

## No Patient Left Behind

UNDOUBTEDLY, many readers will find it curious to see an article<sup>1</sup> summarizing perceptions of teamwork in the operating room (OR) in ANESTHESIOLOGY, a journal typically filled with anesthesia-related clinical and biomedical science. Although we would hopefully all agree that teamwork is important in the increasingly complex OR environment, many will wonder how subjective perceptions of teamwork can be turned into a metric useful in improving care. And, most important, how can such seemingly vague assessments of teamwork ultimately benefit our patients?

Concern about teamwork in complex healthcare settings is not new. The now-familiar 1999 Institute of Medicine report,<sup>2</sup> which highlighted anesthesiology's progress and leadership in patient safety, recommended that healthcare organizations enhance their patient safety culture, in which "effective team functioning" was identified as one of five principles for creating safe hospital systems. In response, at least nine surveys purporting to measure patient safety climate have emerged, of which the Safety Attitudes Questionnaire (SAQ) seems most robust.<sup>3</sup> A modification of a survey developed for critical care settings from an aviation survey, SAQ is a 30-question survey designed for intrainstitutional and interinstitutional comparisons. Its six domains—teamwork climate, safety climate, job satisfaction, perceptions of management, stress recognition, and working conditions—reflect distinct dimensions based on studies in aviation and health care. Higher SAQ scores have been associated with shorter duration of stay, fewer medication errors, and lower bloodstream infection and ventilator-associated pneumonia rates, as well as lower nurse turnover and risk-adjusted patient mortality rates.

The article<sup>1</sup> in this issue of ANESTHESIOLOGY evaluates how well the teamwork climate domain in an SAQ version enhanced for OR personnel reflects the personnel's perceptions of teamwork climate, which is defined here as the quality of collaboration among those in the work setting. Measuring teamwork climate is challenging principally because it is a concept or construct that cannot be measured directly; instead, it is assessed indirectly by

asking, in this case, 6 of the 30 questions (or "items") in the SAQ survey (or "instrument"). The responses to the 6 questions are converted to numerical scores that, in turn, are combined and arrayed on a 0–100 scale as a "domain score." Although the methodology presented may seem arcane, it relies on the same item-measurement theory on which more familiar generic and disorder-specific quality-of-life scales (e.g., Medical Outcomes Study Short Form-36 Health Survey, visual analog scale for pain) are based.<sup>4,5</sup> If the items have been selected appropriately and the scaling has been done properly, the resulting domain scores should reflect the underlying construct, should differ in a given circumstance by only random error of measurement, and should have important properties that provide the basis for the evaluation.<sup>4,5</sup>

Among those properties is *coverage* of the construct: All aspects of teamwork climate that are meaningful to OR personnel should be addressed. This seems to have been satisfied in the development of the modified SAQ through the use of literature review, focus groups, behavioral observation of OR personnel, and critiques of the draft survey by OR personnel. A second property is *reliability*, which in its most general usage is the consistency of a measurement under constant conditions. For this instrument, two specific types of reliability were tested: Internal reliability, or the consistency with which raters used the 6 items in making their assessments of teamwork climate, was evaluated using Cronbach's  $\alpha$ , whose values were uniformly high for the different caregiver types. Consistency with which personnel of each type made their assessments was determined with an intraclass correlation coefficient, whose values were similarly high. The third property is *validity*, a multidimensional characteristic that, overall, means the domain measures what it is claimed to measure. Given the absence of an existing teamwork metric for use as a comparator, it is not possible to explore correlations with other ways to measure teamwork; therefore, we cannot assess convergent, criterion, or discriminant validity.

Potential users of this instrument will be especially interested in its ability to satisfy a fourth property, *sensitivity*: the instrument's ability to reflect true differences in teamwork climate. The investigators used the instrument in 60 hospitals in a large health system, achieved high participation rates among all OR personnel types, and found widely varying perceptions of "good teamwork climate" by hospital. All respondents in 6 hospitals agreed that a good teamwork climate was present, whereas in the majority of study hospitals, less than 50% of respondents shared that assessment. Given aforementioned psychometric characteristics, this phe-

◆ This Editorial View accompanies the following article: Sexton JB, Makary MA, Tersigni AR, Pryor D, Hendrich A, Thomas EJ, Holzmueller CG, Knight AP, Wu Y, Pronovost PJ: Teamwork in the operating room: Frontline perspectives among hospitals and operating room personnel. ANESTHESIOLOGY 2006; 105:877–84.

