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Sickle Cell and Anesthesia: Do Not Abandon Well-established Practices without Evidence

To the Editor:—Firth and Head[1] are to be congratulated for providing a comprehensive review of the pathophysiology of sickle cell disease and erudite discussion of its implications for anesthesiologists. We also appreciate their attempts to apply evidence-based knowledge to our understanding of the perioperative care of these patients. Although this will undoubtedly become a valuable resource for anesthesiologists, we are compelled to provide some corrections in the text and tables as well as provide alternative interpretations of some of the evidence.

The authors refer to a randomized no-transfusion group in their discussion of Vichinsky *et al.* (reference 98, page 776).[2] In fact, there was not a randomized no-transfusion group. The authors seemed to have missed the fact that this report and several more by the same authors were reports of subpopulations of the work by this group. In this and subsequent articles from the Preoperative Transfusion in Sickle Cell Disease Study Group as initially reported by Vichinsky *et al.*,[3] the groups were the same (described below). Furthermore, the second to last sentence in the third paragraph on page 776 should read, "This [acute chest syndrome] occurred in 21% of cases in both the aggressive transfusion and the *nonrandomized* nontransfusion group, 8% in the conservative transfusion group, and 3% in the nonrandomized *transfusion* group," as described in table 4.

In table 4 on page 775, regarding Haberkern *et al.,* "1995,"[4] the numbers and percents for "cholecystectomies, complications" for the four groups are in fact the numbers of patients in the groups and the percents of sickle cell events, not the numbers and percents of complications. (This study was actually published in 1997.) The percentages of total complications and acute chest syndrome in the four groups (as listed) are in fact as follows: group 1, randomized aggressive transfusion: 36%/9%; group 2, randomized simple transfusion: 39%/11%; group 3, nonrandomized nontransfusion: 43%/19%; and group 4, nonrandomized transfusion: 41%/7%. These groups are the same in all of the studies reported by the Preoperative Transfusion in Sickle Cell Disease Study Group. These corrected data underscore concerns regarding the risk of perioperative complications in the nontransfusion group.

In the discussion of Griffin and Buchanan,[5] the authors concluded that "any potential benefit from transfusion would therefore be low and risks of transfusion were not justified for minor procedures." However, the actual conclusion from this report stated that "operative transfusions *might* be avoided in children with sickle cell disease who undergo most minor surgical procedures." The overall complication rate was 26%, thoracotomy/laparotomy 50%, tonsillectomy and adenoidectomy 56%, others 5%. This report neither provided evidence to withhold transfusion in any group nor lobbied against transfusions.

In their table 5 on page 777 (Guidelines for the use of Perioperative Prophylactic Erythrocyte Transfusion), the foundation for this table is not clear and certainly not evidence based. It suggests guidelines for perioperative transfusion that are misleading given the absence of prospective, randomized data to support a nontransfusion approach.

We acknowledge the lack of a proven causal relation between hypoxia, dehydration, and hypothermia and sickling events in the perioperative clinical setting (page 782). However, in the context of sickle cell disease, we are compelled to prove that *no* such relation exists before abandoning practices that have been associated with decreased perioperative morbidity and mortality in these patients.

A conservative approach to children with sickle cell disease in the perioperative period has been and continues to be adequate hydration and correction of anemia. To propose a therapeutic nihilistic approach to the treatment of these patients in the absence of substantive evidence is dangerous. Despite the best care today, the perioperative mortality rate in patients with sickle cell disease of 1 in 100 is severalfold greater than that in nonsickle adults, approximately 1 in 300,000, and in nonsickle children, 1 in 50,000–80,000. Before our current practice patterns for these children are changed, prospective randomized studies that examine anesthetic practices in this and other diseases should be conducted.

Salvatore R. Goodwin M.D.,* Charles Haberkern, M.D., Mark Crawford, M.B.B.S., Jerrold Lerman, M.D., Thomas Mancuso, Myron Yaster, M.D. * Nemours Children's Clinic, Jacksonville, Florida. sgoodwin@nemours.org

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In Reply:—We wish to thank the correspondents for their interest in our review[1] and for correcting the typographical errors. Although a small typographical error in the sickle genetic code has extensive consequences, the equivalent inaccuracies in the review fortunately do not have similarly far-reaching effects on our conclusions. Regarding the work by Vichinsky *et al.*,[2–4] the fact that this was analysis of subpopulations of the same patient group was explicitly stated in the relevant studies. Our motivation for reviewing these new studies in detail was the additional information provided, not ignorance of the database from which it originated. The data from Haberkern *et al.*[2] (Complications, page 1534) are in fact correctly reported in table 4 of the original article,[1] which is repeated now as table 1 in this reply. The correspondents are confusing sickle-specific events with overall complications, rates that variously included fever, transfusion reactions, and postoperative surgical

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Table 1. Outcomes from Recent Studies of Perioperative Blood Transfusion*

Reference	Study Details	Categories	R-XTF	R-TF	NR-TF	NR-NTF
Griffin and Buchanan[96] (1993)	Retrospective nonrandomized; 66 children	Minor procedures				46
		Complications				2%
		Other procedures				20
		Complications				15%
Koshy *et al.*[87] (1995)	Retrospective nonrandomized; 1,079 adults, children; low- and moderate-risk surgical procedures	Hb SS—low risk			248	145
		Complications			4.8%	12.9%
		Hb SS—moderate risk			390	43
		Complications			7.9%	4.7%
		Hb SS—high risk			12	0
		Complications			16.7%	
Vichinsky *et al.*[88] (1995)	Prospective randomized; 604 assorted procedures	Procedures	303	301		
		Complications	15%	15%		
		Transfusion complications	14%	7%		
Haberkern *et al.*[89] (1997)	Prospective randomized, nonrandomized; 364 patients	Cholecystectomies	110	120	97	37
		Complications	12%	19%	18%	32%
		Transfusion complications	15%	8%	9%	3%
Vichinsky *et al.*[98] (1999)	Prospective randomized, nonrandomized groups; 138 procedures	Orthopedic procedures	34	40	40	24
		ACS	21%	8%	3%	21%
		Transfusion complications	24%	15%		

* This table is an amended version of table 4 from the original article.

Complications refers to sickle cell disease–specific complications, such as pain crises or acute chest syndrome.

ACS = acute chest syndrome; Hb SS = patients homologous for hemoglobin S; NR-NTF = nonrandomized nontransfusion; NR-TF = nonrandomized conservative or aggressive transfusion; R-TF = randomized conservative transfusion; R-XTF = randomized aggressive transfusion.

problems.[2] These general outcomes are not the appropriate endpoints by which to assess the need for or effect of transfusion.

