologic impairment ($P < 0.001$). Over time, investigators will have to learn what role, if any, an inflammatory response, either locally or systemically, plays in ION in this setting.

It is ironic that many "experts" in medicolegal cases involving perioperative blindness in spine surgery patients are absolutely sure that they know why these patients develop their vision loss. They often speak of substandard care provided by the defendant anesthesiologist, frequently noting that intraoperative anemia or episodes of hypotension reflect poor anesthetic care. The Postoperative Visual Loss Study Group did not find an independent effect of intraoperative anemia or blood pressure more than 40% below baseline for 30 congruent or additive minutes. Case reports and case series, the only clinical data available on this rare event until the current study, do not provide sufficient data to allow analyses of these two oft-cited intraoperative variables. For now, we can be thankful to the authors that they have provided data that raise doubt as to the veracity of standard of care claims by "experts" on these two issues and have offered us constructive ideas to study as we search for ways to reduce the incidence of this catastrophic problem.

How should we use the information from the report by The Postoperative Visual Loss Study Group in our care of patients? The results suggest that the American Society of Anesthesiologist's 2006 Practice Advisory[6] on this issue is still relevant. Basically, it is prudent to attempt to reduce venous congestion in the optic canal. That is, we should consider using positions that allow the patients' heads to be level with or higher than their hearts. It may be helpful to use colloids as well as crystalloids to maintain intravascular volume. Intraoperative positioning that helps reduce intraabdominal pressure and, therefore, venous congestion, may be useful. The use of the Wilson frame and other positioning devices should be assessed carefully, with a goal to reduce pressure on the abdomen and to keep the head level with or higher than the heart. Since the authors found duration of anesthesia to be an independent risk factor for ION in this population, it may be prudent to work with our spine surgeons to determine if there is merit to limiting the duration of surgeries that are anticipated to be prolonged, especially 6 h or longer. Staging these procedures may be helpful.

For clinical researchers, this report suggests many new questions for study. Until now, there have been no data to support speculation on etiologies of ION in this setting. Can we determine the role that inflammation may play in perioperative ION? What really happens in the optic canal during these surgeries? Does venous congestion occur, and does it reduce optic nerve perfusion? Can we develop radiologic techniques or biologic/physiologic markers to study the optic nerve and canal in prone-positioned patients? Is there an impact of estrogen or other hormones on the development (and therefore, potentially the prevention) of central or peripheral neuropathies? Can new spine fusion techniques and intraoperative positioning mechanics impact optic nerve perfusion or reduce operative times and blood loss?

The lead authors and the many contributors to this study deserve our congratulations for creatively providing insights that finally allow us to move forward with additional studies. They have opened the door, even if only a crack. Their work offers hope that we may one day reduce or eliminate perioperative blindness in spine surgery patients.

Mark A. Warner, M.D., Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota. warner.mark@mayo.edu

References

1. The Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. Anesthesiology 2012; 116:15–24
2. Egorova EN, Kuz′mina MI, Mazur W, Kalinkin MN, Mazur ES: Trends in systemic inflammatory factors and aminoterminal brain natriuretic propeptide in the treatment of chronic heart failure. Ter Arkh 2011; 83:56–9
3. Brand A: Immunological aspects of blood transfusions. Transpl Immunol 2002; 10:183–90
4. Hunter JD: Effects of anaesthesia on the human immune system. Hosp Med 1999; 60:658–63
5. Staff NP, Engelstad J, Klein CJ, Amrami KK, Spinner RJ, Dyck PJ, Warner MA, Warner ME, Dyck PJ: Post-surgical inflammatory neuropathy. Brain 2010; 133:2866–80
6. American Society of Anesthesiologists Task Force on Perioperative Blindness: Practice advisory for perioperative visual loss associated with spine surgery: A report by the American Society of Anesthesiologists Task Force on Perioperative Blindness. Anesthesiology. 2006; 104:1319–28

Risk Factors Associated with Ischemic Optic Neuropathy after Spinal Fusion Surgery

The Postoperative Visual Loss Study Group*

ABSTRACT

Background: Perioperative visual loss, a rare but dreaded complication of spinal fusion surgery, is most commonly caused by ischemic optic neuropathy (ION). The authors sought to determine risk factors for ION in this setting.

Methods: Using a multicenter case-control design, the authors compared 80 adult patients with ION from the American Society of Anesthesiologists Postoperative Visual Loss Registry with 315 adult control subjects without ION after spinal fusion surgery, randomly selected from 17 institutions, and matched by year of surgery. Preexisting medical conditions and perioperative factors were compared between patients and control subjects using stepwise multivariate analysis to assess factors that might predict ION.

Results: After multivariate analysis, risk factors for ION after spinal fusion surgery included male sex (odds ratio [OR] 2.53, 95% CI 1.35–4.91, $P = 0.005$), obesity (OR 2.83, 95% CI 1.52–5.39, $P = 0.001$), Wilson frame use (OR 4.30, 95% CI 2.13–8.75, $P < 0.001$), anesthesia duration (OR per 1 h = 1.39, 95% CI 1.22–1.58, $P < 0.001$), estimated blood loss (OR per 1 l = 1.34, 95% CI 1.13–1.61, $P = 0.001$), and colloid as percent of nonblood replacement (OR per 5% = 0.67, 95% CI 0.52–0.82, $P < 0.001$). After cross-validation, area under the curve = 0.85, sensitivity = 0.79, and specificity = 0.82.

Conclusions: This is the first study to assess ION risk factors in a large, multicenter case-control fashion with detailed perioperative data. Obesity, male sex, Wilson frame use, lon-

What We Already Know about This Topic

- Visual loss after spinal fusion surgery is a devastating complication most commonly caused by ischemic optic neuropathy (ION)
- The risk factors for ION after spinal fusion surgery have not been systematically evaluated with detailed perioperative data

What This Article Tells Us That Is New

- In a case-control examination of 80 patients with ION compared with 315 matched control subjects, independent risk factors were male sex, obesity, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and lower percent colloid administration

* Members of The Postoperative Visual Loss Study Group are listed in the appendix.

Received from the Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington. Submitted for publication June 8, 2011. Accepted for publication September 27, 2011. Supported in part by the American Society of Anesthesiologists (ASA) as part of the ASA Closed Claims Project, Park Ridge, Illinois; the Washington State Society of Anesthesiologists Seafair Grant; and the Department of Anesthesiology and Pain Medicine seed funding grant, University of Washington School of Medicine, Seattle, Washington. Dr. Newman reports receiving partial research support from Research to Prevent Blindness, Inc, New York, New York, *via* an unrestricted grant and the Lew Wasserman Award to the Department of Ophthalmology, Emory University, Atlanta, Georgia. The funding organizations had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. Information on previous presentation of the information reported in this manuscript: An abstract with preliminary data from a subset of the control cases only (100 out of 315 controls) regarding range of anesthetic management in spine surgery was presented at the American Society of Anesthesiologists (ASA) annual meeting, on October 19, 2009, in New Orleans, Louisiana, as Abstract #A1013. An abstract on the predictive model for ischemic optic neuropathy was submitted to the ASA annual meeting, held October 15–19, 2011, in Chicago, Illinois, for the Late-Breaking Scientific Abstracts Session. No other presentations or publications from this study have been made.

Address correspondence to Dr. Lorri A. Lee: Department of Anesthesiology and Pain Medicine, Box 356540, University of Washington, 1959 NE Pacific Avenue, Seattle, Washington 98195-6540. lorlee@u.washington.edu. Anesthesiology 2012; 116:15–24

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

◆ This article is accompanied by an Editorial View. Please see: Warner MA: Cracking open the door on perioperative visual loss. ANESTHESIOLOGY 2012; 116:1–2.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

ger anesthetic duration, greater estimated blood loss, and decreased percent colloid administration were significantly and independently associated with ION after spinal fusion surgery.

ALTHOUGH many patients have improved quality of life and function with instrumented spinal fusion surgery, the procedure is often associated with large blood loss, long operative duration, and other complications.[1,2] One of the most devastating complications is postoperative visual loss (POVL), frequently caused by ischemic optic neuropathy (ION).[3] Visual deficits range from blurred vision to complete blindness, usually without significant recovery.[4] Estimates of ION after prone spinal fusion surgery from multicenter or national databases range from 0.017% to 0.1% (direct or derived estimates[5–7]), and the condition can occur in healthy individuals of all ages. Suggested factors associated with ION include anemia, hypotension, blood loss, large fluid shifts, venous congestion of the orbits, and coexisting diseases such as atherosclerotic vascular disease, diabetes, obesity, and hypertension.[3] These factors are also common in patients who have undergone spinal fusion and who do not develop ION, and hence it has not been possible to determine whether they have a causative role in this complication.

Prior studies of ION after spine surgery have been hindered either by small numbers of similar patients with ION from single institutions, or by lack of detailed perioperative data from national inpatient databases.[5–8] The American Society of Anesthesiologists (ASA) POVL Registry database contains the largest collection to date of ION cases associated with spine surgery with detailed anesthetic and postoperative data.[4] Anesthetic records provide frequent intraoperative values for physiologic parameters, fluid and blood product transfusion management, and timing of events. An analysis of the initial 83 ION cases reported to the ASA POVL Registry demonstrated that these cases were characterized by prolonged duration in the prone position and large blood loss; however, the lack of a control group prevented identification of risk factors.[4] We used the ION cases associated with prone spine surgery from the ASA POVL Registry in a multiinstitutional case-control study to identify risk factors for this devastating perioperative complication.

Materials and Methods

Study Design

The study design was multiinstitutional case control, in which preexisting conditions and perioperative factors of patients with ION after spinal fusion from the ASA POVL Registry (n = 80) were compared with control subjects who did not develop ION (n = 315). Institutional review board approval was obtained from the University of Washington and from all participating centers. ION cases from the ASA POVL Registry were collected by voluntary submission using a detailed data collection form.[4]† For the purpose of this analysis, inclusion criteria for ION cases from the ASA POVL Registry were: age ≥18 yr, spine fusion as the first or only spine surgery on index admission, surgery date between 1991 and 2006, prone position for a portion of the procedure, anesthetic duration ≥4 h, and surgical site that included any of the interspaces T1 through S5. Exclusion criteria were any history of perioperative cardiopulmonary resuscitation or cerebrovascular stroke; multiple (staged) spine procedures preceding ION on the index admission, and inadequate/incomplete data. A total of 80 ION cases from the ASA POVL Registry met inclusion and exclusion criteria.