Accepted for publication July 26, 2006. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

**Table 1. Percentage of Caregivers Reporting Good Collaboration with Other Members of the Operating Room Team**

Caregiver Position Performing Rating	Caregiver Position Being Rated			
	Surgeon	Anesthesiologist	Operating Room Nurse	Nurse Anesthetist
Surgeon	85	84	88	87
Anesthesiologist	70	96	89	92
Operating Room Nurse	48	63	81	68
Nurse Anesthetist	58	75	76	93

Modified, with permission, from figure 4 in Makary *et al.*<sup>6</sup>

nomenon suggests that the instrument is sensitive to differences in teamwork climate. The instrument was also sensitive to perceptions among different caregiver types after adjusting for hospital, although differences were much smaller. Using the same data, the investigators probed deeper into differences in caregiver-specific assessments in a recent publication,<sup>6</sup> yielding fascinating perspectives on OR teamwork climate: Anesthesiologists believe that they enjoy good collaboration with other anesthesiologists near uniformly and with both nurse anesthetists and OR nurses almost as commonly, whereas with surgeons, good collaboration is much less prevalent. A high proportion of surgeons think they have good collaborations with all other OR caregivers. In contrast, both types of nurses rate teamwork with other caregivers much more poorly than the physicians do, with only approximately half of nurses believing that they enjoy good collaboration with surgeons and a slightly higher proportion regarding the teamwork climate with anesthesiologists favorably (table 1).

Related to sensitivity is the fifth property, *responsiveness*: the instrument's ability to reflect true change in teamwork climate. Clearly, if this instrument is to be useful as a metric in improvement work, it must be able to document changing perceptions as the teamwork climate improves. That this instrument can reveal differences in teamwork climate across 60 hospitals in a cross-sectional study design is evidence of sensitivity but not necessarily responsiveness. A longitudinal design, with repeated measures using this instrument as an improvement initiative progresses, is needed to demonstrate responsiveness.

Even if this instrument is shown to be responsive to change in teamwork climate, we must not forget that the "culture of safety" described in the Institute of Medicine report<sup>2</sup> is very much multidimensional. As we continue to model our efforts on the successes that occurred in aviation,<sup>7</sup> we should not forget that the aviation industry's culture of safety not only encourages good communication but also includes a fairly rigorous regulatory approach that is not present in medicine. Although both pilots and medical residents cannot work beyond a specified number of hours, only pilots must meet minimum sleep requirements to

be able to work, are trained in fatigue management, and more likely to be selected for random drug screens. Although both pilots and most physicians must undergo recertification to demonstrate proficiency in their craft, pilots do so much more frequently, using more rigorous simulation techniques to test knowledge, and face mandatory retirement. Although both pilots and physicians have strong concerns about the safety of their charges, only pilots have mandatory safety reporting systems in place, use national systems to evaluate and learn from adverse events, and suffer the same consequences as their charges when adverse events occur.

Improving communications and satisfaction is an important step in achieving a safety climate<sup>8</sup> in the OR. However, achieving a culture of safety in health care is likely to require additional steps to have a documentable and lasting impact on patient outcomes.

**Fredrick K. Orkin, M.D., M.B.A., M.Sc.,\* William B. Weeks, M.D., M.B.A.†**

\* Yale University, New Haven, Connecticut. Clinical Epidemiology Research Center, West Haven VA Connecticut Health System, West Haven, Connecticut. fred.orkin68@post.harvard.edu. † VA National Quality Scholars Fellowship Program, Veterans Affairs Medical Center, White River Junction, Vermont. Health Services Research & Development Enhancement Award Program, and White River Junction Field Office, VA National Center for Patient Safety, Veterans Affairs Medical Center, White River Junction, Vermont. Departments of Psychiatry and of Community and Family Medicine, Dartmouth Medical School, Hanover, New Hampshire.

## References

1. Sexton JB, Makary MA, Tersigni AR, Pryor D, Hendrich A, Thomas EJ, Holzmueller CG, Knight AP, Wu Y, Pronovost PJ: Teamwork in the operating room: Frontline perspectives among hospitals and operating room personnel. *ANESTHESIOLOGY* 2006; 105:877-84
2. To Err is Human: Building a Safer Health System. Edited by Kohn LT, Corrigan JM, Donaldson MS. Washington, D.C., National Academy Press, 1999
3. Colla JB, Bracken AC, Kinney LM, Weeks WB: Measuring patient safety climate: A review of surveys. *Qual Saf Health Care* 2005; 14:364-6
4. Testa MA, Simonson DC: Assessment of quality-of-life outcomes. *N Engl J Med* 1996; 334:835-40
5. Streiner DL, Norman GR: *Health Measurement Scales: A Practical Guide to Their Development and Use*, 3rd ed. New York, Oxford University Press, 2003
6. Makary MA, Sexton JB, Freischlag JA, Holzmueller CG, Millman EA, Rowen L, Pronovost PJ: Operating room teamwork among physicians and nurses: Teamwork in the eye of the beholder. *J Am Coll Surg* 2006; 202:746-52
7. Sexton JB, Thomas EJ, Helmreich RL: Error, stress, and teamwork in medicine and aviation: Cross sectional surveys. *BMJ* 2000; 320:745-9
8. Makary MA, Sexton JB, Freischlag JA, Millman EA, Pryor D, Holzmueller C, Pronovost PJ: Patient safety in surgery. *Ann Surg* 2006; 243:628-35

## Predicting Trouble in Airway Management

FOR an anesthetist, there can be few, if any, more alarming clinical situations than the unexpected total inability to manage a patient's airway. That this occurs rarely is of course a good thing, although its rarity itself both encourages complacency and makes it difficult to study.