With respect to the work of Griffin and Buchanan,[5] the correspondents seem to have formed their opinions from the abstract summary. We refer the correspondents to the tables, text, and prominent citations[6,7] discussed by Griffin and Buchanan.[5] The complications comprising the rates cited by the authors were largely atelectasis and transient, uncomplicated postoperative pyrexia, which the investigators[5] emphasized were not specific to sickle cell disease. Again, it is misleading to cite the incidence of a heterogeneous group of complications in a heterogeneous population as motivation for an intervention against the lower occurrence of a specific subset of complications in a specific subpopulation. The incidence of complications specific to sickle cell disease in the relevant minor procedure subpopulation was, as reported,[1] 2% (n = 1 in 46).[5] The sole patient with the sickle complication of acute chest syndrome had significant preexisting cardiopulmonary dysfunction. The researchers[5] cited these facts in their extensive discussion of the limits of any potential role for transfusion. They concluded, "our data support the concept that preoperative blood transfusions may be unnecessary for children with sickle cell disease . . . undergoing most minor operations (who) might therefore be spared the cost, inconvenience, and risks of infection, alloimmunization and transfusion reactions inherent in RBC transfusions" (page 685).[5]

In response to the suggestion that table 5, Guidelines for the Use of Perioperative Prophylactic Erythrocyte Transfusion, from the original article is not evidence based, we refer the correspondents to the text of the review and relevant selected references.[1] Some of the rationale and evidence that simple transfusion be avoided in low-risk situations has been reemphasized above. As the correspondents' call for prospective randomized trials acknowledges, the evidence for the efficacy of simple transfusion in intermediate-risk situations is incomplete, and we cannot therefore say conclusively that transfusion is or is not indicated. Our guidelines for high-risk cases were based on a systematic review of the primary neuroanesthetic and cardiothoracic literature of the preceding four decades, although we limited our citations of this fragmentary evidence to a short selection at the request of the ANESTHESIOLOGY reviewers. We concede that our guidelines for transfusion in uncomplicated pain crises are not evidence based—simply because we are unaware of conclusive evidence to support or refute the practice of transfusion. We cannot advocate an intervention in the absence of supportive evidence and concur with authoritative peer opinion that transfusion is not indicated.[8] A detailed critique of practice based on the largely uncontrolled data on transfusion for acute chest syndrome was beyond the scope of an already lengthy review.[1] The guidelines on acute chest syndrome are consequently limited to the well-documented evidence that transfusion can improve arterial hemoglobin oxygenation, a predictable and possibly nonspecific physiologic consequence of increasing mixed venous saturation and pulmonary capillary transit time by correction of anemia in the face of pulmonary shunting and impaired gas exchange. The guidelines are therefore based on what data are available. Because this evidence is incomplete, we simply provided guidelines, rather than making more proscriptive recommendations.

The correspondents state that we are compelled to prove that no causal relation exists between hypoxia, dehydration, and hypothermia and acute perioperative complications before abandoning practices associated with decreased perioperative morbidity and mortality. The only definitive way to do this, subjecting patients to these injuries in a well-constructed study, is practically difficult and ethically impossible. The studies cited, including exposure to inhalational and hypobaric hypoxia, the use of occlusive arterial tourniquets, and the coexistence of sickle cell disease and cyanotic heart disease, strongly suggest that hypoxia-induced sickling (and by extension acute cellular dehydration) are not triggers of acute complications.[1] The relevant practices that are associated with an apparent decrease in morbidity and mortality are probably the overall general improvements in basic anesthetic and perioperative care, not specific unproven deviations from standard practice. We do not advocate therapeutic nihilism, as the correspondents aver, but rather, we encourage adherence to these basic standards of anesthetic care.

We are surprised by the correspondents' continued enthusiasm for transfusion, given their familiarity with the relevant literature.[2–4] The previously widespread adoption of a practice, exchange transfusion, in the absence of controlled studies, was no guarantee of efficacy or lack of harm.[2–4] Although the liberal use of transfusion may be well established in the correspondents' practice, this is similarly not proof of efficacy or freedom from injury. For considerations of effect, we direct

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them to long-established alternative approaches of avoiding perioperative transfusion.[6,7] For evidence of harm, consider a recent study of 150 multiply transfused American patients that found an incidence of hepatitis C infection of 35.3%, a sobering demonstration of iatrogenic inury.[9] By contrast, in Jamaica, where transfusion practices are far more conservative, a study of 250 patients documented an infection rate of 2%.[10] Rather than preventing acute sickle problems, transfusion can actually precipitate acute pain[11] and pulmonary complications.[12] We do not suggest that our review is the last word on management or even that the model we outline explains all aspects of sickle cell disease. We therefore strongly support the call for prospective randomized studies of anesthetic practice for sickle cell disease. Given the proven potential for iatrogenic injury, we urge the correspondents to consider the cautious methods of others[1,5–8,12] and, in the absence of conclusive evidence, not to abandon a well-established practice: First do no harm.

Paul G. Firth, M.B., Ch.B., C. Alvin Head, M.D.* * Medical College of Georgia, Augusta, Georgia. ahead@mcg.edu

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Circadian Influences, Low-dose Isoflurane, and the Ventilatory Response to Hypoxia

To the Editor:—Pandit *et al.*[1] are to be congratulated on their study on the effects pain and audiovisual stimulation on depression of the acute hypoxic ventilatory response by low-dose halothane. Their results are in good correspondence with some of the key studies in this complex field of research.[2–6] As stated by the authors, there is now ample evidence for the existence of quantitative differences in the ability of low-dose inhalational anesthetics to depress the ventilatory response to acute hypoxia in humans. For example, 0.1% end-tidal halothane depresses the response by 50–60%, whereas the same concentration of isoflurane has much less of an effect (reduction 30–40%).[1–6] The authors discuss several explanations for the observed differences between halothane and isoflurane, such as differences in pharmacokinetics, differences in the production of reactive oxygen species, and differences in their interaction with sites in the central nervous system involved in behavioral control of breathing. Evenly important are issues related to methodology.[7] Often, very small differences in protocols may cause large differences in study outcomes. I would like to give an example of the latter. In three subjects, the ventilatory responses to hypoxia at three time points on one single day were measured: 8:00 AM, noon, and 4:00 PM. At 9:00 AM, one additional response during inhalation of 0.2% end-tidal isoflurane was obtained. The ventilation (Vi) response to five end-tidal P_{O_2} levels was analyzed using the following equation: $Vi = G \exp(-D\ P_{ETO_2}) + y_0$ (G is the hypoxic sensitivity, D is a shape parameter, and y_0 is ventilation at hyperoxia). Control and recovery responses varied considerably by 20–30% for parameter G and 30–40% for parameter y_0 (fig. 1). Consequently, the depression of the isoflurane response relative to the control and recovery responses was evenly variable and varied from 50 to 70%. The picture that emerges is that the circadian rhythm has important influences on the ventilatory response to hypoxia and consequently on the influences that low-dose anesthetics have on the response. How the behavioral control system interacts with circadian influences remains unknown. Although I realize that the study I present here is of small sample size, it points toward (1) an important and complex role for circadian