Control subjects were selected from 17 academic medical centers that perform a large volume of spine fusion surgery using the following Current Procedural Terminology codes:[9] 22610 (arthrodesis, posterior or posterolateral, single level; thoracic), 22612 (arthrodesis, posterior or posterolateral, single level; lumbar), 22614 (arthrodesis, posterior or posterolateral, single level; each additional vertebral segment), 22630 [arthrodesis, posterior or interbody technique, including laminectomy or diskectomy, to prepare interspace (other than for decompression) single interspace; lumbar], 22632 [arthrodesis, posterior or interbody technique, including laminectomy or diskectomy, to prepare interspace (other than for decompression), each additional interspace], 22800 (arthrodesis, posterior, for spinal deformity, with or without cast; up to 6 vertebral segments), 22802 (arthrodesis, posterior, for spinal deformity, with or without cast; 7–12 vertebral segments), 22804 (arthrodesis, posterior, for spinal deformity, with or without cast; 13 or more vertebral segments), 22842 (posterior segmental instrumentation; 3–6 vertebral segments), 22843 (posterior segmental instrumentation; 7–12 vertebral segments), 22844 (posterior segmental instrumentation; 13 or more vertebral segments), 22848 [pelvic fixation (attachment of caudal end of instrumentation to pelvic bony structures) other than sacrum], 22849 (reinsertion of spinal fixation device), 22850 (removal of posterior nonsegmental instrumentation, *e.g.*, Harrington rod), and 22852 (removal of posterior segmental instrumentation). A total of 43,410 control subjects were identified with eligible Current Procedural Terminology codes for the control database. Four control subjects per ION case were randomly selected from this control database and matched by year of surgery to the eligible cases. (Matching by year of surgery was not used in the analysis but was conducted for sample selection to mirror possible practice changes in spinal fusion surgery that may have occurred during the study period). After selection, medical records of control subjects were checked for the same inclusion/exclusion criteria as ION cases. In addition, control subjects were excluded for any new perioperative complaint of visual disturbance (excepting isolated corneal abrasion).

† http://depts.washington.edu/asaccp/eye/providers/packet.pdf. Accessed August 28, 2011.

For each control subject designated to be drawn from a center, an additional seven replacements were randomly selected from the same center from the pool of control subjects matched to the case. Replacement control subjects were selected sequentially by each center if the initial control subject did not meet all study criteria, so that the next randomly selected control subject would be included. In the event all replacements were exhausted at a center without meeting study criteria, replacement control subjects were randomly selected from the entire control database, matched by year of surgery to the ION case. A total of 160 control records (50% of the randomly selected control subjects) met all inclusion/exclusion criteria on the first match; the remainder were abstracted from replacements. The most commonly encountered inclusion criteria not met by the first matches were surgical procedure criteria such as surgical site, prone position, duration, and age. The most common exclusion criteria necessitating replacement selection were missing records and staged procedures. Five of 320 control subjects submitted were excluded from the study for failure to meet study criteria during final assessment, leaving 315 control subjects for comparison.

To prevent any one or two centers from dominating the control group, each center was limited to contributing up to 50% more than or 10 patients more than (whichever was larger) its expected total contribution based on caseload for all years combined. Similarly, to avoid random exclusion of centers, each center was required to contribute a minimum of half its expected proportion based on caseload, or a minimum of one control case, whichever was smaller. The centers provided an electronic roster of eligible control subjects along with the required matching data (year of surgery). We randomly selected four control subjects (and seven potential replacements randomly selected from the same center) for each case from the pool of control subjects matched to the case. We compared the percentage distribution of the selected control subjects with the corresponding percentage distribution of eligible control subjects per year and center in the electronic roster to verify similarity of the distributions. If any center had a disproportionate excess or deficit of control subjects, then the sampling process was repeated until an acceptable distribution of controls was obtained.

A subset of patient and perioperative factors from the data available from the ASA POVL Registry was compared between ION cases and control subjects. These factors were hypothesized to be possibly associated with ION. Patient preexisting conditions included age, sex, and the following comorbidities: hypertension, diabetes, smoking, atherosclerosis (any coronary artery disease/myocardial infarction, or cerebrovascular disease), and obesity (defined by either clinical assessment or body mass index $\geq$30). Other patient factors examined included fusion location (lumbar *vs.* nonlumbar), indication for surgery (tumor, trauma, or other), and clinic blood pressure. Predetermined procedural factors included type of surgical frame, number of levels of fusion, and the headrest type. Potentially modifiable intraoperative procedural factors included anesthetic duration and estimated blood loss (EBL). Potentially modifiable intraoperative management factors included decrease in blood pressure (measured as reduction for a minimum of 30 consecutive or nonconsecutive min in the following ranges: 0–20% below baseline; 21–40% below baseline; and >40% below clinic baseline for either systolic blood pressure or mean arterial pressure), lowest hematocrit, fluid management variables (total volume replacement [all blood products, crystalloid, and colloid], total nonblood product replacement [crystalloid and colloid], total volume replacement:EBL ratio, and colloid [hydroxyethyl starch or albumin] as percent of total nonblood replacement), and use of vasopressors.

Data from the ION cases from the ASA POVL Registry with a high proportion of missing values such as increased cholesterol/lipids, tilt of surgical table, facial swelling, airway edema, and other factors, or undefined variables such as deliberate hypotension with wide interpretation were not included in this analysis. Similarly, factors such as cardiopulmonary bypass, use of cyclosporine, and primary anesthetic technique (general, regional, or monitored anesthesia care) that were not relevant for major spinal surgery were not included in this analysis. Factors with very low incidence (less than 5%) in patients and control subjects such as glaucoma, cataracts, macular degeneration, hypothermia, and seizures were also not included in this analysis.

Statistical Analysis

Univariate analysis of the association between patient and perioperative factors and the risk of developing ION was carried out using logistic regression (table 1). The effect of each factor is presented as the odds ratio (OR) from the logistic regression with the corresponding 95% CI and P value. A cutoff of $P < 0.2$ was used as a filter for determining appropriate factors for the multivariate analysis.

For the multivariate analysis, preexisting conditions and perioperative factors were grouped into stages according to their modifiability and role in the surgery (table 1). The stages form a sequence, starting with preexisting conditions (stage 1); predetermined procedural factors (stage 2), potentially modifiable intraoperative procedural factors (stage 3), and potentially modifiable intraoperative management factors (stage 4). Correlation coefficients were determined between potentially interrelated perioperative factors (table 2). The multivariate model was built using the four stages of variables in sequence (table 3). Initially, stage 1 variables with $P < 0.2$ in the univariate analysis were considered for inclusion. Next, additional variables with $P < 0.2$ were selected from stage 2, then sequentially from stages 3 and 4. Variables were selected using the forward stepwise selection technique with $P < 0.05$ for inclusion in the model. Variables selected in previous stages were retained in the model. At the end of each stage, we assessed two-way interactions among all vari-

Table 1. Univariate Analysis of Coexisting Conditions and Perioperative Factors

Stage*	No. Controls/ Cases	Controls Mean ± SD or n (%) Positive	Cases Mean ± SD or n (%) Positive	OR (95% CI)	*P* Value
Stage 1: Preexisting Conditions					
Age (yr), OR per 10 yr	315/80	51.6 ± 17.0	51.3 ± 13.2	1.00 (0.98–1.01)	0.9
ASA 1 and 2 *vs.* 3 and 4	314/78	115 (37%)	25 (32%)	0.82 (0.48–1.37)	0.5
Male	315/80	145 (46%)	55 (69%)	2.58 (1.55–4.41)	<0.001
Obesity	309/80	108 (35%)	43 (54%)	2.16 (1.32–3.57)	0.002
Diabetes	309/80	25 (8%)	13 (16%)	2.20 (1.04–4.47)	0.03
Smoking	310/79	161 (52%)	39 (49%)	0.90 (0.55–1.48)	0.7
Hypertension	314/80	114 (36%)	38 (48%)	1.59 (0.97–2.61)	0.07
Atherosclerosis	311/79	41 (13%)	6 (8%)	0.54 (0.20–1.24)	0.2
Clinic systolic BP (mm), OR per 20 mm	314/79	132 ± 19	136 ± 17	1.27 (0.97–1.66)	0.08
Clinic MAP (mm), OR per 20 mm	314/79	95 ± 13	97 ± 10	1.36 (0.90–2.04)	0.14
Lumbar location (Yes/No)	315/77	281 (89%)	70 (91%)	1.21 (0.54–3.08)	0.7
Year of surgery, OR per yr	315/80	2,000 (3)	2,000 (3)	1.00 (0.92–1.09)	0.99
Stage 2: Predetermined Procedural Factors					
No. of fusions, OR per three fusions	310/76	3.2 ± 2.6	3.6 ± 3.1	1.18 (0.91–1.52)	0.2
Frame	—	—	—	—	<0.001
Jackson	315/80	141 (45%)	23 (29%)	Reference	—
Wilson	315/80	43 (14%)	31 (39%)	4.42 (3.25–8.45)	<0.001
Neither Jackson nor Wilson	315/80	131 (42%)	26 (32%)	1.22 (0.66–2.25)	0.5
Mayfield pins or Gardner-Wells Tongs	315/80	44 (14%)	15 (19%)	1.42 (0.75–2.71)	0.3
Stage 3: Potentially Modifiable Intraoperative Procedural Factors					
Anesthesia duration (h), OR per 1 h	315/80	7.1 ± 2.4	9.6 ± 3.0	1.37 (1.25–1.51)	<0.001
Estimated blood loss (l), OR per 1 l	313/80	1.4 ± 1.4	3.1 ± 3.5	1.43 (1.27–1.65)	<0.001
Stage 4: Potentially Modifiable Intraoperative Management Factors					
BP >40% below baseline 30 min	314/79	56 (18%)	23 (29%)	1.93 (1.09–3.38)	0.02
Lowest intraoperative HCT (%), OR per 5%	231/58	29.2 ± 5.6	27.3 ± 4.6	0.72 (0.54–0.95)	0.02
Vasopressors during maintenance	315/80	114 (36%)	26 (32%)	0.85 (0.50–1.42)	0.5
Total volume replacement (l), OR per 1 l	315/79	6.0 ± 3.3	11.6 ± 6.5	1.30 (1.22–1.40)	<0.001
Total volume replacement/EBL ratio	313/79	6.5 ± 4.3	6.8 ± 8.4	1.01 (0.96–1.05)	0.7
Crystalloid as % of total volume replacement, OR per 10%	315/79	84.6 ± 15.8	84.3 ± 12.0	0.99 (0.84–1.17)	0.9
Total nonblood replacement (l), OR per 1 l	315/79	5.3 ± 2.5	9.7 ± 4.5	1.49 (1.36–1.65)	<0.001
Colloid as % of nonblood replacement, OR per 5%	315/79	8 ± 12	4 ± 6	0.78 (0.65–0.92)	0.005

Blood pressure (BP) >40% below baseline 30 min denotes 40% reduction below baseline BP, for either systolic BP or MAP, for ≥30 min. Total volume replacement is defined as all blood products, crystalloid and colloid administered. Total nonblood replacement is defined as the sum of crystalloid, hydroxyethyl starch, and albumin administered. Colloid is defined as the sum of hydroxyethyl starch and albumin administered. Atherosclerosis is defined as any history of myocardial infarction/cardiovascular or cerebrovascular disease.