The first problem is defining the problem. Historically, anesthetists have focused on tracheal intubation, perhaps because it has traditionally been an exclusive anesthetic skill and is seen as the definitive airway technique, and because difficult or failed intubation has been such an important cause of anesthetic morbidity and mortality over the years. However, difficult intubation is not easy to define, because there are degrees of difficulty and they may vary between intubators. Defining *failed* intubation might seem, on the face of it, easier, but there are different thresholds for declaring failure, depending on the would-be intubator, the urgency of the situation, and who or what else is available, and a second person (or even a third) may succeed when the first has failed. These difficulties, plus the rarity of failure, have led to use of the view obtained at direct laryngoscopy—albeit using different methods of grading the view—as a surrogate for difficult or failed intubation in clinical studies (reviewed recently by Shiga *et al.*<sup>1</sup>). These studies generally find the same thing: that certain clinical features are more likely to be present in patients in whom laryngoscopy is difficult, but because most laryngoscopies are easy, most patients who have such features actually pose no problems.

But even if it were possible to predict difficult laryngoscopy accurately, this is not quite what we need to know. First, an endotracheal tube may be easy to place despite a poor laryngoscopic view, and even a reasonable view may be associated with difficulty passing a tube. Second, failed intubation alone may not necessarily lead to disaster, because there are alternative ways of maintaining oxygenation, the most simple of which is ventilation by facemask.

Surprisingly, predicting difficult mask ventilation has attracted little attention—perhaps, again, at least partly because of its rarity and difficulty in defining it. In this issue of the Journal, Kheterpal *et al.*<sup>2</sup> have added to the work of Langeron *et al.*<sup>3</sup> in this area, both groups finding

that obesity, older age, snoring, and the presence of a beard stood out as risk factors for difficulty (both groups suggesting that beards that stood out too much should perhaps be removed, although they do not suggest remedial action for obesity). As with tracheal intubation, though, most people, including those with these risk factors—difficulty defining snoring or beards notwithstanding—are easy to ventilate by mask. And, as with intubation, predicting difficult mask ventilation does not give us what we really need to know: More useful would be the ability to predict which patients are at risk from difficulty with both intubation and mask ventilation, because if there is trouble with one technique, the anesthetist can simply use the other in most cases. Kheterpal *et al.* looked at this too, and although numbers were small, they identified obesity, snoring, limited jaw movement, and abnormal neck anatomy as risk factors.

But is this what we really need to know either? With the laryngeal mask airway now such a valued component of airway management strategies<sup>4,5</sup> and so widely and readily available, perhaps we should strive to predict in which patients there will be difficulty with intubation, mask ventilation, and ventilation with the laryngeal mask airway? Kheterpal *et al.* found only 37 patients out of 22,660 in whom mask ventilation was impossible; intubation was difficult in 10 of these, and surgical cricothyrotomy was required in 1. Details of other methods of airway management that were attempted in this single case are not provided, but it is difficult to imagine cricothyrotomy being performed without trying the laryngeal mask airway or equivalent first. A definitive study of this aspect would be challenging, mainly because the number of patients unfortunate enough to fulfill these criteria is tiny.

All of this brings us to the next problem, at which I have been hinting above—*i.e.*, the limited usefulness of predictive tests when the thing they are trying to predict is very rare. In such a situation, unless there is near 100% sensitivity and specificity, the positive and negative predictive values will be low. In the case of airway management, most patients are easy to manage and most patients predicted to be difficult are not, whereas a few who are predicted to be easy are anything but. Understanding this limitation is important if the so-called predictive tests are to be used sensibly.<sup>6</sup>

Finally, a weakness of most prediction studies is that their findings only relate to the sample from which they were derived. Kheterpal *et al.* should be commended for gathering data from more than 22,000 patients; their findings must now be validated in another sample, and one can only hope that the same group, or another one, is ready to take up the challenge, if not the beard trimmers.

This Editorial View accompanies the following article: Kheterpal S, Han R, Tremper KK, Shanks A, Tait AR, O'Reilly M, Ludwig TA: Incidence and predictors of difficult and impossible mask ventilation. ANESTHESIOLOGY 2006; 105:885-91.