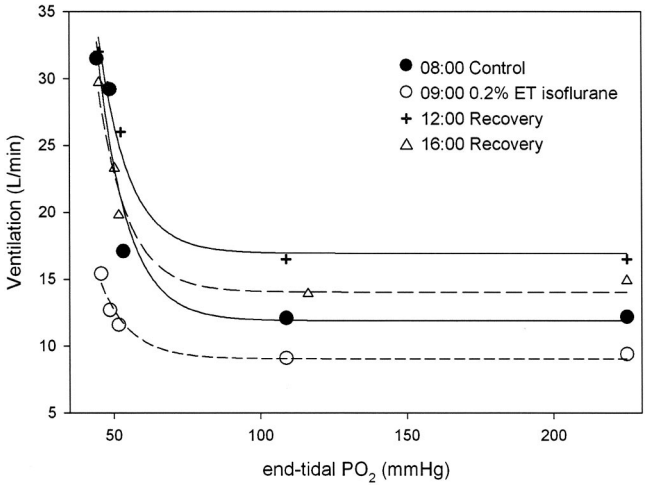

Fig. 1. Ventilatory response to hypoxia obtained at five oxygen levels in a 25-yr-old woman. Nondrug studies were performed at 8:00 AM, noon, and 4:00 PM. At 9:00 AM, the effect of 0.2% end-tidal isoflurane was measured. The *lines* through the data are curve fits to the data using the following equation: $Vi = G \exp(-D\ P_{ETO_2}) + y_0$. The variability among control and recovery responses is apparent. P_{O_2} = partial pressure of oxygen.

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influences on the interaction between anesthesia and behavioral and chemical control of breathing and (2) the need for identical protocols when comparing agents and studies on the influence of low-dose anesthetic agents on ventilatory control.

Albert Dahan, M.D., Ph.D., Leiden University Medical Center, Leiden, The Netherlands. a.dahan@lumc.nl

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In Reply:—I thank Dr. Dahan for his interest in my article.[1] He presents data from three subjects (he acknowledges that this is a very small sample) that show some "within-day variation" in the acute hypoxic ventilatory response (AHVR). The figure he presents for one subject indicates that minute ventilation in euoxia is lowest in the morning, highest at midday, and in-between in the afternoon. I do not know whether this same pattern is the same in all subjects. The minute ventilation in euoxia was as high as approximately 20 l/min, and this implies either that the end-tidal partial pressure of carbon dioxide (P_{CO_2}) of Dahan's subject varied widely during the day or that, if end-tidal P_{CO_2} was constant, the metabolic CO_2 output of the lung must have varied widely during the day. The AHVR variation must therefore have correlated with end-tidal P_{CO_2} and/or CO_2 output in Dahan's small series. However, neither Sahn *et al.*.[2] nor Zhang and Robbins[3] were able to find such correlations.

Nonetheless, the within-day variation reported by Dahan may indeed be a "circadian" influence, and I agree that the observation needs further study. Variation in the AHVR within individuals on repeat testing is well established,[4] but it seems that *between-day* variation is greater than *within-day* (circadian) variation.[2,3] The study of Zhang and Robbins[3] sheds important light on the issue of variation. They found that the method of inducing hypoxia (they studied square wave hypoxic input, incremental hypoxic steps, and simulated rebreathing) did not influence the AHVR measured. So it seems that the methodologic influences to which Dahan refers may not be as influential as we all (intuitively) might think them to be. This is perhaps further supported by my analysis that there is no actual difference in the result of studies using rebreathing as compared with those using step hypoxia in assessing the reduction in AHVR by low-dose anesthetic.[5]

Zhang and Robbins[3] also found that between-day variation was greater than within-day (circadian) variation, so although the within-day variation found by Dahan is of interest, it is possible that between-day variation is more important.

There are two practical questions: (1) Does this variation in AHVR impact upon the results of the relevant studies, and (2) how can we account for it or control for it experimentally?

With regard to the first question, if the variation in AHVR influenced the outcome of studies, it might prove difficult (because of the large confidence intervals) to show, for example, that anesthetics blunt AHVR. However, this is not the case, and many different studies consistently find that halothane, enflurane, and sevoflurane reduce AHVR. The only agent for which there is less consistency in different studies' results is isoflurane. Although this may be a result of inherent variation in AHVR, it is also possible (and perhaps more likely) to be due to some property of isoflurane that gives it a more variable effect than other agents.

With regard to the second question, there seem to be two general ways to control for variation. One is to conduct each experimental period in a study at precisely the same time of day. However, this does not control between-day variability (which seems more important). The second way is to conduct experimental periods at random times of day in a suitable number of different subjects, ideally using repeated experimental periods in the same subject, and then average the results to reduce any systematic variation. One problem is that repeated exposure is often (ethically) undesirable in anesthetic studies, but where possible, I prefer this second approach.

Jaideep J. Pandit, D.Phil., F.R.C.A., John Radcliffe Hospital, Oxford, United Kingdom. jaideep.pandit@physiol.ox.ac.uk

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Position of the Shoulder for Subclavian Approach

To the Editor:—We read with interest the article by Kitagawa *et al.*[1] regarding the proper shoulder position for subclavian vein (SCV) puncture. They are to be congratulated for performing an important study about the anatomical backgrounds of SCV catheterization. The major finding of their article was that, when compared with neutral and elevated positions, the lowered shoulder position is the best for

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the SCV approach. However, we would like to make a few comments regarding the article.

First, the longest overlap length between the lower border of the clavicle and the SCV in the inner third of the clavicle was one of the main reasons for quoting the lowered shoulder position. However, a needle path aiming at the suprasternal notch may cross the lower border of the clavicle somewhere between the midclavicular line and the inner third of the clavicle. In addition, the shaded overlap area in figure 1 of the article[1] extends out of the SCV, even to the innominate vein.