* The four groups of variables correspond to the four stages described in the text.

ASA = American Society of Anesthesiologists Physical Status 1–6, a physical status classification based on condition of the patient independent of the planned operation, where ASA 1 is a normal healthy patient; ASA 2, a patient with mild systemic disease that results in no functional limitation; ASA 3, a patient with severe systemic disease that results in physical limitation, ASA 4, a patient with severe systemic disease that is a constant threat to life; ASA 5, a moribund patient who is not expected to survive without the operation; ASA 6, a declared brain-dead patient for organ donation; EBL = estimated blood loss; HCT = hematocrit; MAP = mean arterial pressure; OR = odds ratio.

ables already in the model and added any interactions with $P < 0.01$ to the model.

Alternative multivariate models were constructed by repeating the four-stage variables selection process, but at each stage we used backward elimination variable selection technique ($P > 0.05$ for exclusion) instead of forward stepwise selection. We calculated area under the receiver operating characteristic curve (AUC), and sensitivity and specificity for the model completed after each stage. A sensitivity and specificity combination was selected to maximize the sum of sensitivity and specificity. Two tenfold cross-validations, one for the forward stepwise and one for the backward elimination variable selection technique, were conducted to validate the model-building process. AUC, sensitivity, specificity, and frequency of variable selection in the cross-validation were calculated. Unless noted otherwise, AUC, sensitivity, and specificity are from the cross-validation.

The ORs from the final multivariate model and the ION rates of 0.017% and 0.1% from the literature were used as a basis to estimate a range of absolute ION rates for patients with a specified risk factor profile.[5,7] In calculating the absolute ION rates, our control group was assumed to be representative of the population to which the absolute rate of 0.017% (or 0.1%) applied. Using the multivariate model, an absolute rate of ION can be calculated corresponding to the risk factor profile for each patient in the control group. We multiplied all these rates by a common factor to force the average rate in the control group to be equal to either 0.017% or 0.1%.

The value $P < 0.05$ was used to denote statistical significance. Calculations were carried out in R version 2.12.0

Table 2. Pearson Correlation Coefficients among Intraoperative Variables

Variables Compared	No.Controls/ Cases	Correlation	*P* Value
Obesity and diabetes	303/80	0.19	<0.001
Total volume replacement and anesthesia duration	315/79	0.70	<0.001
Total volume replacement and EBL	313/79	0.75	<0.001
Total nonblood replacement and anesthesia duration	315/79	0.71	<0.001
Total nonblood replacement and EBL	313/79	0.63	<0.001
Total blood replacement and EBL	313/79	0.80	<0.001
Colloid as % of nonblood replacement and anesthesia duration	315/79	0.08	0.13
Colloid as % of nonblood replacement and EBL	313/79	0.14	0.008
Anesthesia duration and EBL	313/80	0.50	<0.001
Lowest HCT and EBL	229/58	−0.36	<0.001
Lowest HCT and anesthesia duration	231/58	−0.33	<0.001
Lowest HCT and total volume replacement	231/57	−0.42	<0.001
Lowest HCT and total nonblood replacement	231/57	−0.37	<0.001
BP >40% below baseline 30 min and anesthesia duration	315/78	0.07	0.14
BP >40% below baseline 30 min and EBL	313/78	0.20	<0.001

Blood pressure (BP) >40% below baseline 30 min denotes 40% reduction below baseline BP for either systolic BP or mean arterial pressure, for ≥30 min. Correlation coefficients of potentially interrelated perioperative variables. Because of the high correlation of total nonblood volume and total volume replacement variables with anesthesia duration or estimated blood loss (EBL), colloid as percent of nonblood replacement was chosen as the volume variable considered in stage 4 of the multivariate analysis.
HCT = hematocrit.

(Vienna, Austria). The sample size was selected to provide 80% power at $P < 0.05$ with two-sided tests to detect an OR of 1.4 (or larger), corresponding to a 1 SD increase in the covariate for continuous variables.

Results

Univariate Analysis

In the univariate analysis, male sex, obesity, diabetes, use of the Wilson frame, anesthesia duration, EBL, and blood pressure more than 40% below baseline values for ≥30 min were associated with a significantly increased risk of ION (table 1). There were no statistically significant associations of case/control status with age, ASA physical status, other preexisting conditions, type of headrest, number of levels fused (table 1), or with indication for surgery (tumor, trauma, or other diagnosis; results not shown).

Higher nadir hematocrit was associated with a decreased risk of developing ION (table 1). This comparison excludes approximately 100 surgeries with unavailable hematocrit data, but there was no statistically significant difference in the risk of ION between those with and those without hematocrit data ($P = 0.9$). Higher total volume replacement and total nonblood replacement conferred an increased risk of developing ION, but the percent crystalloid in the total volume replacement and the total volume replacement to EBL ratio had no statistically significant effect (table 1). The colloid as percent of total nonblood volume replacement was associated with a reduced risk of developing ION (table 1), although most (more than 93%) of control subjects did not exceed 1,500 ml colloid.

Colloid as percent of total nonblood replacement was only weakly correlated with anesthesia duration and EBL, whereas total volume and total nonblood volume variables were highly correlated with these variables (table 2).

Multivariate Regression Model

The final multivariate model after the four stages of the stepwise selection contained the risk factors of male sex (OR 2.53, 95% CI 1.35–4.91, $P = 0.005$), obesity (OR 2.83, 95% CI 1.52–5.39, $P = 0.001$), Wilson frame (OR 4.30, 95% CI 2.13–8.75, $P < 0.001$), anesthetic duration (OR 1.39 per 1 h, 95% CI 1.22–1.58, $P < 0.001$), EBL (OR 1.34 per 1 l, 95% CI 1.13–1.61, $P = 0.001$), and colloid as percent of total nonblood replacement (OR 0.67 per 5% colloid, 95% CI 0.52–0.82, $P < 0.001$) (table 3 cross-validated AUC = 0.85, and fig. 1). During cross-validation analysis, the number of fusions came into every model in stage 2; however, it became a nonsignificant predictor ($P = 0.7$–1.0) when anesthetic duration and EBL were added later in stage 3. Number of fusions appears to be a surrogate marker for anesthesia duration and EBL, which are the significant predictors in the model. Two alternative multivariate models were considered, using alternative fluid replacement variables and an interaction factor for variables in stage 4 (see tables 1 and 2, Supplemental Digital Content 1, http://links.lww.com/ALN/A793, which are tables showing alternative multivariable models for predicting ION that include the total nonblood replacement variable and interaction factor for total nonblood replacement: anesthesia duration in stage 4).

Using the final multivariate forward selection stepwise model in table 3, and using an ION incidence of either 0.017% or 0.1%, the absolute and relative risk of patients developing ION was calculated based on the presence of one or more risk

Table 3. Multivariate Regression Analysis*

—	Stage 1 Model Preexisting Conditions		Stage 2 Model Predetermined Procedural Factors		Stage 3 Model Potentially Modifiable Intraoperative Procedural Factors		Stage 4 Model Potentially Modifiable Intraoperative Management Factors	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male	2.80 (1.66–4.85)	<0.001	2.49 (1.46–4.37)	0.001	2.72 (1.47–5.18)	0.002	2.53 (1.35–4.91)	0.005
Obesity	2.38 (1.43–3.99)	<0.001	2.07 (1.22–3.53)	0.007	2.35 (1.30–4.32)	0.005	2.83 (1.52–5.39)	0.001
Wilson	—	—	3.40 (1.90–6.06)	<0.001	4.87 (2.48–9.68)	<0.001	4.30 (2.13–8.75)	<0.001
Anesthesia duration (hr), OR per 1 h	—	—	—	—	1.32 (1.18–1.50)	<0.001	1.39 (1.22–1.58)	<0.001
Estimated blood loss (l), OR per 1 l	—	—	—	—	1.31 (1.12–1.54)	<0.001	1.34 (1.13–1.61)	0.001
Colloid as % of nonblood replacement, OR per 5%	—	—	—	—	—	—	0.67 (0.52–0.82)	<0.001
AUC (all data/ cross-validation)	0.64/0.60	—	0.71/0.71	—	0.85/0.83	—	0.87/0.85	—
Sensitivity† (all data/cross-validation)	0.69/0.36	—	0.55/0.63	—	0.85/0.88	—	0.81/0.79	—
Specificity† (all data/cross-validation)	0.54/0.86	—	0.80/0.73	—	0.73/0.65	—	0.82/0.80	—

* Only variables with $P < 0.2$ in the univariate analysis (table 1) were considered. Selection criterion: $P < 0.05$. At the end of each stage, interactions were tested for variables in the model and were added if $P < 0.01$ (no interactions in this model had P values < 0.01). The same model was derived using backward elimination ($P > 0.05$ for exclusion). The following variables were considered: stage 1: sex, obesity, diabetes, hypertension, atherosclerosis, clinic systolic blood pressure, clinic mean arterial blood pressure; stage 2: Wilson frame; stage 3: anesthesia duration and estimated blood loss, stage 4: lowest intraoperative hematocrit, systolic or mean arterial blood pressure >40% below baseline 30 min, and colloid as percent of nonblood replacement. Because of the high correlation with anesthesia duration, estimated blood loss, total volume replacement and total nonblood replacement variables (table 2), colloid as percent of nonblood replacement was chosen as the volume variable considered in stage 4 of the multivariate analysis (see Discussion). Alternative multivariate models including total nonblood replacement in stage 4 are shown in Supplemental Digital Content 1, tables describing these models, http://links.lww.com/ALN/A793. † This combination of sensitivity and specificity optimizes the sum of the two. Other combinations can be calculated with trade-offs between better/worse sensitivity combined with worse/better specificity, respectively.

AUC = area under the curve; OR = odds ratio.

factors (table 4). This table can be used to evaluate the increased absolute and relative risks of ION by changing one or more variables in the model such as sex, surgical frame, anesthesia duration, EBL, or colloid as % of nonblood replacement.