Accepted for publication June 16, 2006. 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.

Steve M. Yentis, B.Sc., M.B.B.S., F.R.C.A., M.D., M.A., Magill Department of Anaesthetics, Intensive Care and Pain Management, Chelsea & Westminster Hospital, London, United Kingdom. s.yentis@imperial.ac.uk

## References

1. Shiga T, Wajima Z, Inoue T, Sakamoto A: Predicting difficult intubation in apparently normal patients: A meta-analysis of bedside screening test performance. *ANESTHESIOLOGY* 2005; 103:429-37

2. Kheterpal S, Han R, Tremper KK, Shanks A, Tait AR, O'Reilly M, Ludwig TA: Incidence and predictors of difficult and impossible mask ventilation. *ANESTHESIOLOGY* 2006; 105:885-91

3. Langeron O, Masso E, Huraux C, Guggiari M, Bianchi A, Coriat P, Riou B: Prediction of difficult mask ventilation. *ANESTHESIOLOGY* 2000; 92:1229-36

4. Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *ANESTHESIOLOGY* 2003; 98:1269-77

5. Henderson JJ, Popat MT, Latto IP, Pearce AC: Difficult Airway Society guidelines for management of the unanticipated difficult intubation. *Anaesthesia* 2004; 59:675-94

6. Yentis SM: Predicting difficult tracheal intubation: Worthwhile exercise or pointless ritual? *Anaesthesia* 2002; 57:105-9

Anesthesiology 2006; 105:872-3

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

# Pressure-support Ventilation in the Operating Room

## Do We Need It?

ADVANCES in technology have contributed to our ability to better care for critically ill patients. New methods of ventilatory support (such as pressure-support, pressure-controlled inverse ratio, and airway pressure-release ventilation) in the intensive care unit (ICU) have allowed for easier weaning and a decrease in barotrauma.<sup>1</sup> The study by Jaber *et al.*<sup>2</sup> compares the pressure-support ventilatory (PSV) mode in ICU ventilators with the recently introduced pressure support in ventilators used in operating room (OR) anesthesia workstations.

The initial method of mechanical ventilation in the OR was pressure-controlled ventilation. In this mode, the ventilator is set to deliver a certain pressure to the airway and maintain that pressure through the period of inspiration. As gas flows through the pressurized system to the patient's lungs, a tidal volume is generated (inspiration). The duration of inspiration depends on the respiratory rate and the inspiratory-to-expiratory ratio set by the operator. In some other ventilators, the inspiratory-to-expiratory ratio is set by increasing or decreasing the gas flow rate (increasing the flow rate during inspiration shortens the inspiratory time and prolongs exhalation, whereas decreasing the flow rate results in the opposite).

The tidal volume delivered to the patient by this mode is dependent on the lung compliance and the airway resistance. In stiff lungs (pulmonary edema, interstitial fibrosis, and adult respiratory distress syndrome), the compliance of the lung is low (unable to expand), and this results in a smaller tidal volume for the given preset pressure. In cases

of bronchial asthma, mucus plugging, or kinking of the endotracheal tube, the preset pressure is reached quickly, and the delivered tidal volume is also low.

The pressure-support mode of ventilation is derived from the pressure-controlled mode. In the pressure-support mode of ventilation, the ventilator senses the patient's initiation of a breath by either a decrease in the flow rate or a decrease in the circuit pressure. When this reaches a preset threshold, usually  $-2$  cm H<sub>2</sub>O, the ventilator is triggered and delivers a preset pressure (5-15 cm H<sub>2</sub>O) to augment the patient's tidal volume. In the latter part of inspiration, the flow rate starts to decrease. When the inspiratory flow rate reaches another preset value, (usually a decline of approximately 25%), the ventilator ceases to deliver the preset pressure. This then allows the patient to exhale. The tidal volumes vary, as in the pressure-control mode.

In this well-designed study, the authors test the performance of the ventilators in five anesthesia work stations against the performance of four traditional ICU ventilators. The results showed that three of the five anesthesia ventilators performed close to the ICU ventilators in time delay and pressurization at different levels of pressure support. Spontaneous ventilation in critically ill patients with multiple medical problems can be quite advantageous. Therefore, the ability to ventilate these patients in the OR with the same level of ventilatory support they were receiving in the ICU may prove to be the least disruptive to their oxygenation and ventilation status, which is already compromised.

This study was performed in a laboratory setting under controlled conditions. Studies need to be performed in the clinical setting to evaluate the actual advantages and disadvantages of the PSV mode in anesthetized patients. In their study, Jaber *et al.* found that two of the five anesthesia ventilators that they tested did not perform up to the ICU ventilator standards. We do not know whether these differences are clinically significant. However, if they are clinically important, it would be incumbent on the anesthesiologist to ensure that new OR

This Editorial View accompanies the following article: Jaber S, Tassaux D, Sebbane M, Pouzeratte Y, Battisti A, Capdevila X, Eledjam JJ, Joliet P: Performance characteristics of five new anesthesia ventilators and four intensive care ventilators in pressure-support mode: A comparative bench study. *ANESTHESIOLOGY* 2006; 105:944-52.