Second, one of the most important factors for successful catheterization is probability of contact between the puncture needle and the SCV. Because the cross-sectional area rather than the diameter on a plane is more important for the probability of contact, the cross-sectional area of the SCV beneath the inner third of the clavicle should be regarded as a major factor. If the cross-sectional area is not available, there may be another way of analyzing the probability of contact. Overlap length of the SCV on an imaginary line drawn between the needle entry point and the midportion of the clavicular head seems to be more relevant than that on the lower border of the clavicle. In figure 1 of the article,[1] we can realize that the neutral and lowered positions are comparable, but the elevated position has the shortest overlap length on the imaginary line.

Third, with regard to the small clinical trial, why were the neutral and lowered positions not compared? Where was the catheter tip located? Were there any catheters directed to the internal jugular vein (IJV)? As explained in figure 4 of the article,[1] the angle formed between the SCV and the innominate vein becomes narrower with the shoulder lowered. Considering the fact that, in children, a right SCV catheter is frequently positioned in the IJV because the angle formed between the SCV and the innominate vein is more acute,[2] there seems to be a risk of directing the SCV catheter into the IJV when the shoulder is lowered.

Last, changing the shoulder position after successful venipuncture, as suggested in the article,[1] carries the risk of withdrawing the puncture needle out of the vein. Even changing the shoulder position after advancing the guide wire may not be helpful, because a guide wire may already be directed to the IJV because of the short distance between the SCV puncture point and the confluence of the IJV and the SCV. If SCV catheterization is attempted with the shoulder lowered, tilting the head toward the catheterization side without movement of the shoulder may be more helpful in reducing the incidence of catheter malposition into the IJV.[3]

All the above-mentioned concerns should be clarified before deciding whether we should adopt the lowered shoulder position during SCV catheterization.

Jae-Hyon Bahk, M.D.,* **Ho-Geol Ryu, M.D.** * Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea. bahkjh@snu.ac.kr

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In Reply:—We thank Drs. Bahk and Ryu for their interest in our article[1] and valuable comments. We would like to take the opportunity to address the issues raised by their insights, point by point.

First, the longest overlap length between the lower border of the clavicle and the subclavian vein (SCV) in the inner third of the clavicle was cited as one of the principal reasons for recommending a lowered shoulder position. Drs. Bahk and Ryu describe concern about cases in which a needle may cross the lower border between the midclavicular line and inner third of clavicle. However, a lowered shoulder seems to offer a more appropriate position than other shoulder positions, because overlap increases with extension to the lateral side from the inner third of the clavicle, as described in our article. The lowered shoulder also increases the proximity of the SCV to the undersurface of the clavicle. This allows reliable SCV puncture and reduces the risk of complications such as pneumothorax during the use of basic SCV puncture technique (needle advancement contacting the undersurface of the clavicle), because the needle is not advanced beyond the necessary depth. The shaded area in figure 2 of our article[1] extends from the SCV to the innominate vein because we were using the definition of overlap described by Land[2] as the area of clavicle overlapping with the SCV, including the innominate vein.

Second, although we assessed probability of contact between the needle and the SCV using the longest and shortest diameters of the vein, assessment using SCV cross-sectional area may be more suitable, as indicated by Drs. Bahk and Ryu. We therefore reevaluated contact probabilities using the products of both halves of the longest and shortest diameters and the circular constant, expressing the area of an ellipsoid, and then compared values among the three shoulder positions, because the cross-sectional area of the SCV can be regarded as an ellipsoid, as indicated in figure 2 of our article.[1] The result was $\text{Area}_{\text{down}} \approx \text{Area}_{\text{neutral}} \approx \text{Area}_{\text{upl}}$, being consistent with the results as assessed using SCV diameters, resulting in being substantially comparable in the contact probability among the three shoulder positions. Although we assessed overlap using the same methods described by Land[2] and Tan *et al.*[3] as mentioned before, we agree with the proposal by Drs. Bahk and Ryu that overlap length of the SCV on an imaginary line drawn between the needle entry point and the midportion of the clavicular head is more relevant than using a point on the lower border of the clavicle. We are grateful to both doctors for making this recommendation.

Regarding the third and fourth comments made by Drs. Bahk and Ryu, the small number of patients participating in this clinical trial limited comparisons of SCV cannulation success rates between elevated and lowered positions only, where comparisons were expected to identify the most marked differences. From our experience, we believe that a clinical trial with a sufficient sample population will confirm the superiority of a lowered shoulder position over a neutral position in terms of success rates for SCV puncture. However, this issue must be clarified in a randomized clinical trial in the future. All catheterizations performed in the present trial were inserted into the right SCV, and no catheters were directed into the internal jugular vein. With our procedure inserting a catheter or guide wire into the SCV, advancement after a change in shoulder position from lowered to neutral may contribute to leading the catheter or guide wire toward the innominate vein. In addition, although Drs. Bahk and Ryu express concern regarding the risk of withdrawing the puncture needle from the SCV during the change in shoulder position after successful venipuncture, we believe that the risks associated with the procedure in actual practice are not as large as they suggest. Even if shoulder position changes from a lowered to a neutral or even a slightly elevated position, we have experienced minimal movement of the puncture needle. This is due to movement of the needle and syringe in an integrated manner along with the clavicle and surrounding tissue and

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due to the motionless area of the sternoclavicular joint, resulting in the needle remaining relatively still in the region of insertion. However, we do not recommend marked shoulder elevation. Shoulder movement after SCV puncture in infant cases may also increase the risks associated with withdrawing the needle. We think that our procedure can be applied to school-aged children and older patients, but not to children younger than school age, and infants in particular. In the case of infants, tilting the head toward the side of catheterization may help to reduce the incidence of catheter malposition into the internal jugular vein, as recommended by Drs. Bahk and Ryu.[4]

Norihito Kitagawa, M.D.,* **Mayuko Oda, M.D., Masatoshi Morimoto, M.D., Noriaki Miyazaki, M.D.** * Tsuruta Hospital, Ushizu, Saga, Japan. kitagawa@mail.anes.saga-med.ac.jp

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Myocardial Performance Index and Tissue Doppler Systolic Wave Velocity Are Preload Dependent

To the Editor:—We read with great interest the article about myocardial performance index and tissue Doppler imaging in patients with single ventricles, comparing two anesthetic regimens, sevoflurane and fentanyl–midazolam.[1]

The authors found no change in myocardial performance index, which is a global index of both systolic and diastolic function. However, they describe a significant decrease of both myocardial Doppler imaging systolic (Sm) and early diastolic (Em) wave velocities from baseline to dose 1 and dose 2 with fentanyl–midazolam (table 3 in their article). Nevertheless, both (neo)aortic flow and time–velocity integral decreased significantly.