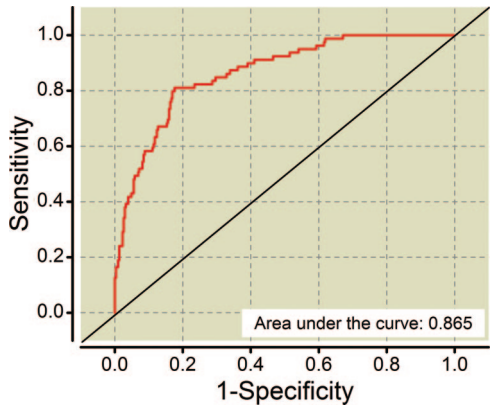

Fig. 1. Receiver operating characteristic curve for final (stage 4) multivariate model. Area under the curve = 0.87. Plot of the false negative rate (1-Specificity) *versus* the true positive rate (Sensitivity) for the final multivariate regression model in table 3. Area under the curve after cross validation = 0.85.

Discussion

This is the first multicenter study to identify risk factors for ION patients compared with patients without ION after prone spinal fusion surgery using detailed perioperative data. This study design is unique because of the large number of ION cases obtained from a national registry, the large multiinstitutional dataset of control subjects, and the detailed perioperative information in anesthetic and postoperative records. This data analysis identified novel risk factors for ION after spine surgery including male sex, Wilson frame use, longer anesthetic duration, greater EBL, and decreased percent colloid administration, and confirmed the risk factor of obesity identified in a previous study.[5] Although one previous study found that longer anesthetic duration and greater EBL were associated with POVL after spine surgery, the cases used were a heterogeneous mix of POVL diagnoses including ION, cortical blindness, and central retinal artery occlusion.[10] The predictive model identified from these data may allow clinicians to estimate the risk of ION for specific patients undergoing spine surgery.

Table 4. Risk Prediction for ION after Major Spine Surgery: Effect of Changes in Variables on ION Risk

Sex	Obesity	Wilson Frame	Anesthesia (h)	EBL (l)	Colloid (%)*	Absolute Risk of ION per 10,000 Procedures† (Based on 0.017% Overall Rate)	Absolute Risk of ION per 10,000 Procedures† (Based on 0.1% Overall Rate)	Relative Risk‡
Female	**No**	**No**	**5**	**1**	**10**	0.08	0.45	1.00§
Female	**Yes**	No	5	1	10	0.22	1.27	2.83
Female	No	**Yes**	5	1	10	0.33	1.93	4.30
Female	No	No	**7.5**	1	10	0.17	1.01	2.26
Female	No	No	**10**	1	10	0.39	2.30	5.12
Female	No	No	5	**2**	10	0.10	0.60	1.34
Female	No	No	5	**3**	10	0.14	0.80	1.78
Female	No	No	5	1	**0**	0.17	1.00	2.24
Female	**Yes**	**Yes**	**10**	**3**	**0**	18.98	111.67	249.27
Male	No	No	5	1	10	0.19	1.14	2.53
Male	**Yes**	No	5	1	10	0.55	3.21	7.17
Male	No	**Yes**	5	1	10	0.83	4.89	10.91
Male	No	No	**7.5**	1	10	0.44	2.57	5.74
Male	No	No	**10**	1	10	0.99	5.82	12.98
Male	No	No	5	**2**	10	0.26	1.52	3.39
Male	No	No	5	**3**	10	0.34	2.03	4.52
Male	No	No	5	1	**0**	0.43	2.54	5.67
Male	**Yes**	**Yes**	**10**	**3**	**0**	48.11	283.00	631.73

Variables in bold and shaded areas indicate changes in risk factors from the female reference patient with the lowest risk variables in this table (bold, first line), to demonstrate the effect on the range of absolute and relative risks of ION using examples of common clinical scenarios. For example, a male patient has an increased relative risk = 2.53 for ION compared with the reference female patient, with an absolute risk range of 0.19–1.14 per 10,000 procedures; an obese female patient has an increased relative risk = 2.83 for ION compared with the reference nonobese female patient, with an absolute risk range of 0.22–1.27 per 10,000 procedures; a female patient placed on a Wilson frame has an increased relative risk = 4.30 for ION compared with the reference female patient (non-Wilson frame), with an absolute risk range of 0.33–1.93 per 10,000 procedures; *etc*. The highest risk variables for females and males are shown in the last row of each sex group. In this table, the clinical scenario with the highest risk variables for males (obese, Wilson frame use, 10-h duration, 3 l EBL, no colloid in the total nonblood replacement) has a 631-fold increased risk of ION compared with the clinical scenario with the lowest risk variables for females (nonobese, no Wilson frame use, 5-h duration, 1 l EBL, and 10% colloid of total nonblood replacement).

* Colloid as % of total non-blood replacement, where total non-blood replacement = (crystalloid + albumin + hetastarch). † Range of low and high absolute risks of ION based on the literature from multicenter studies or national databases.[5–7] ‡ Relative risk of ION compared with the lowest risk set of patient variables in this table: first row (bold, no shading), reference value = 1 · 0. § Reference category for relative risk: female, non-obese, non-Wilson frame, 5 h anesthesia duration, 1 l EBL, and 10% colloid of non-blood replacement administered, first row (bold, no shading).

EBL = estimated blood loss; ION = ischemic optic neuropathy.

Limitations

The use of a voluntary registry with anonymous submission for obtaining ION cases has limitations. Bias and inaccuracy may be introduced by its retrospective nature and the type of cases submitted; however, the reliability of ION case data were previously found to be acceptable to excellent.[4] Cases with anterior and posterior ION occurring after major spine surgery were combined because of the lack of any significant differences between groups in the variables studied herein, similarities in ophthalmologic findings, and their occurrence after the same procedure.[4] This supposition could influence the effect of variables on the outcome. Data on control subjects were collected in a more rigorous fashion than for cases because all control entries were made by study investigators. Variables such as operative table tilt noted to have a substantial percentage of missing values in the ION cases were excluded from the study. We cannot eliminate the possibility of missing an effect of these variables or other unmeasured variables on the development of ION. Although the anesthesia time was the most accurate record of time in the operating room, it is a surrogate for operative time. We also cannot exclude the possibility that the cases come from a different mix of institutions than control subjects and that some of the effect of risk factors may be a facility effect. Due to the limited number of ION cases (n = 80) available for modeling, there was no dataset available to validate the predictive model. Due to these limitations, quantitative estimates of risk must be interpreted with caution. Although only statistically significant factors in the multivariate model ($P < 0.05$) are considered to have an independent effect on ION, the effect of other statistically significant factors from the univariate analysis cannot be excluded with absolute certainty.

Risk Factors

The higher proportion of men developing perioperative ION after spinal fusion surgery (69%) is much greater than the almost equivalent proportion of men and women under-

going spine surgery.‡ It is almost identical to the proportion of men who develop perioperative ulnar neuropathy (70%).[11] There are no known sex-related anatomic differences in the anatomy of the anterior visual pathways, but some animal studies suggest a protective effect of estrogen with specific optic nerve disease.[12] Our multivariate analysis found no statistically significant independent effect on ION of older age, hypertension, atherosclerosis, smoking, or diabetes. These data are in agreement with case reports of ION in children after major spine surgery, and with literature reviews demonstrating that most ION patients after prone spine surgery are relatively healthy.[3,13,14] These findings suggest that the etiology of ION may be more strongly influenced by intraoperative physiologic perturbations than by any known preexisting disease or vasculopathy.

Obese patients may have increased intraabdominal and central venous pressures in the prone position related to increased abdominal girth, thereby causing increased venous pressure in the head. These physiologic changes reduce systemic venous return and cardiac output, leading to reduced end organ blood flow. Similarly, the Wilson frame is a rounded, hump-shaped frame that places the patient's head much lower than the heart, and may greatly exacerbate venous congestion in the head over time. Prolonged acute elevation of venous pressure in the orbit can lead to interstitial edema formation and reduced perfusion pressure, which may also negatively affect oxygen delivery to the optic nerve.

The finding of increasing duration in the prone position and increasing EBL as risk factors for ION is consistent with case series and literature reviews.[3,4,7] This effect may have been larger if all prone spine operations had been included, instead of only those with ≥4 h anesthetic duration. Larger EBL increases fluid shifts, capillary leak, interstitial edema, and systemic inflammation. It also predisposes to periods of reduced cardiac output and end-organ blood flow. Prolonged duration allows for increased blood loss and subsequent increased fluid administration, and exposes the patient for longer periods to the physiologic perturbations predisposing to ION.

The addition of fluid replacement variables to the model did not substantially change the AUC for predicting ION because of strong correlations between total volume variables, anesthetic duration, and EBL (tables 2 and 3). Separating specific effects of these variables was not possible with this retrospective nonrandomized study design. Percent colloid of nonblood replacement was chosen as the fluid replacement variable in the multivariate model because it was only weakly correlated with anesthetic duration and EBL. Moreover, inclusion of total volume variables would conceal potentially significant differences in volume expansion and transcapillary leakage between crystalloid, colloid, and blood products. Despite its high statistically significant effect on ION, the difference in the average percent colloid of nonblood replacement between control subjects and cases was 4%, making its clinical significance less certain.

The lack of an independent effect of anemia or any blood pressure more than 40% below baseline for 30 min in the multivariate analysis demonstrates the importance of using detailed perioperative data on control subjects to assess whether or not the effect of these factors remains significant when other relevant intraoperative data such as anesthesia duration, EBL, and volume administration are analyzed. These data, uniquely available in the current study, were not available from the National Inpatient Sample database, case series, or literature reviews.[3–7]

Acute Venous Congestion

We have previously hypothesized that ION associated with prone spine surgery may be related to the acutely increased venous pressure in the head and neck,[4] because other procedures with similar physiology in the head such as bilateral radical neck operations and robotic prostatectomies in the steep head-down position are also associated with ION.[15,16] Placing a patient in the prone position increases intraabdominal, intrathoracic, and intraocular pressures.[17,18] It is theorized that the increased venous pressure in the head and neck leads to interstitial fluid accumulation from capillary leak, decreased venous outflow, and decreased perfusion of the optic nerve. After a critical period of time, damage to the optic nerve could occur *via* various mechanisms, including ischemia caused by compression of small pial arteries supplying the nerve, venous infarction from reduced venous outflow, or even direct mechanical damage from the elevated interstitial pressures. Most perioperative ION cases associated with spine surgery occur in the posterior optic nerve where there is poor collateral flow, making the nerve vulnerable to prolonged pathophysiologic changes in blood flow, both venous and arterial.[4,15,16] Almost all of the variables selected into the multivariate model in table 3 including obesity, Wilson frame, anesthetic duration, EBL, and % colloid of nonblood volume, could exacerbate these proposed pathophysiologic mechanisms.