Accepted for publication July 31, 2006. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

ventilators were functionally equivalent to their ICU counterpart before purchasing new machines.

However, we suspect that only a small number of ICU patients would actually benefit from the PSV mode in the OR. Most ICU patients who are on PSV are in the process of being weaned from mechanical ventilation. These patients are particularly vulnerable to respiratory depressant drugs. When they come to the OR, they require inhalation anesthesia and/or narcotics that cause respiratory depression. The previous settings for PSV that maintained adequate ventilation may no longer be adequate to prevent hypoxia or hypercapnia. This results in the need to increase ventilatory support. Also, the surgical procedure may require the patient to be in certain positions, (*i.e.*, lateral, prone, or steep Trendelenburg), which may not be well tolerated by an already compromised patient who is breathing spontaneously. Finally, if the surgical procedure required muscle relaxants, it would be impossible to continue using the PSV mode.

The PSV mode may be used in the OR in spontaneously breathing patients who are undergoing peripheral surgery with a laryngeal mask airway or an endotracheal tube. Potential advantages of this are an increase in tidal volume and a decrease in the work of breathing. Many of these patients are healthy and have a large respiratory reserve. When using the PSV mode in these patients, some prolongation in delay time, triggering, or pressurization probably will not have an adverse effect.

However, Jaber *et al.* did not study the ventilators in PSV mode with changes in resistance or compliance; therefore, it is not possible to know what effects, if any, this would have on ventilation. There are also issues of patient safety. Devitt *et al.*<sup>3</sup> showed that in patients ventilated with a laryngeal mask airway, as the inflation

pressure increased, so did the leak around the laryngeal mask airway, as well as the amount of gas entering the stomach. Currently, it is unknown how a leak around the laryngeal mask airway (using the PSV mode) would affect the tidal volume delivered or the anesthesiologist's ability to detect a decrease in minute ventilation.

Continuing advances in ventilator technology could greatly affect the outcome of critically ill patients. By including these new modes of ventilation into anesthesia workstations, anesthesiologists may be able to minimize adverse effects that can occur when a critically ill patient comes to the OR. We see this study as an important addition to the literature because it shows that technology improvements in traditional intensive care ventilators can be transferred to the OR. Unlike the early OR ventilators, which were merely pressure generators or time cycled-flow generators with a preset maximum pressure limit, the modern OR ventilators are microprocessor-driven, sophisticated machines. However, as with any new technology, the anesthesiologist must understand its indications and limitations, know how to properly implement it, and determine its cost effectiveness.

**Hossam Tantawy, M.B.Ch.B.,\* Jan Ehrenwerth, M.D.,\***  
\*Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. jan.ehrenwerth@yale.edu

## References

1. Burchardi H: New strategies in mechanical ventilation for acute lung injury. *Eur Respir J* 1996; 9:1063-72
2. Jaber S, Tassaux D, Sebbane M, Pouzeratte Y, Battisti A, Capdevila X, Eledjam JJ, Joliet P: Performance characteristics of five new anesthesia ventilators and four intensive care ventilators in pressure-support mode: A comparative bench study. *ANESTHESIOLOGY* 2006; 105:944-52
3. Devitt JH, Wenstone R, Noel AG, O'Donnell MP: The laryngeal mask airway and positive-pressure ventilation. *ANESTHESIOLOGY* 1994; 80:550-5

Anesthesiology 2006; 105:873-6

Copyright © 2006, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## *If You Prick Us, Do We Not Bleed?*

IN Shylock's soliloquy in *The Merchant of Venice*,<sup>1</sup> in his appeal for lack of bias, Shakespeare invoked a physiologic event (the title of this editorial) that would have been known as well to the 17th-century audience as it is to 21st-century anesthesiologists. Although that Elizabe-

This Editorial View accompanies the following article: Zufferey P, Merquiol F, Laporte S, Decousus H, Mismetti P, Auboyer C, Samama CM, Molliex S: Do antifibrinolytics reduce allogenic blood transfusion in orthopedic surgery? *ANESTHESIOLOGY* 2006; 105:1034-46.

Accepted for publication July 25, 2006. The author is an employee of Novo Nordisk A/S, the developer and manufacturer of recombinant activated coagulation factor VII, rFVIIa, NovoSeven®.