An important limitation of this study, the preload dependency of both parameters used, was not fully discussed. It has to be speculated that anesthetics, in a setting as used in this study, although not shown, induce major changes in loading conditions.[2] Assessment of ventricular function implies that load-independent methods should be used. It has been indirectly suggested in the literature that myocardial performance is preload dependent: Broberg *et al.*[3] described a close relation between this index and dP/dtmax, the latter being strongly preload dependent.[4] Recently, this preload dependency was also suggested by our group when we described a close relation between myocardial performance index and preload adjusted maximal power.[5]

In addition, the same problem arises with the systolic flow wave velocity of the tissue Doppler imaging. Our group recently showed clearly that this flow wave velocity is load dependent.[6] Therefore, a decrease in the length of the myocardial fibers due to a decrease in EDV will lead to decreases in stroke volume, the velocity of shortening, and systolic tissue velocity obtained with tissue Doppler imaging.

Echocardiographic parameters as myocardial performance indexes and systolic Doppler myocardial velocity must be used cautiously in view of various physiologic and pathophysiologic interfering factors, in particular when one is assessing hemodynamics in conjunction with various dose regimens of anesthetics.

Jan Poelaert, M.D., Ph.D., * **Amà Ruggero, M.D.** * Ghent University Hospital, Gent, Belgium. jan.poelaert@ugent.be

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In Reply:—The load dependence of the myocardial performance index in congenital heart disease has been evaluated. No significant change was found before or after surgical correction of atrial septal defect (right ventricular preload), pulmonic stenosis (right ventricular afterload), or congenitally corrected transposition of the great vessels (right ventricular preload and afterload).[1] Acute changes in myocardial performance index with manipulation of preload/afterload have been demonstrated in adult volunteers with healthy hearts—to Valsalva maneuver, leg lifting, and nitroglycerine administration. However, the patients in this study with previous myocardial infarction and abnormal ventricular function did not exhibit any changes in myocardial performance index.[2]

Doppler tissue imaging has load dependence[3,4] but has been demonstrated to be more independent of preload than conventional Doppler measures of mitral inflow.[5,6] In addition, in patients with ventricular dysfunction, changes in preload affect Doppler tissue imaging velocities much less and correlate well with invasive measures of left ventricular diastolic pressure.[6] Significant increases in afterload seen in patients with aortic stenosis do decrease Doppler tissue imaging velocity.[7] However, no significant impact on Doppler tissue imaging

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Table 1. Combined Systemic and Pulmonary Vascular Resistance Index

Group	Baseline	Dose 1	Dose 2
Sevoflurane (n = 16)	597 ± 260	484 ± 228*	494 ± 223*
Fentanyl–midazolam (n = 14)	621 ± 344	575 ± 343	598 ± 344

Results are presented as mean ± SD; combined systemic and pulmonary vascular resistance index units are dyn · s · cm^{-5} · m^2.

* $P < 0.05$, different from baseline by one-way repeated-measures analysis of variance.

velocities of increased left ventricular preload with ventricular septal defects was noted.

With regard to the loading conditions for the patients in our current study,[8] preload was not specifically assessed, largely because of the inability to use conventional methods to compute left ventricular end-diastolic volume, because of the irregular geometry of the functional single ventricle. Central venous pressure, a rough estimate of preload, was not changed with either of the two anesthetic levels with the two regimens we studied. In a previous study of two-ventricle patients with congenital heart disease, we demonstrated that neither fentanyl–midazolam nor sevoflurane, in doses similar to those used in the current study, had any effect on left ventricular end-diastolic volume measured by the biplane method of Simpson.[9] In the same previous study, neither fentanyl–midazolam nor sevoflurane changed systemic vascular resistance index, calculated echocardiographically. In the current study, we did not specifically calculate systemic vascular resistance index because the patients had a functional single ventricle, and systemic and pulmonary blood flow both occurred in the aorta of most patients, so the conventional concept of systemic vascular resistance did not apply. However, if one was to calculate a combined systemic and pulmonary vascular resistance index in the patients of our current study, by dividing the difference between mean arterial pressure and central venous pressure (assuming no change in central venous pressure from baseline) by the aortic or neoaortic outflow, there is no change in systemic and pulmonary vascular resistance index with fentanyl–midazolam but a significant decrease with sevoflurane at both anesthetic levels (table 1).

Therefore, the changes in loading conditions induced by the anesthetic regimens for congenital heart disease can be estimated to be no change with fentanyl–midazolam and a 17% decrease in afterload with sevoflurane.

Although we agree with the caution of Drs. Poelaert and Amà to consider changes in loading conditions and other pathophysiologic factors when performing and interpreting echocardiographic studies assessing response to anesthetics, we believe our conclusions are valid for single-ventricle infants. Myocardial performance index in particular represents an appropriate method to assess myocardial function in patients with abnormal ventricular geometry, such as those with a functional single ventricle.

Dean B. Andropoulos, M.D.,* Benjamin W. Eidem, M.D., Wanda C. Miller-Hance, M.D., Louis I. Bezold, M.D. * Baylor College of Medicine/Texas Children's Hospital, Houston, Texas. dra@bcm.tmc.edu

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Transsacrococcygeal Ganglion Impar Block for Postherpetic Neuralgia

To the Editor:—I read with interest the case report about sacral postherpetic neuralgia and the excellent results in its treatment using the paramedial approach to the ganglion impar.[1] The authors included in their discussion the different approaches that have been undertaken in the past to block the ganglion impar. It was also impressive to see the double-bent needle used to achieve this block. Many practitioners have elected not to perform this block because of their impression of its complexity and technical difficulty. Unfortunately, this has led to a decrease in popularity of this effective block in pain medicine.

In the past, I described a case in which coccydynia was controlled with the blockage of the ganglion impar through the sacrococcygeal junction.[2] The authors briefly mentioned this technique, but I am afraid their description could be interpreted to mean that this approach is of minimal value. They state, "This approach can be useful in patients with normal anatomy but may prove challenging in patients with arthritic changes in the bones and calcification of the ligaments of the sacrum and coccyx." I have to disagree with the authors and would like to clarify that this approach is quite simple, straightforward, and equally effective. Minimal arthritic changes occur in this area, and, if any, the bone changes seldom are major challenges with this approach. de Leon-Casasola[3] described the transsacrococcygeal approach as the easiest way of performing the ganglion impar block. Over the years, many practitioners have tried to simplify the approach, and many reports have been published advocating the transsacrococcygeal route for its simplicity and effectiveness.[4,5]

I believe that the message we should be sending to practitioners is that ganglion impar block could be performed through an easily achieved technique under fluoroscopy and that it is effective in the

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management of sacral pathologies, including postherpetic neuralgia. It is discouraging to see a good intervention fade into disfavor because of the complexity of the technical aspect of its performance when a technically simple alternative is present and equally effective.