Prevention

At this point, preventive strategies are the only option to reduce the effect of this complication, as effective treatment has not been identified. Using this model, the only preoperative factor that is practically modifiable is surgical frame selection and position. Maneuvers to keep the head at or above heart level to reduce venous congestion in the head have been recommended in the ASA practice advisory for perioperative visual loss associated with spine surgery.[19] Minimizing duration in the prone position and maximizing hemostasis may also be beneficial, although the utility of staging complex procedures would require further study to

‡ Merrill C, Elixhauser A: Hospital stays involving musculoskeletal procedures, 1997–2005, Statistical Brief #34 from the Healthcare Cost and Utilization Project and the Agency for Healthcare Research and Quality. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb34.pdf. Accessed February 3, 2011.

assess the relative risks and benefits. Theoretically, using colloid along with crystalloid, also suggested in the ASA practice advisory,[19] may reduce the edema formation, but also requires further study as colloids are associated with dose-related deleterious side effects and increased mortality in critically ill patients.[20,21] The low incidence of perioperative ION may preclude randomized controlled trials demonstrating benefit from these suggested interventions.

The prediction table for ION (table 4) uses examples of different typical values of the variables from the final multivariate model to provide an absolute risk (rate per 10,000 procedures) and relative risk assessment for patients, surgeons, and anesthesiologists. Validation of this multivariate model will require testing in a new population. Patients undergoing lengthy spine surgery in the prone position should be informed of the increased risk for ION.[22] In this era of informed and shared decision-making with patients, these data might influence patients' and surgeons' decisions between conservative management and various options for surgical treatments. Anesthesiologists could use these data to guide fluid administration.

In conclusion, this study demonstrates that obese and male patients have an increased risk of developing ION after major spinal surgery in the prone position. Avoidance of the Wilson frame and minimizing the anesthetic duration and EBL may decrease the risk of developing ION. Use of colloid along with crystalloid may decrease the risk of developing ION, but its overall risk-to-benefit profile in major spine surgery cannot be adequately evaluated using this study design. Prediction tables for ION based on this study may help inform patients, surgeons, and anesthesiologists of the absolute and relative risk for patients developing ION, and guide decision-making.

Appendix: The Postoperative Visual Loss Study Group Investigators

Core Investigators

Lorri A. Lee, M.D., Associate Professor, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington; Steven Roth, M.D., Professor, Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois; Michael M. Todd, M.D., Professor and Head, Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, Iowa; Karen L. Posner, Ph.D., Research Professor, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington; Nayak L. Polissar, Ph.D., Affiliate Associate Professor, Statistical Consultant, Department of Biostatistics, University of Washington, Seattle, Washington, and The Mountain-Whisper-Light Statistics, Seattle, Washington; Moni B. Neradilek, M.S., Statistical Consultant, The Mountain-Whisper-Light Statistics, Seattle, Washington; James Torner, Ph.D., M.S., Professor, Department of Epidemiology, University of Iowa Carver College of Medicine, Iowa City, Iowa; Nancy J. Newman, M.D., Professor, Departments of Ophthalmology and Neurology, Emory University, Atlanta, Georgia; Karen B. Domino, M.D., M.P.H., Professor, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington.

Other Site Investigators

Kathryn K. Lauer, M.D., Professor, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin; Rachel Budithi, M.D., Assistant Professor, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin; Suneeta Gollapudy, M.D., Assistant Professor, Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin; Thomas N. Pajewski, Ph.D., M.D., Associate Professor, Department of Anesthesiology and Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia; David C. Scalzo, M.D., Research Associate, Department of Anesthesiology and Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia; Rafi Avitsian, M.D., Associate Professor, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio; Michael J. Brown, M.D., Assistant Professor, Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota; Shonie Buenvenida, B.S.N., Research Study Coordinator, Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota; George A. Mashour, M.D., Ph.D., Assistant Professor, Departments of Anesthesiology and Neurosurgery, University of Michigan Medical School, Ann Arbor, Michigan; Laurel E. Moore, M.D., Assistant Professor, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan; Satwant K. Samra, M.D., Professor Emeritus, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan; Jeremy Lieberman, M.D., Professor, Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California; Rondall K. Lane, M.D., Assistant Professor in Residence, Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California; Ramachandran Ramani, M.D., Associate Professor, Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut; Jessica Wagner, M.D., Resident in Anesthesiology, Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut; Rene Tempelhoff, M.D., Professor, Department of Anesthesiology, Washington University, St. Louis, Missouri; Cynthia M. Monsey, M.D., Ph.D., Assistant Professor, Department of Anesthesiology, Washington University, St. Louis, Missouri (current affiliation: Meds and Food for Kids, St. Louis, Missouri); Steven A. Robicsek, M.D., Ph.D., Clinical Associate Professor, Department of Anesthesiology, University of Florida, Gainesville, Florida; Melissa M. Vu, M.D., Clinical Assistant Professor, Department of Anesthesiology, University of Florida, Gainesville, Florida; Julie Weeks, M.P.T., Research Program Associate, Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, Iowa; Pirjo H. Manninen, F.R.C.P.C., M.D., Associate Professor, Department of Anesthesia, Toronto Western Hospital, University Health Network University of Toronto, Toronto, Ontario, Canada. Eugene S. Fu, M.D., Associate Professor, Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida; Greys C. Sanchez-Yanes, M.D., Resident in Anesthesiology, Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida; Robert A. Peterfreund, M.D., Ph.D., Associate Professor, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Meredith A. Albrecht, M.D., Instructor, Department of Anesthe-

sia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Kenneth J. Sapire, M.D., Professor, Department of Anesthesiology and Perioperative Medicine, The University of Texas, MD Anderson Cancer Center, Houston, Texas; Verna L. Baughman, M.D., Professor, Department of Anesthesiology, University of Illinois College of Medicine at Chicago, Chicago, Illinois; Robert A. Caplan, M.D., Clinical Professor, University of Washington, Seattle, Washington, and Attending Anesthesiologist, Virginia Mason Medical Center, Seattle, Washington; Frederick W. Cheney, M.D., Professor Emeritus, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington; Julia Metzner, M.D., Assistant Professor, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington.

The authors gratefully acknowledge the following individuals for acquisition of data: Robin A. Bruchas, M.S.W., Research Study Coordinator, and John Campos, M.A., Research Consultant, Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, Washington; Melissa Passe, R.R.T., Study Coordinator, Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota; Xing Fu, M.D., Resident in Anesthesiology, Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut; Aki Honda, M.D., Research Assistant, Department of Anesthesiology, Washington University, St. Louis, Missouri; Elaine Hrinyo, B.S., C.P.C., Professional Fee Billing Manager, and Sharon Jakubczyk, B.S.N., Research Nurse, Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois; Stephanie Davis, M.D., Resident, and John Klein, M.D., Resident, Department of Anesthesia, University of Iowa Carver School of Medicine, Iowa City, Iowa; Yiqing Yin, M.D., Anesthesia Fellow, and Qanwei Luo, M.D., Research Assistant, Department of Anesthesia, Toronto Western Hospital, University of Toronto, University Health Network University of Toronto, Toronto, Ontario, Canada; Theresa A. Morris, R.N., Quality Assurance Coordinator, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Sonya Meyers, M.D., Medical Student (at time of data collection), Department of Anesthesiology, University of Illinois College of Medicine at Chicago, Chicago, Illinois. The authors acknowledge Lynn Akerlund, Research Coordinator, Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington, for contributions to the project coordination and expert secretarial assistance.

References

1. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG: Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. JAMA 2010; 303:1259–65
2. Fritzell P, Hagg O, Wessberg P, Nordwall A, Swedish Lumbar Spine Study Group: Chronic low back pain and fusion: A comparison of three surgical techniques: A prospective multicenter randomized study from the Swedish lumbar spine study group. Spine 2002; 27:1131–41
3. Ho VT, Newman NJ, Song S, Ksiazek S, Roth S: Ischemic optic neuropathy following spine surgery. J Neurosurg Anesthesiol 2005; 17:38–44
4. Lee LA, Roth S, Posner KL, Cheney FW, Caplan RA, Newman NJ, Domino KB: The American Society of Anesthesiologists Postoperative Visual Loss Registry: Analysis of 93 spine surgery cases with postoperative visual loss. ANESTHESIOLOGY 2006; 105:652–9; quiz 867–8
5. Patil CG, Lad EM, Lad SP, Ho C, Boakye M: Visual loss after spine surgery: A population-based study. Spine 2008; 33: 1491–6
6. Shen Y, Drum M, Roth S: The prevalence of perioperative visual loss in the United States: A 10-year study from 1996 to 2005 of spinal, orthopedic, cardiac, and general surgery. Anesth Analg 2009; 109:1534–45
7. Stevens WR, Glazer PA, Kelley SD, Lietman TM, Bradford DS: Ophthalmic complications after spinal surgery. Spine 1997; 22:1319–24
8. Holy SE, Tsai JH, McAllister RK, Smith KH: Perioperative ischemic optic neuropathy: A case control analysis of 126,666 surgical procedures at a single institution. ANESTHESIOLOGY 2009; 110:246–53
9. American Medical Association: Current Procedural Terminology 2006: Professional Edition. Chicago, AMA Press; 2005
10. Myers MA, Hamilton SR, Bogosian AJ, Smith CH, Wagner TA: Visual loss as a complication of spine surgery. A review of 37 cases. Spine 1997; 22:1325–9
11. Warner MA, Warner ME, Martin JT: Ulnar neuropathy: Incidence, outcome, and risk factors in sedated or anesthetized patients. ANESTHESIOLOGY 1994; 81:1332–40
12. Giordano C, Montopoli M, Perli E, Orlandi M, Fantin M, Ross-Cisneros FN, Caparrotta L, Martinuzzi A, Ragazzi E, Ghelli A, Sadun AA, d'Amati G, Carelli V: Oestrogens ameliorate mitochondrial dysfunction in Leber's hereditary optic neuropathy. Brain 2011; 134:220–34
13. Kim JW, Hills WL, Rizzo JF, Egan RA, Lessell S: Ischemic optic neuropathy following spine surgery in a 16-year-old patient and a ten-year-old patient. J Neuroophthalmol 2006; 26:30–3
14. Chang SH, Miller NR: The incidence of vision loss due to perioperative ischemic optic neuropathy associated with spine surgery: The Johns Hopkins Hospital Experience. Spine 2005; 30:1299–302
15. Pazos GA, Leonard DW, Blice J, Thompson DH: Blindness after bilateral neck dissection: Case report and review. Am J Otolaryngol 1999; 20:340–5
16. Weber ED, Colyer MH, Lesser RL, Subramanian PS: Posterior ischemic optic neuropathy after minimally invasive prostatectomy. J Neuroophthalmol 2007; 27:285–7
17. Soliman DE, Maslow AD, Bokesch PM, Strafford M, Karlin L, Rhodes J, Marx GR: Transoesophageal echocardiography during scoliosis repair: Comparison with CVP monitoring. Can J Anaesth 1998; 45:925–32
18. Cheng MA, Todorov A, Tempelhoff R, McHugh T, Crowder CM, Lauryssen C: The effect of prone positioning on intraocular pressure in anesthetized patients. ANESTHESIOLOGY 2001; 95:1351–5
19. American Society of Anesthesiologists Task Force on Perioperative Blindness: Practice advisory for perioperative visual loss associated with spine surgery: A report by the American Society of Anesthesiologists Task Force on Perioperative Blindness. ANESTHESIOLOGY 2006; 104:1319–28
20. Hartog CS, Bauer M, Reinhart K: The efficacy and safety of colloid resuscitation in the critically ill. Anesth Analg 2011; 112:156–64
21. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007; 357:874–84
22. Corda DM, Dexter F, Pasternak JJ, Trentman TL, Nottmeier EW, Brull SJ: Patients' perspective on full disclosure and informed consent regarding postoperative visual loss associated with spinal surgery in the prone position. Mayo Clin Proc 2011; 86:865–8

suspect many clinicians would be uncomfortable with use of SpHb readings in this manner. Our finding of larger bias and wider limits of agreement at lower hemoglobin values suggests an area for further algorithm or device refinement. Perhaps a user-selectable "low hemoglobin range" setting could be developed to provide tighter limits of agreement in this lower range.