David C. Wartier, M.D., Ph.D., served as Handling Editor for this article.

than trespass was surely less severe than is modern spinal reconstruction, total hip arthroplasty, or sternotomy and cardiopulmonary bypass, the qualitative result is the same: hemorrhage. Countless studies have examined hemorrhage, including many evaluating a substantial variety of therapeutic and pharmacologic maneuvers aimed at reducing hemorrhage and the ensuing complications when hemorrhage is not treated adequately. Despite the many pleas for the elimination of bias, as was Shylock's, those requests have not been heeded fully. His own plea presaged his being thwarted in obtaining a pound of flesh, because he could not perform the surgery without blood loss<sup>2</sup> any more than it can be accomplished today.

In this issue of *ANESTHESIOLOGY*, Zufferey *et al.*<sup>3</sup> examine a modern therapy aimed at decreasing hemorrhage in-

duced by surgical trauma. They provide a meta-analysis examining an unapproved use (frequently called “off-label” or “investigational”) of aprotinin, a protease inhibitor with antifibrinolytic properties, and tranexamic acid, an inhibitor of plasminogen activation and plasmin, in orthopedic surgery. In doing so, they have made an exceptional effort to eliminate bias, and thus provide a better meta-analysis than is usual. They contacted investigators to verify published data and obtain additional information when that available was insufficient; did not consider trials without a specific transfusion protocol; provided separate analyses with and without clinical trials that were not randomized and double-blind; examined and presented “funnel plots”; and performed repetitive analyses to ensure that one trial did not exert a dominating influence on the results. They concluded that both aprotinin and tranexamic acid are efficacious in reducing the proportion of patients receiving transfusion of allogeneic erythrocytes.

However, Zufferey *et al.* pooled data from all doses, even when more than one was given in a single study—a *post hoc* procedure generally not accepted, especially by regulatory authorities. Thus, no individual dose was assessed as efficacious, and we are not presented with an understanding of the lowest efficacious dose. Second, there was not a full assessment of the magnitude of the transfusion decrease or blood loss. Statistical significance does not necessarily equate with clinical importance. Both pharmaceuticals reduced by approximately half the fraction of patients given allogeneic erythrocytes. However, although nearly all of the randomized, double-blind trials with tranexamic acid found this statistical reduction, only two of the similar seven trials with aprotinin did so. Other results related to transfusion also differed between the two compounds. For tranexamic acid, none of the randomized, double-blind trials reduced intraoperative blood loss, although most trials reduced total perioperative blood loss (median 31%) and reported a statistically significant decrease in volume of transfused erythrocytes (median 1.5 units). For aprotinin, of the seven double-blind, randomized trials assessed by Zufferey *et al.*, most demonstrated a reduction in intraoperative blood loss (median 29%) and a reduction in total perioperative blood loss (median 32%). However, the reduced blood loss did not uniformly result in decreased transfused volume of allogeneic erythrocytes. Only three of the seven trials found a statistically significant reduction of the volume of transfused erythrocytes (median 1.3 units). Although the study with the largest number of patients (280) found a statistically significantly reduced blood loss, the magnitude (intraoperative, approximately 100–140 ml; total perioperative, approximately 300 ml) did not reduce erythrocyte transfusion (not surprisingly in view of the relatively modest reduced blood loss).

A meta-analysis can be no better than the data on which

it depends, and the analysis itself is subject to biases introduced in the methodology used and the criteria for trial and endpoint selection. Clinical trials regarding transfusion present special difficulties. Prominent among these are the problems in conducting double-blind trials, selection and assessment of appropriate efficacy endpoints, and ensuring that transfusion protocols are identical for all institutions and physicians and are implemented fully and followed without exception. None of the trials that made up the current meta-analysis reported the degree of adherence to their transfusion protocol. The endpoint selected by Zufferey *et al.* (proportion of patients not transfused with erythrocytes), although endorsed by regulatory authorities,<sup>4</sup> may not be the most clinically appropriate. If possible, the endpoint should closely reflect the pharmacologic action. Tranexamic acid and aprotinin seem efficacious in decreasing blood loss in at least some types of orthopedic surgery, but apparently insufficiently so to reliably decrease the volume of erythrocytes transfused, perhaps owing to the limited blood loss associated with those procedures.