Abdallah I. Kabbara, M.D., Louis Stoke VA Hospital of Cleveland, Case Western Reserve University, Cleveland, Ohio. draikabbara@yahoo.com

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Ganglion Impar Block in Noncancer Perineal Pain: What Drugs, What Strategy?

To the Editor:—We read[2] with great interest the recently published case report by McAllister *et al.* [1] describing the successful management of postherpetic neuralgia in the perineal area using repeated ganglion impar blockade by a local anesthetic solution. This is one of the first case reports describing the efficacy of blockade of the terminal part of the sympathetic chain in non–cancer-related pain. We congratulate the authors on their therapeutic success, but several questions remain to be answered.

Ganglion impar blockade is not a routinely used analgesic procedure. Initial articles have reported chemical neurolysis of the ganglion impar as adjuvant therapy of cancer-related pain in the perineal region. In their overview, De Medicis and de Leon-Casasola provide a summary of studies evaluating the efficacy and complication rate of ganglion impar blockade.[2] They conclude there have been only two studies reporting good efficacy of neurolytic blockade using 6% phenol for visceral perineal pain of cancer origin in a total of 36 patients. There is only one study addressing the efficacy of ganglion impar inhibition in noncancer pain. The procedure was found to be ineffective in 20 patients with coccygodynia.[3] In addition to this study, there have been only a couple of case reports on the successful management of perineal pain of noncancer etiology using this technique of blockade.[1,4]

In their patient with postherpetic neuralgia, McAllister *et al.* used a corticosteroid as an additive to a local anesthetic, administering it to the presacral area. The analgesic efficacy of corticosteroids to sacral sympathetic structures has not been demonstrated to date, and the mechanism of its analgesic activity remains unclear.

Another thing we found surprising was the long-term analgesic effect of local anesthetic solution (3–5 months). The common duration of the analgesic effect of local anesthetics administered to that area in diagnostic/prognostic blockade is 2–7 days.[2]

In our experience with the management of noncancer perineal pain in 26 patients with chronic pain after perineal surgery, vulvodynia, and vulvar pruritus to date, we are able to make a preliminary outcome determination using the ganglion impar procedure: A testing blockade with a local anesthetic has an analgesic efficacy of 2–5 days. Multiple blockade was accomplished in these patients using a mixture of a local anesthetic with clonidine (10 ml bupivacaine, 0.375%, plus 75 μg clonidine). In this pilot study, clonidine extended the analgesic effect to as long as 14 days. Clonidine administered to the sympathetic nervous system presumably prolongs the duration of blockade, as demonstrated by Kimura *et al*.[5] Still, to achieve long-term analgesic effect in this cohort, most patients required chemical ganglion impar neurolysis or radiofrequency thermolesion.†

Further larger and randomized clinical studies are needed to confirm the acceptability of ganglion impar blockade and destruction in noncancer perineal pain.

Pavel Michalek, M.D., Ph.D.,* Libor Dolecek, M.D., Petr Stadler, M.D. * Na Homolce Hospital, Prague, Czech Republic. pafkam@seznam.cz

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† Michalek P, Dutka J: The efficacy of ganglion impar block in chronic non-malignant perineal pain. World Congress of Anaesthesiologists; April 2, 2004; Paris, France. Abstract PO336. Available at: www.wca2004.com. Accessed March 28, 2005.

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In Reply:—I would like to thank Dr. Kabbara for his further information and clarification of the ease of the transsacrococcygeal approach to the ganglion impar. It was not my intent to impugn the utility of this approach, but to highlight the ease of the paramedial approach to the ganglion impar as a useful alternative. It is my hope that this potentially useful sympathetic block will find favor with clinicians, by either approach, and that many patients will benefit from it.

The interest and comments of Michalek *et al.* are appreciated. They note that the duration of efficacy of sympathetic block of the ganglion impar with local anesthetics and steroids in my case report does not

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match the duration of relief that they have seen in treating patients with perineal pain of noncancer etiology (chronic postoperative perineal pain, vulvodynia, and vulvar pruritus). However, the mechanism of pain in postherpetic neuralgic (PHN), although not completely understood, seems to be quite different from that in the patient population treated by Michalek *et al.*

Treatment of PHN with sympathetic blocks, with or without steroids, is controversial but has been described in several studies with favorable results far outlasting the normal duration of action of the local anesthetic or steroid. Forrest[1] injected 1–2 ml bupivacaine, 0.5%, with 60–120 mg methylprednisolone once a week for 3 weeks. At 1 month, 57% of patients were pain free, and 6 months later, 86% of these patients continued to be pain free. Forrest also reported on 37 patients with longstanding PHN who were treated with three epidural steroid injections given at 1-week intervals. Significant reductions in visual analog scale ratings were noted at 1 month, and 89% of the patients were pain free at 1 yr.[2] Milligan and Nash[3] also reported favorable long-lasting relief of PHN after stellate ganglion blocks. The mechanism of the prolonged effect is unclear. Hetherington[4] advocated consideration of sympathetic blocks as a major adjunctive therapy for all PHN patients, although it is recognized that there are no guidelines as to how many to perform or how often to perform them.

Therefore, the experience of Michalek *et al.* with duration of efficacy may not necessarily apply to PHN due to complex and differing mechanisms of pain. I agree that further investigation is warranted. However, because PHN in the sacral dermatomes is uncommon, it will be difficult to conduct a well-controlled study to find more definitive answers.

Russell McAllister, M.D., Scott & White Memorial Hospital and Clinic; Scott, Sherwood, and Brindley Foundation; the Texas A&M University Health Science Center College of Medicine; Temple, Texas. rmcallister@swmail.sw.org

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Valve Leaks with New Disposable Extraglottic Airway Devices

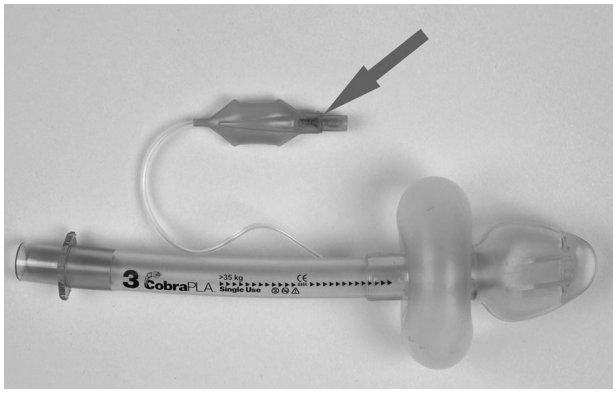

Fig. 1. *Arrow* indicates where leak exists between cuff valve deflator and surroundings of the pilot balloon cuff of the CobraPLA®.