Comparison of our results to others is important. We found larger bias and wider limits of agreement in patients with larger blood loss or lower hemoglobin. As pointed out, the limits of agreement we found (−2.3 to + 3.3 g/dl) are similar to those reported by Miller *et al.*[3] (−3.2 to + 3.7 g/dl) and Lamhaut *et al.*[4] (−2.7 to + 2.75 g/dl); slightly larger than that reported by Berkow *et al.*[5] (−2.0 to + 1.8 g/dl); but larger than that reported by Frasca *et al.*[6] (−1 to + 1 g/dl). Of note in the study by Frasca *et al.*, sample pairs from patients who were treated with norepinephrine infusion more than 0.2 mcg/kg/min or obtained when the perfusion index was less than 0.5 had greater bias and wider limits of agreement (−1.4 to + 1.4 g/dl). Miller *et al.*[7] reported that digital nerve block performed on the finger to which the sensor was applied improved accuracy of pulse hemoglobin compared with standard laboratory cooximetry. This finding suggests that differences between intensive care and intraoperative blood loss could induce changes in peripheral circulation that affect the accuracy of pulse cooximetry. We believe this is an important area of future research.

We are impressed by the innovations Masimo has brought to patient care. The company has demonstrated sincere commitment to improving their devices. We are convinced that pulse cooximetry could be used to inform clinical transfusion decisions. We also believe that differences in clinical situations in which blood loss occurs may have important effects on peripheral circulation, and thus potentially influence the accuracy of pulse cooximetry. Dr. O'Reilly noted that Ehrenfeld *et al.*[8] reported less transfused blood was given to patients monitored with pulse cooximetry in comparison with standard care. However, transfusion was expected in only 4.5% of patients they studied, whereas 55% of our patients received ≥1 unit of transfused erythrocytes during surgery. We do not have access to all information about patients in the abstract from Ehrenfeld *et al.*, but the average blood loss they reported was nearly 600 ml less than in our study. The larger amounts of blood loss and transfusion in our patients could be associated with changes in peripheral circulation affecting pulse cooximetry accuracy and thus would seem to make patients similar to those we studied more appropriate for determining the effect of pulse cooximetry on transfusion decisions.

Further research is warranted to delineate which patient or intraoperative factors contribute to larger differences between pulse cooximetry and invasive hemoglobin measurements. We believe this will lead to studies that verify a positive effect of SpHb® on patient care and perioperative outcome.

Richard L. Applegate II, M.D.,* Steven J. Barr, M.D., Carl E. Collier, D.O., Martin W. Allard, M.B.Ch.B., F.R.C.A.
*Loma Linda University School of Medicine, Loma Linda, California. rapplegate@llu.edu

References

1. Applegate RL II, Barr SJ, Collier CE, Rook JL, Mangus DB, Allard MW: Evaluation of pulse cooximetry in patients undergoing abdominal or pelvic surgery. ANESTHESIOLOGY 2012; 116: 65–72
2. Macknet MR, Allard M, Applegate RL 2nd, Rook J: The accuracy of noninvasive and continuous total hemoglobin measurement by pulse CO-Oximetry in human subjects undergoing hemodilution. Anesth Analg 2010; 111:1424–6
3. Miller RD, Ward TA, Shiboski SC, Cohen NH: A comparison of three methods of hemoglobin monitoring in patients undergoing spine surgery. Anesth Analg 2011; 112:858–63
4. Lamhaut L, Apriotesei R, Combes X, Lejay M, Carli P, Vivien B: Comparison of the accuracy of noninvasive hemoglobin monitoring by spectrophotometry (SpHb) and HemoCue® with automated laboratory hemoglobin measurement. ANESTHESIOLOGY 2011; 115:548–54
5. Berkow L, Rotolo S, Mirski E: Continuous noninvasive hemoglobin monitoring during complex spine surgery. Anesth Analg 2011; 113:1396–402
6. Frasca D, Dahyot-Fizelier C, Catherine K, Levrat Q, Debaene B, Mimoz O: Accuracy of a continuous noninvasive hemoglobin monitor in intensive care unit patients. Crit Care Med 2011; 39:2277–82
7. Miller RD, Ward TA, Shiboski S, Cohen NH: Digital regional nerve block and accuracy of non-invasive hemoglobin monitor. Presented at the Annual Meeting of the International Anesthesia Research Society. Vancouver, British Columbia, Canada, May 2011, S-223
8. Ehrenfeld JM, Henneman JP. Impact of continuous and noninvasive hemoglobin monitoring on intraoperative blood transfusions. Presented at the Annual Meeting of the American Society of Anesthesiologists, October 18, 2010, San Diego, California, LB05

(Accepted for publication April 25, 2012.)

Perioperative Ischemic Optic Neuropathy and Spine Surgery: Are We Asking the Right Questions?

To the Editor:

The recent article and editorial regarding intraoperative vision loss in the prone position continue to promote real advances in understanding and reducing the occurrence of this devastating complication.[1,2] The importance of prone positioning, obesity, gender, and use of the Wilson frame clearly invite the conclusion of perioptic venous back pressure and edema formation as causative mechanisms. However, the commonality for all four factors is perhaps, at least partially, one of simple geometry. The gender factor may not

These letters were sent to the author of the mentioned Editorial View, who felt that a reply was not necessary.—James C. Eisenach, M.D., Editor-in-Chief.

be hormonal differences. Women typically are shorter than men. Fixation on body mass index as the index of obesity obscures the gender difference in absolute height, also imparting a different absolute "thickness." The combination of increased thickness and length together may contribute to significant differences in periocular congestion and edema. The Wilson frame's absolute height may be fixed, but measurements of "thicker" and longer males will result in a greater total prone body height as measured from base (eyes) to apex (skin incision site) geometrically (Pythagorus). This is minimized by Jackson style frames, where the shoulders and hips are preferentially supported in a level position. The shortest female's face may never reach to the base of the Wilson's arch.

Geometry has been implicated as a significant factor in vision loss in prolonged *supine* surgical positioning: robotic prostatectomy.[3,4] Certainly the prone and head-down positions impart increased ventilation pressures to increase central venous pressure and venous pressure in the optic area, with prolonged surgery promoting intensification of edema accumulation. If we accept the geometry theory of this process, the rational conclusion to eliminate ischemic optic neuropathy is clear: Perform prolonged spinal surgery only in the left lateral position! The head is now uniformly placed above the heart, facilitating minimal venous back pressure from gravity and ventilation, while maximizing the filling pressure of the now "dependent" heart. Can geometric considerations drive a change in "routine standard neurosurgical practice?" Is the prone position primarily used for obsolete "historical reasons?" Geometry considerations have reduced sitting craniotomy numbers to an unparalleled historical minimum only by exposing the dangers of air embolism, which was also a "rare event." Is ischemic optic neuropathy any less devastating? Can the authors examine the geometry factors in their available data because the published material is inadequate in this regard? Can surgeons be led to use the lateral position, especially for prolonged surgical procedures? What problems would be introduced or need solutions? Is it time to reexamine the premise and study this theory prospectively as optimal preventive strategy?

The suggestion that staging procedures may represent a preventative strategy deserves consideration here. Staging recently has been demonstrated to impart increased morbidity and possibly mortality in major spinal surgery.[5] The multicenter retrospective data indicate, but do not prove, that increased morbidity and mortality, prolonged hospital stay, increased costs, and infections are to be expected. It is also possible that nonarteritic ischemic optic neuropathy occurring during prone surgeries simply reflects coincidental occurrences found in the general nonsurgical population, given the relatively similar frequency of occurrence.[6] Vasopressors commonly used during these surgeries or delayed detection in the intensive care unit with causative association to surgery may also play a role.[7] Clearly, comparing prone to lateral surgery in a prospective fashion may be the single most effective means to improve patient outcome and clarify cause *versus* effect in this devastating surgical complex.

Paul Martin Kempen, M.D., Ph.D., Cleveland Clinic, Cleveland, Ohio. kempenp@ccf.org

References

1. Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. Anesthesiology 2012; 116:15–24
2. Warner MA: Cracking open the door on perioperative visual loss. Anesthesiology 2012; 116:1–2
3. Weber ED, Colyer MH, Lesser RL, Subramanian PS: Posterior ischemic optic neuropathy after minimally invasive prostatectomy. J Neuroophthalmol 2007; 27:285–7
4. Awad H, Santilli S, Ohr M, Roth A, Yan W, Fernandez S, Roth S, Patel V: The effects of steep Trendelenburg positioning on intraocular pressure during robotic radical prostatectomy. Anesth Analg 2009; 109:473–8
5. Passias PG, Ma Y, Chiu YL, Mazumdar M, Girardi FP, Memtsoudis SG: Comparative safety of simultaneous and staged anterior and posterior spinal surgery. Spine 2012; 37:247–55
6. Hayreh SS: Ischemic optic neuropathy. Prog Retin Eye Res 2009; 28:34–62
7. Lee LA, Nathens AB, Sires BS, McMurray MK, Lam AM: Blindness in the intensive care unit: Possible role for vasopressors? Anesth Analg 2005; 100:192–5

(Accepted for publication April 26, 2012.)

Could the Open Door Crack on Perioperative Visual Loss Be Even Bigger?

To the Editor:

The recent study of postoperative visual loss after spinal surgery identified long duration anesthesia, male gender, obesity, and the need for larger blood transfusion as risk factors for postoperative visual loss.[1] The authors believe the core mechanism for visual loss is a vascular one causing optic nerve ischemia. The accompanying editorial emphasized the possible role anesthesia-associated inflammation may play in visual loss and referenced the article of Staff *et al.,* who first described postoperative inflammatory neuropathy.[2,3] The inflammatory neuropathy cases described by Staff *et al.* all involved peripheral nerves. Perhaps there is a common risk factor in perioperative visual loss and postoperative inflammatory peripheral neuropathy. That factor could be the use of nitrous oxide. It would be interesting if information on the use of nitrous oxide were available from these two reports' databases.