Presumably, the major goal of reducing transfusion is the reduction of the associated risk, although surgical visibility, direct tissue damage, and conservation of blood components are also considerations. The risk of transfusion is largely a function of the number of units or donors to which the recipient is exposed. Calculations from the estimates presented by Fiebig and Busch<sup>5</sup> produce an estimated total risk of transmission of any one of the following viruses—hepatitis A, B, C; HIV; human T-cell lymphotropic virus types I and II; parvovirus B19; West Nile virus—as approximately less than 1:100,000 per unit of blood component, but cannot include the emergence of new pathogens. The risk of fatal hemolytic transfusion reaction after erythrocyte transfusion is thought to be approximately 1:1,000,000 units transfused<sup>6</sup>; the risk of clinically important transfusion-related acute lung injury after erythrocyte transfusion is unclear; and the risk of symptomatic bacterial infection transmitted by transfusion of erythrocytes seems to be 1:1,000,000 units.<sup>5</sup> The persistence of donor leukocytes in recipient blood for more than 1 yr after transfusion,<sup>7</sup> despite leukoreduction of donated blood,<sup>8</sup> is worrisome and possibly reflective of the uncertain immunomodulatory risks of transfusion.<sup>9</sup>

It would seem that an endpoint that would better quantify the decrease of risk of transfusion is one that encompasses the risk from all blood components: a comparison of the number of donors to which the recipient is exposed, rather than only avoidance of transfusion of just erythrocytes. The reports of the trials examined by Zufferey *et al.* regarding the use of aprotinin (approved only for use in cardiac surgery with cardiopulmonary bypass) or tranexamic acid (approved only for use in hemophilia) in orthopedic surgery did not contain sufficient data to enable analysis of this clinically relevant endpoint. Therefore, even among those trials that found a decrease of erythrocyte transfusion, a potential reduc-

tion of total allogeneic transfusion-related risk could not be quantified.

Shylock had something to say about safety, as well. Only two phrases after discussing bleeding, he further observed, “. . . if you poison us, do we not die?”<sup>1</sup> Modern therapeutics rarely cause lethality, owing in part to careful evaluations by pharmaceutical companies and regulatory authorities, but nearly all have undesirable effects, some of them potentially serious. Determination of safety of pharmaceuticals can be more difficult than demonstration of efficacy, owing to the generally low incidence of important adverse effects, requiring large sample sizes for their elucidation. Zufferey *et al.* concluded appropriately that the trials they examined had insufficient information to document the safety of use of antifibrinolytics in orthopedic surgery.<sup>3</sup> Adding to this uncertainty are three retrospective analyses of cardiac surgery databases<sup>10-12</sup> that have highlighted a question related to aprotinin that had been raised previously<sup>13</sup>: that of renal damage. This controversial issue has been addressed recently by several authors.<sup>14-16</sup> No matter the level of sophistication of statistical approaches, applications, and data examination in an effort to reduce bias, elimination of bias is exceedingly unlikely in retrospective evaluations of databases, including when propensity analysis is used. Indeed, the central purpose of a prospective, randomized, blinded clinical trial is to eliminate such bias.

The implications of the analysis of Zufferey *et al.* extend beyond the immediate aims of the authors. Their report should stimulate anesthesiologists to maintain an interest and understanding of the increasingly complex fields of coagulation and natural and exogenous inhibitors of clotting. We have learned much in the past decade or so, in part owing to the development of recombinant coagulation factors, and the research associated not only with their development, but that permitted by their availability as pure zymogens or enzymes, rather than as a mix of many components. Current knowledge regarding coagulation has been well reviewed in this journal.<sup>17</sup> As we have learned about the many steps involved and their precise biochemical nature, so has been developed a variety of pharmaceuticals targeted at specific individual steps of the many reactions. A few are in the clinical domain, but many more are likely to be available clinically in the next few years. Their use, either singly or in combination, for the many patients with risk for thromboembolic disease, will pose substantial intraoperative and postoperative challenges.

We have also learned much about the innate systems that limit unneeded coagulation or eliminate clots after their formation. There are numerous native molecules that stimulate or inhibit fibrinolysis. The many interactions between coagulation and fibrinolysis have been reviewed recently.<sup>18</sup> When coagulation factor or platelet concentrations are reduced (as occurs routinely during

surgery: hemodilution—significant blood loss, and appropriate consumption without clotting factor or platelet replacement) or are absent (as in hemophilia), a loosely formed network of fibrin that is poorly resistant to lysis by plasmin is produced.<sup>19</sup> This has led some to label this condition as “hyperfibrinolysis;” however, it seems likely that it represents *in vivo* normal fibrinolytic activity that has been initiated consequent to thrombin production and fibrin formation, acting on a poorly structured fibrin network, as has been shown *in vitro*. Clinically, it is exceedingly difficult to distinguish between poor fibrin formation or excessive plasmin activity as a potential cause of inappropriate or excessive bleeding. It is possible that the efficacy of aprotinin may be related to fibrinolysis during states of poor clot formation when coagulation factors (and perhaps platelets) have been decreased by loss and dilution.