To the Editor:—We would like to report six cases of spontaneous cuff deflation that occurred during a clinical trial of a new disposable extraglottic airway device, the CobraPLA® (Engineered Medical Systems, Inc., Indianapolis, IN).[1] The cuff pressure decreased to almost zero during maintenance of anesthesia. These events were detected by continuous cuff pressure monitoring using a transducer attached to a monitor (S/5 AM; Datex-Ohmeda, Helsinki, Finland) during the maintenance phase of anesthesia and did not influence the clinical performance of the device, primarily because the patients were breathing spontaneously. The patients were not moved during surgery, with the transducer positioned on the patient's shoulder throughout the duration of the procedure. The devices' cuffs were checked for leaks before use as recommended by the manufacturers. When checked after removal of the device, the cuff itself did not show any defect, but submersion in water revealed tiny bubbles of air escaping from the pilot balloon valve, showing a continuous leak at the cuff deflator valves with their surroundings (fig. 1).

A similar problem has been reported with another new extraglottic airway mask, the Marshall Laryngeal Airway Device (Marshall Products Ltd., Bath, United Kingdom). In the United Kingdom, the Medical Devices Regulatory Agency issued a Medical Device Alert† in 2003 regarding cuff failure due to a small number of pilot balloon valves leaking. This led to the manufacturer's recall of the product.

Cuff deflation is undesirable because it can lead to a loss of seal with the respiratory/gastrointestinal tracts and put the patient at risk of ventilatory failure, aspiration, and gastric insufflation.[2]

We urge the manufacturers of new extraglottic devices to ensure better quality control of their products, including the cuff deflator valves. However, because one cannot guarantee 100% quality control at all times, we also urge clinicians to incorporate cuff pressure monitoring into their routine practice.

André van Zundert, M.D., Ph.D., F.R.C.A., * Al-Shaikh Baha, F.R.C.A., Joseph Brimacombe, M.D., F.C.A.R.C.S.I., F.R.C.A., Ch.B., M.B., Eric Mortier M.D., Ph.D. * Catharina Hospital–Brabant Medical School, Eindhoven, The Netherlands. zundert@iae.nl

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† Laryngeal Airway Device Recall Notice UK MDA/2003/027. Available at: http://www.medicaldevices.gov.uk/mda/mdawebsitev2.nsf/webvwSearchResults/FDE3B3C0A919083280256D8E004946A0. Accessed August 27, 2003.

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In Reply:—We fully agree with Dr. van Zundert *et al.* that manufacturers of extraglottic devices (and all other medical devices) should assure quality control of their products.

Since the CobraPLA® (Engineered Medical Systems, Inc., Indianapolis, IN) was introduced into clinical practice in 2003, Engineered Medical Systems has ensured the quality of the cuff deflator valve with a comprehensive validation and production procedure of every product made, which includes a pressure test of the deflator valve and a full 16-h inflation test of the deflator valve/cuff assembly, with no leakage allowed.

For a manufacturer to fully assess and address a valve issue such as Dr. van Zundert *et al.* describe, it is imperative that the products in question be promptly returned to the producer (in its original condition at the time of use) for evaluation. Unfortunately, Engineered Medical Systems never received the six devices in question back at our facility for a proper inspection to be conducted. When we visited Dr. van Zundert in the Netherlands after receiving a copy of his correspondence to ANESTHESIOLOGY, we were presented with a bundle of more than 30 CobraPLAs®, which had been used and then cleaned. There was no documentation as to which ones had been used in his report. As a result, we cannot be certain as to the cause of the failures.

Considering the fact that Engineered Medical Systems has not received a single other report of a cuff deflator valve failure from all the units distributed worldwide, we might assume that a very limited number of devices (the ones used by Dr. van Zundert *et al.*) had a minimal leak that could not be identified at preoperative check. Alternatively, we have been notified by another investigator that in some units, during continuous cuff pressure monitoring, a small leak can occur *at the monitoring connection site and not from the device itself*; that clinician did not think that the valve was malfunctioning. Finally, damage to the devices in question could have also occurred during forceful cleaning before the postuse submersion test. It is reassuring to Engineered Medical Systems that the deflated cuff did not influence the clinical performance of the device or the end-tidal carbon dioxide measurement during the study of Dr. van Zundert *et al.*, which speaks highly to the performance of the CobraPLA®.

Although we cannot state with certainty that the experience of Dr. van Zundert *et al.* was unique, it seems that it was isolated and that valve failure has not posed a significant clinical problem for clinicians. We are confident that the CobraPLA® meets the rigorous quality standards clinicians and patients deserve in their medical products.

Brad Quinn, Engineered Medical Systems, Indianapolis, Indiana. bquinn@engmedsys.com

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Life-threatening Ventilatory Obstruction due to a Defective Tracheal Tube during Spinal Surgery in the Prone Position

To the Editor:—In the current days of high-tech equipment and well-defined safety regulations, technical failures are less likely to occur, and so are we to consider them when clinical complications happen. Endotracheal tube defects are probably seen by today's anesthesiologists as a thing of the past. A review of the literature showed that all of the cases reported in relation to defective tubes occurred when tubes were submitted to repeated sterilizations.

A 39-yr-old woman, with insignificant past medical history, was scheduled to undergo lumbar discectomy. General anesthesia was induced with thiopental (450 mg), fentanyl (150 μg), and vecuronium (8 mg). Tracheal intubation was performed with a 7-mm reinforced endotracheal tube (Safety Flex; Mallinckrodt Medical, Athlone, Ireland; expiration date 2006-09). The patient was positioned in prone position. Normal breath sounds were heard equally in both lungs. Anesthesia was maintained with sevoflurane (1.0–1.5%) and nitrous oxide (67%) in oxygen, and muscle relaxation was achieved with vecuronium bolus. Approximately 2 h after induction, we started to experience difficulties in ventilating the patient's lungs. Peak inspiratory pressure started to increase while compliance and tidal volume decreased. Pulmonary auscultation remained normal. The capnograph showed a positive deflection on the inspiratory phase; it was assumed that relaxation was insufficient, and a 4-mg bolus of vecuronium was administered. A suction catheter was used to remove possible airway secretions. It was noted that the catheter did not pass through the tube. Tube obstruction was then suspected. Ventilation became very difficult, even using bag ventilation. The patient was quickly returned to the supine position. The face, neck, and upper trunk showed congested veins. Bradycardia with bigeminism occurred and ventilation became impossible, but oxygen saturation did not decrease below 98%. The endotracheal tube was replaced with a new one. All abnormal variables returned to baseline. The patient was repositioned for surgery, and the procedure was completed without further complications. Recovery and the postoperative period were uneventful.