Nitrous oxide anesthesia increases plasma homocysteine.[4] Nitrous oxide does this by disrupting a metabolic chain involving folate, vitamin B6, and vitamin B12. Speculatively, the nitrous-oxide–induced increase in homocysteine effects could be greater in individuals who have a preexisting deficiency of these vitamins or a subclinical or undiagnosed

variant of the known congenital biochemical abnormalities involving these vitamins, such as hyperhomocystinemia.

Nitrous-oxide–induced increases in plasma homocysteine have been correlated positively with altered endothelial function.[4] Increased plasma homocysteine concentration have strong association with increased inflammation.[5,6] Increased homocysteine concentrations are strongly correlated with the microvascular complications of diabetes, including neuropathy.[7] The ENIGMA trail suggested that if nitrous oxide is used for more than 2 h in patients, it increases their long-term myocardial infarction risk.[8] Hyperhomocystinemia is also well described as a factor for central retinal artery occlusion and central retinal vein occlusion.[9–11] This is precisely what the injury in perioperative visual loss seems to be.

If this speculated link between nitrous oxide use and perioperative vision loss should ever find any more supporting scientific evidence, it could suggest utility of simple protective strategies to avoid both postoperative visual loss and inflammatory peripheral neuropathy. One remedy could be to administer folate and vitamins B6 and B12 as premedication to patients before they undergo long duration surgery, especially spinal surgery, when using nitrous oxide in the anesthetic. In one preoperative study of 390 patients scheduled for major surgery, 0.2% individuals had a preexisting folate deficiency and 7.5% individuals had preexisting increased plasma homocysteine concentrations.[12] Those individuals could possibly be a higher risk for blindness or postoperative inflammatory neuropathy than are the other patients. The authors proposed administering routine preanesthetic folate and vitamin supplements when nitrous oxide was planned to be used on patients undergoing major surgery. The alternative protective remedy would be to avoid use of nitrous oxide surgeries that present the risk of vision loss.

Nitrous oxide is not devoid of benefits and has been shown to reduce long-term pain, possibly *via* its *N*-methyl-D-aspartic acid receptor blocking effects.[13] Thus, the overall place of nitrous oxide use in anesthesia remains a matter of debate.

It is likely that multiple risk factors for visual loss after long duration spinal surgery will remain, and all have a complex interplay with no single remedy being able to eliminate the risk of blindness.

Robert M. Raw, M.D., University of Iowa, Iowa City, Iowa. rob-raw@uiowa.edu

References

1. Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. Anesthesiology 2012;116:15–24
2. Warner MA: Cracking open the door on perioperative visual loss. Anesthesiology 2012;116:1–2
3. Staff NP, Engelstad J, Klein CJ, Amrami KK, Spinner RJ, Dyck PJ, Warner MA, Warner ME, Dyck PJ: Post-surgical inflammatory neuropathy. Brain 2010; 133:2866–80
4. Myles PS, Chan MT, Kaye DM, McIlroy DR, Lau CW, Symons JA, Chen S: Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. Anesthesiology 2008; 109:657–63
5. Gori AM, Sofi F, Marcucci R, Giusti B, Franco Gensini G, Abbate R: Association between homocysteine, vitamin B(6) concentrations and inflammation. Clin Chem Lab Med 2007; 45:1728–36
6. McCully KS: Chemical pathology of homocysteine. IV. Excitotoxicity, oxidative stress, endothelial dysfunction, and inflammation. Ann Clin Lab Sci 2009; 39:219–32
7. Ambrosch A, Dierkes J, Lobmann R, Kühne W, König W, Luley C, Lehnert H: Relation between homocysteinaemia and diabetic neuropathy in patients with Type 2 diabetes mellitus. Diabet Med 2001; 18:185–92
8. Leslie K, Myles PS, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Williamson E: Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. Anesth Analg 2011; 112:387–93
9. Pianka P, Almog Y, Man O, Goldstein M, Sela BA, Loewenstein A: Hyperhomocystinemia in patients with nonarteritic anterior ischemic optic neuropathy, central retinal artery occlusion, and central retinal vein occlusion. Ophthalmology 2000; 107:1588–92
10. Kawasaki A, Purvin VA, Burgett RA: Hyperhomocysteinaemia in young patients with non-arteritic anterior ischaemic optic neuropathy. Br J Ophthalmol 1999; 83:1287–90
11. Stanger O, Weger M, Obeid R, Temmel W, Meinitzer A, Steinbrugger I, Schmut O, Herrmann W: Impairment of homocysteine metabolism in patients with retinal vascular occlusion and non-arteritic ischemic optic neuropathy. Clin Chem Lab Med 2005; 43:1020–5
12. Myles PS, Chan MT, Forbes A, Leslie K, Paech M, Peyton P: Preoperative folate and homocysteine status in patients undergoing major surgery. Clin Nutr 2006; 25:736–45
13. Chan MT, Wan AC, Gin T, Leslie K, Myles PS: Chronic postsurgical pain after nitrous oxide anesthesia. Pain 2011; 152:2514–20

(Accepted for publication April 26, 2012.)

It's Still the Water

To the Editor:

After publication of the first report by the American Society of Anesthesiologists Visual Loss Registry Study Group,[1] I submitted a Letter to the Editor in which I stated that administration of excessive volumes of crystalloid fluid may be the cause of ischemic optic neuropathy (ION) and recommended that crystalloid fluid therapy not exceed 40 ml/kg, regardless of the duration of the posterior spinal surgery.[2] In reply, Dr. Warner stated that my recommendation was dogmatic and unsubstantiated, which was true, but he also did not provide any documentation that it was invalid. Now we have additional evidence that my recommendation regarding crystalloid fluid therapy was on target.

In their recent report, the Visual Loss Study Group did a retrospective comparison of a number of variables in their database of 80 patients with ION with those from 315 carefully selected, matched control subjects who underwent posterior spinal surgery but did not experience ION.[3] The Study Group identified a number of highly significant differences ($P = 0.001$) between the ION and control subjects. Three significant differences that are interrelated stand out. The

total volume of fluid replacement and the total nonblood fluid replacement were greater in the ION patients, and the administration of colloid as a percentage of the total nonblood replacement was less in the ION patients. The only remaining fluid in this analysis would be crystalloid. These findings directly support the concept that the crystalloid fluid volume was significantly greater in the ION patients, although a direct comparison of the volume of crystalloid administered in the two groups did not reach significance.

Other significant differences between the two groups included gender, obesity, use of the Wilson frame, duration of anesthesia, and estimated blood loss. Both the Study Group and Dr. Warner in his editorial[4] suggested that ION may be less common in women than men because of the protective effect of estrogen. A simpler and more reasonable explanation for the difference is that most anesthesia providers are more likely to give larger volumes of crystalloid fluid to men weighing 80–120 kg than they are to women weighing 60–80 kg. With respect to obesity, the Study Group suggested that positioning the obese patient prone may increase intraabdominal, intrathoracic, intraocular, and venous pressures and produce ischemia of the optic nerve by a variety of mechanisms. Another more plausible explanation would be that if prone positioning did increase venous pressure in the obese patients, it would be manifest most profoundly as blood loss at the operative site, which in turn, would necessitate greater fluid administration, including crystalloid fluid. Finally, the Study Group suggested that the reason that ION was more common with use of the Wilson frame was because the head is more dependent with its use. However, this explanation is only conjecture because the exact positioning of the head was not documented in all of the patients who experienced ION while on the Wilson frame. When using the Wilson frame, the head need not be dependent because it can be supported in the neutral position with pillows and head supports, and this may have been done in some of the ION patients on the Wilson frame. I do not believe that exactness in head position is necessary provided crystalloid fluid volume administration is limited. We do a large number of robotic-guided, laparoscopic, retropubic radical prostatectomies with the patients in a very steep Trendelenburg position for 4–6 h. The crystalloid fluid volume is limited to less than 1 l until the patient is returned to the level position to avoid fluid collection in the bladder, which will obscure the operative field when the bladder is opened. We have not had a case of ION in this population. Two things stand out in the reported cases of ION occurring after prostate surgery: the patients were in a Trendelenburg position for 4–6 h, and they received approximately 5–10 l crystalloid fluid.

The recent report of the American Society of Anesthesiologists Task Force on Perioperative Visual Loss[5] advocates the use of both colloid and crystalloid fluids but does not recommend any limit on the latter. Based on the evidence to date, which admittedly is mostly circumstantial, I would urge anesthesia providers to strongly consider limiting crystalloid fluid therapy to less than 40 ml/kg regardless of operative length. With this change alone, I believe that we will experience a measurable decrease in the incidence of ION.

C. Philip Larson, Jr., M.D.C.M., David Geffen School of Medicine at University of California, Los Angeles, California; Ronald Reagan UCLA Medical Center, Los Angeles, California. plarson@ucla.edu

References

1. Lee LA, Roth S, Posner KL, Cheney FW, Caplan RA, Newman NJ, Domino KB: The American Society of Anesthesiologists Postoperative Visual Loss Registry: Analysis of 93 spine surgery cases with postoperative visual loss. ANESTHESIOLOGY 2006; 105:652–9
2. Larson CP Jr: Excessive crystalloid infusion may contribute to ischemic optic neuropathy [letter]. ANESTHESIOLOGY 2007; 106: 1249
3. Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. ANESTHESIOLOGY 2012; 116:15–24
4. Warner MA: Cracking open the door on perioperative visual loss. ANESTHESIOLOGY 2012; 116:1–2
5. American Society of Anesthesiologists Task Force on Perioperative Visual Loss: Practice advisory for perioperative visual loss associated with spine surgery: An updated report by the American Society of Anesthesiologists Task Force on Perioperative Visual Loss. ANESTHESIOLOGY 2012; 116:274–85

(Accepted for publication April 26, 2012.)

In Reply:

We would like to thank Drs. Kempen, Raw, and Larson for their interest in our study on determining risk factors for perioperative ischemic optic neuropathy (ION) after spinal fusion surgery in the prone position.[1] Dr. Kempen's suggestion to perform spine surgery in the lateral position, instead of the prone position, is intriguing. We have also considered this possibility in the past and queried our surgical colleagues. In special situations, such as second or third trimester pregnancy, when postponement of surgery is not feasible, spine surgery has been performed in the lateral position. However, the "up-down" manipulations required in the lateral position are technically more difficult than the more symmetric "right-left" manipulations in the prone position. Achieving ideal spinal alignment is much more challenging technically in the lateral position. Many surgeons rely on the lordosis imparted by some of the spinal frames in the prone position to provide optimal "anatomic" alignment for fusion.