Four hundred years after the writing of *The Merchant of Venice*, it is still debated whether Shylock was intended to be portrayed as a villain or as a sympathetic victim of bias. Without appropriate information, we cannot ascertain Shakespeare’s intent or the benefit:risk of the use of aprotinin or tranexamic acid in orthopedic surgery. Existing data from previously conducted prospective randomized clinical trials may be adequate to answer questions regarding the safety of aprotinin in cardiac surgery but do not seem adequate to allow any conclusion regarding its safety in orthopedic surgery. In view of the limited efficacy in orthopedic surgery, clinicians would be well advised to consider such off-label use exceedingly carefully until we have appropriate information from well-designed, well-executed, prospective, randomized, double-blind trials to provide the best, least biased results to guide therapy.

**Richard B. Weiskopf, M.D.**, Novo Nordisk A/S, Bagsvaerd, Denmark, and Professor Emeritus, University of California, San Francisco, California. [rwes@novonordisk.com](mailto:rwes@novonordisk.com)

## References

1. Shakespeare W: The Merchant of Venice. Act III, Scene I, Quatro. The British Museum. London, 1600 (likely written between 1594 and 1597)
2. Shakespeare W: The Merchant of Venice. Act IV, Scene I, Quatro. The British Museum. London, 1600 (likely written between 1594 and 1597)
3. Zufferey P, Merquiol F, Laporte S, Decousus H, Mismetti P, Auboyer C, Samama CM, Molliex S: Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *ANESTHESIOLOGY* 2006; 105:1034-46
4. Silverman T, Aebbersold P, Landow L, Lindsey K: Regulatory perspectives on clinical trials for trauma, transfusion, and hemostasis. *Transfusion* 2005; 45 (suppl 1):14S-21S
5. Fiebig E, Busch M: Emerging infections in transfusion medicine. *Clin Lab Med* 2004; 24:797-823
6. Szazma K: Transfusion errors: Scope of the problem, consequences, and solutions. *Curr Hematol Rep* 2003; 2:518-21
7. Lee T-H, Paglieroni T, Ohto H, Holland PV, Busch MP: Survival of donor leukocyte subpopulations in immunocompetent transfusion recipients: Frequent long-term microchimerism in severe trauma patients. *Blood* 1999; 93:3127-39
8. Lee T-H, Paglieroni T, Utter G, Chafets D, Gosselin R, Reed W, Owings J, Holland PV, Busch MP: High-level long-term white blood cell microchimerism after transfusion of leukoreduced blood components to patients resuscitated after severe traumatic injury. *Transfusion* 2005; 45:1280-90
9. Klein HG: Immunomodulatory aspects of transfusion: A once and future risk? *ANESTHESIOLOGY* 1999; 91:861-65

10. Mangano D, Tudor J, Dietzel C: The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354:353-65
11. Karkouti K, Beattie W, Datillo K, McCluskey S, Ghannam M, Hamdy A, Wijeyesundera D, Fedorko L, Yau T: A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46:327-38
12. Kincaid E, Ashburn D, Hoyle J, Reichert M, Hammon J, Kon N: Does the combination of aprotinin and angiotensin-converting enzyme inhibitor cause renal failure after cardiac surgery? *Ann Thorac Surg* 2005; 80:1388-93
13. D'Ambra MN, Akins CW, Blackstone EH, Bonney SL, Cohn LH, Cosgrove DM, Levy JH, Lynch KE, Maddi R: Aprotinin in primary valve replacement and reconstruction: A multicenter, double-blind, placebo-controlled trial. *J Thorac Cardiovasc Surg* 1996; 112:1081-9
14. Weiskopf RB: Assessment of hemostasis through the retrospectroscope. *J Thromb Haemost* 2006; 4:2074-8
15. Levy JH: Aprotinin is useful as a hemostatic agent in cardiopulmonary surgery: Yes. *J Thromb Haemost* 2006; 4:1875-8
16. Karkouti K, Beattie WS: Aprotinin is useful as a hemostatic agent in cardiopulmonary surgery: No. *J Thromb Haemost* 2006; 4:1879-81
17. Roberts HR, Monroe DM, Escobar M: Current concepts of hemostasis: Implications for therapy. *ANESTHESIOLOGY* 2004; 100:722-30
18. Cesarman-Maus G, Hajjar KA: Molecular mechanisms of fibrinolysis. *Br J Haematol* 2005; 129:307-21
19. Collet J, Lesty C, Montalescot G, Weisel J: Dynamic changes of fibrin architecture during fibrin formation and intrinsic fibrinolysis of fibrin-rich clots. *J Biol Chem* 2003; 278:21331-5

Substantially after this editorial was written and accepted for publication, and only a few days before its final typesetting, the Cardiovascular and Renal Drugs Advisory Committee of the FDA met on September 21, 2006 and discussed aprotinin. The FDA had previously expressed concern regarding the safety of aprotinin with respect to hypersensitivity-induced fatalities, and possible adverse renal events. The FDA has not announced their conclusions, but when available, the document should appear on the FDA website, at <http://www.fda.gov/ohrms/dockets/ac/cder06.html#CardiovascularRenal>.