We agree with Dr. Kempen that further study should be performed to examine the relative risks and benefits of staging very prolonged spine surgery with expected high blood loss, as we noted on pages 22 and 23 of our article.[1] The supposition that this injury may reflect the coincidental occurrence of spontaneously occurring ION in a general non-

surgical population is not supported by national incidence data. Data from the Nationwide Inpatient Sample published by Shen *et al.* demonstrates a greatly increased odds ratio of 6.96 for developing ION in spinal fusion surgery compared with the referent abdominal surgery.[2] Its occurrence in children and relatively healthy adults after spinal fusion surgery is not consistent with the high incidence of atherosclerotic risk factors found in the subpopulation of nonsurgical patients who develop nonarteric anterior ION.[3] In addition, the high percentage of cases with bilateral profound loss of vision in perioperative ION is not consistent with the clinical course of nonarteritic anterior ION, which typically presents with unilateral disease with less severe loss of vision.

Lastly, we also considered the possibility, like Dr. Kempen, that vasopressors may be a contributory factor in the development of ION. We did not find a significant association with vasopressor use in the univariate analysis, as noted in table 1 on page 18 of our article.[1]

Dr. Raw offers the interesting hypothesis that perioperative inflammation may contribute to the development of ION after spinal fusion surgery. Given the low incidence of perioperative ION, it may prove difficult to examine this hypothesis with prospective studies. Dr. Raw also notes that increased plasma homocysteine levels and lower vitamin B6 levels are independently associated with the occurrence of nonarteric anterior ION in the nonsurgical population. For this reason, nitrous oxide could play a contributory role. In our 2006 study, less than one-quarter of the 83 patients with ION after spinal fusion received nitrous oxide, making it unlikely that nitrous oxide administration is an important factor in perioperative ION.[4] But a systemic inflammatory syndrome may result from prolonged, complex surgery, and the notion that inflammation is a pathogenic factor in axonal injury or brain injury is supported by experimental studies in animals.[5,6]

We appreciate Dr. Larson's continued interest in perioperative ION and his efforts to provide precise limitations on the amount of crystalloid (40 ml/kg) administered. We remain curious about the 40 ml/kg crystalloid limit. It is not clear if he is encouraging a practice of intentional hypovolemia, or if he is advocating the use of colloid along with crystalloid to maintain euvolemia, as recommended in the American Society of Anesthesiologists' practice advisory.[7] The former practice of intentional hypovolemia in these cases with large blood loss and prolonged duration would subject patients to a high potential for end organ ischemia, or ultimately, cardiovascular collapse. The latter practice of using colloids along with crystalloids may reduce the incidence of ION, as suggested by the results of our multicenter case-control study. However, our studies and understanding of the current literature do not suggest that a specific limit to crystalloid administration, such as 40 ml/kg, will prevent perioperative ION. Of note, the mean crystalloid infusion for the control patients in our study was 4.6 l ± 2.3 l, well above Dr. Larson's limit of 40 ml/kg for most patients. The highest amount of crystalloid infused in a control patient was more than 18 l. Conversely, crystalloid limitation did not protect all patients from ION, as the lowest amount of crystalloid infused in an ION case was 2.2 l. Based on our observations, we do not believe that the 40 ml/kg crystalloid limit prevents ION, nor does it help predict those who might develop ION. Dr. Larson's supposition that the increased risk of ION seen in men was because men received more crystalloid than women was not supported by our data. There were no significant differences in the amount of crystalloid received between men and women, either in cases or controls.

Although we agree that increased venous pressure is likely to increase blood loss and fluid resuscitation, there are many types of surgery where arterial bleeding results in much greater blood loss and fluid resuscitation, but without an associated risk for ION. Therefore, we believe that the increased venous pressure – in the head – is one of the most important risk factors placing prone spinal fusion surgery patients at increased risk for developing ION. This same feature of increased venous pressure in the head is also present in other surgical procedures that carry a high risk for ION groups: bilateral radical neck dissections with ligation of bilateral external and internal jugular veins[8,9] and laparoscopic/robotic prostatectomies with the head placed in steep Trendelenburg for prolonged duration.[10] It is interesting that Dr. Larson has "specialized" fluid management plans for these types of procedures with increased venous pressure in the head and high risk for ION, yet dismisses venous congestion as a significant contributory factor for ION.

We are impressed by Dr. Larson's efforts to prevent ION in robotic prostatectomy patients who require steep Trendelenburg position for 4–6 h. It is not clear to us if cases of that duration for this procedure are at risk for ION. The duration of surgery for the five reported cases of ION after laparoscopic prostatectomy ranged from 6.5 to 9.9 h, with four of these cases lasting 7.9 h or more.[9,10] One additional case of ION occurring after a laparoscopic proctocolectomy also lasted greater than 6 h.[11] We are not aware of cases of ION after 4–6 h of robotic prostate surgery that were associated with Trendelenberg position and 5–10 l of crystalloid administration.

We applaud Dr. Kempen's, Dr. Raw's, and Dr. Larson's interest in this topic and their efforts to minimize the occurrence of perioperative ION. This is a devastating perioperative complication that deserves continued reflection and sound, methodical investigation.

Lorri A. Lee, M.D.,* Steven Roth, M.D., Michael M. Todd, M.D., Karen L. Posner, Ph.D., Nayak L. Polissar, Ph.D., Moni B. Neradilek, M.S., Nancy J. Newman, M.D., Robert A. Caplan, M.D., Frederick W. Cheney, M.D., Karen B. Domino, M.D., M.P.H., for The Postoperative Visual Loss Study Group. *University of Washington School of Medicine, Seattle, Washington. lorlee@uw.edu

References

1. Postoperative Visual Loss Study Group: Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. Anesthesiology 2012; 116:15–24
2. Shen Y, Drum M, Roth S: The prevalence of perioperative visual loss in the United States: A 10-year study from 1996 to 2005 of spinal, orthopedic, cardiac, and general surgery. Anesth Analg 2009; 109:1534–45
3. Mathews MK: Nonarteritic anterior ischemic optic neuropathy. Curr Opin Ophthalmol 2005; 16:341–5
4. Lee LA, Roth S, Posner KL, Cheney FW, Caplan RA, Newman NJ, Domino KB: The American Society of Anesthesiologists Postoperative Visual Loss Registry: Analysis of 93 spine surgery cases with postoperative visual loss. Anesthesiology 2006; 105:652–9
5. Salgado C, Vilson F, Miller NR, Bernstein SL: Cellular inflammation in nonarteritic anterior ischemic optic neuropathy and its primate model. Arch Ophthalmol 2011; 129:1583–91
6. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M: Tumor necrosis factor-α triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci U S A 2010; 107:20518–22
7. American Society of Anesthesiologists Task Force on Perioperative Blindness: Practice advisory for perioperative visual loss associated with spine surgery: A report by the American Society of Anesthesiologists Task Force on Perioperative Blindness. Anesthesiology 2006; 104:1319–28
8. Pazos GA, Leonard DW, Blice J, Thompson DH: Blindness after bilateral neck dissection: Case report and review. Am J Otolaryngol 1999; 20:340–5
9. Weber ED, Colyer MH, Lesser RL, Subramanian PS: Posterior ischemic optic neuropathy after minimally invasive prostatectomy. J Neuroophthalmol 2007; 27:285–7
10. Lee LA, Posner KL, Bruchas R, Roth S, Domino KB: Visual loss after prostatectomy. Paper presented at: annual meeting of the American Society of Anesthesiologists; October 18, 2010; San Diego, California
11. Mizrahi H, Hugkulstone CE, Vyakarnam P, Parker MC: Bilateral ischaemic optic neuropathy following laparoscopic proctocolectomy: A case report. Ann R Coll Surg Engl 2011; 93:e53–4

(Accepted for publication April 26, 2012.)

Author-created Surrogate Time Intervals Misrepresents Actual Times

To the Editor:

We are constantly amazed when the performance of anesthesiologists practicing in the anesthesia care team model (including both private practice and academic settings) is judged by administrators, operating room (OR) managers, and surgeons on "first-case starts." Unfortunately, too many of these nonanesthesiologists use magical thinking and demand that all the ORs start at the same time and without delay. The reality is that in an anesthesia care team model, the anesthesiologist cannot be at two places at once. Therefore, it should be obvious that when starting more than one room first thing in the morning, surgeons and OR teams may have to wait for the anesthesiologist to become available to attend to each patient.

With this understanding of reality, we read Epstein and Dexter's recent publication with great interest.[1] But unfortunately, instead of looking at the first-case starts, the authors chose to also look at other portions of anesthesia care as well. We were dismayed over this methodology because the authors utilized retrospective data that lacked a critical data element necessary to accurately determine anesthesiologist presence. Because their retrospective data from the single center studied did not include the actual time and duration of demanding portions of anesthesia care, the authors had to develop surrogate time interval definitions that would capture the critical portions of anesthesia team care. This deserves emphasis. The authors do not know from the electronic health record data when the actual demanding portions of anesthesia occurred, the duration of those occurrences, and the role the attending anesthesiologist played in managing those events. These surrogate definitions are found in table 2 of their publication.

To illustrate how broad these surrogate time intervals are and how they include not only the critical portion but also many noncritical portions, one only has to look at the first definition: induction of general anesthesia. The authors chose to define this time period as when the patient enters the OR to intubation (or the equivalent) + 3 min. Therefore, they include within their definition of the induction the following events: transportation into the OR, movement of the patient from the stretcher to the bed, placement of the IV (if not done in holding), placement of standard monitors, and waiting for the surgeon to arrive. This overly broad definition creates artificial "conflicts," where none in fact occur. For example, if the anesthesiologist is present in OR A for extubation, and the nonphysician anesthesia provider brings the patient into OR B, then, by the authors' definition of induction, the anesthesiologist is not available for a critical portion and there is a "lapse" identified by the simulation.

One could apply this definition of induction to the surgeon. If the critical portion of the anesthetic begins when the patient arrives in the OR and includes the preoperative briefing (authors' definition), then similarly, a critical portion of surgery should include the time from the patient's arrival into the OR to the briefing. If a surgeon is not present during this period for probably justifiable reasons (*e.g.*, rounding on inpatients, meeting with the family of previous patient, and so on), the surgeon would be found in "lapse" of care by the authors and would contribute to avoidable inefficiencies.

This one example illustrates how using retrospective data and surrogate time intervals will result in exaggeration of so-called lapses. Similar problems exist for all the other definitions in their table 2.

Furthermore, electronic health records do not document the timing, duration, and content of every communication between anesthesiologist and nonphysician anesthesia provider (anesthesiology assistant, nurse anesthetist, or anesthe-