Later inspection of the tube showed a transparent halo on the outside surface. The inner view showed an intramural bubble that completely occluded the lumen. The 3-cm-long bubble was located 11.5 cm from the distal end. A fiberscope was used to obtain a photo of the bubble from the inside of the tube.

Ventilatory distress in the prone position may be a serious complication. The differential diagnosis included consideration of pneumothorax and bronchospasm, but auscultation of both lungs remained possible and was normal. In the case reported, ventilatory distress was due to a bubble protruding into the lumen of the tube. This bubble most probably was not due to any sort of extrinsic damage to the tube during its use. The inclusion of tiny air bubbles in the wall of a reinforced tube can be a result of the production procedure of this kind of tube.[1] Most certainly, nitrous oxide exposure and diffusion was the cause of expansion of the tube defect.[2–4] This would explain the fact that during the initial 2 h of the procedure, no problems were noted. The electrocardiographic changes observed were probably due to increased intrathoracic pressure caused during manual ventilation. This is reinforced by the striking congestion of the neck veins. It is possible that manual ventilation forced gases into the lungs but that some valve mechanism due to the presence of the bubble prevented expiration. This, combined with the 100% oxygen used, would also explain why the oxygen saturation did not decrease. It is interesting to note that oxygen saturation may not be an indicator of severe airway problems. To our knowledge, this is the first report of this kind of endotracheal tube obstruction with a disposable armored tube. It shows that even in modern days of increased attention to quality control, simple technical defects may occur. The manufacturer was notified about the incident.

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Isabel A. Santos, M.D.,* **Carla A. Oliveira, M.D., Leónia Ferreira, M.D.** * Hospital Geral de Santo António, Porto, Portugal. ialex@mail.telepac.pt

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In Reply:—Tyco Mallinckrodt (Athlone, Ireland) would like to point out that unfortunately, in this instance, the Safety Flex product involved in the complaint was not returned to the manufacturer. Therefore, a comprehensive evaluation could not be conducted relating to potential root cause of this problem.

In the absence of the sample in question, we have attempted to simulate the problem described in the letter by Santos *et al.* We have been unable to do so under normal simulated use conditions. However, we were able to create an occlusion in a Safety Flex product by subjecting it to sterilization cycles that are different than those used at our manufacturing site. Using a moist heat sterilization cycle or a high-pressure gas cycle, we managed to create occlusions and other disfigurations in the product.

Mallinckrodt manufactures Safety Flex tracheal tubes with defined validated processes, and the product is checked at several key intervals during manufacture to ensure that all quality criteria associated with this product range are met before release of the product from the plant.

We would like to draw the reader's attention to our Instructions for Use leaflet that is supplied with this product. These instructions clearly specify all warnings/precautions to be taken with this product and suggested directions for use.

We regret that the customer experienced problems using one of our products. We do, however, appreciate their bringing this matter to our attention. Feedback is very important because we strive to maintain a high-quality product and a high level of customer communication and satisfaction.

Deirdre Kennedy, B.Sc., Gregor Bertaggia* * Tyco Healthcare, Hennef, Germany. gregor.bertaggia@emea.tycohealthcare.com

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Fatal Thrombosis in an Adult after Thoracoabdominal Aneurysm Repair with Aprotinin and Deep Hypothermic Circulatory Arrest

To the Editor:—We report a case of fatal aortic thrombosis after aprotinin exposure in an adult undergoing repair of a thoracoabdominal aneurysm using cardiopulmonary bypass and deep hypothermic circulatory arrest (DHCA).

A 78-yr-old woman presented with a ruptured thoracoabdominal aortic aneurysm involving the aortic arch (Crawford type I). The patient was taken emergently to the operating room for repair using our DHCA protocol that has been previously described.[1–6]

Anesthetic induction was with titrated fentanyl and midazolam. Neuromuscular blockade was achieved and maintained with titrated pancuronium. The trachea was intubated with a left-sided double-lumen tube (Tyco Healthcare/Mallinckrodt, St. Louis, MO). Correct endotracheal position was confirmed by serial fiberoptic bronchoscopy. Intraoperative monitoring included American Society of Anesthesiologists routine monitors as well as indwelling radial arterial and pulmonary arterial catheters. Because of the emergent nature of the procedure, a lumbar cerebrospinal fluid drain was not placed. Anesthesia was maintained with isoflurane in oxygen, as well as titrated fentanyl and midazolam.

The patient was given aprotinin (Bayer Corporation, Pittsburgh, PA) as follows: 2 million kallikrein inhibitory units intravenously as a load, followed by an infusion of 0.5 million kallikrein inhibitory units per hour. The cardiopulmonary bypass crystalloid prime was also loaded with aprotinin (2 million kallikrein inhibitory units).

The patient was positioned in the right lateral decubitus position. Surgical incision, dissection, and initiation of cardiopulmonary bypass were uneventful. Heparinization for cardiopulmonary bypass was titrated to maintain the activated coagulation time (kaolin activator) of greater than 600 s. The surgical repair was technically uncomplicated; the aorta was replaced with a Hemashield vascular graft (Boston Scientific, Natick, MA). The cardiopulmonary bypass time was 212 min, with a deep hypothermic circulatory arrest time of 38 min.

After successful separation from cardiopulmonary bypass, protamine was administered in a titrated fashion without adverse reaction. Despite aprotinin and adequate protamine (calculated to neutralize the full dose of heparin), hemostasis in the surgical field was not achieved. There was significant microvascular bleeding. No overt vascular bleeding was detected despite careful surgical inspection. Platelet infusion was begun. Ten minutes after initiation of the platelet infusion, the patient experienced cardiac arrest that was refractory to pharmacologic resuscitation. Transesophageal echocardiography revealed diffuse intraaortic thrombosis (figs. 1 and 2). The patient did not respond to further resuscitative efforts. The family declined a postmortem examination.

Catastrophic thrombosis with aprotinin in DHCA was first noted in the early 1990s.[7] The most likely explanation for these observations was inadequate heparinization because it was only appreciated in the mid-1990s that aprotinin exposure prolongs the activated clotting time.[8] At our institution, we perform 70–80 thoracic aortic procedures with DHCA per year. Our DHCA protocol includes routine application of an antifibrinolytic, either aminocaproic acid or aprotinin. Aprotinin is reserved for the high-risk DHCA population.[1–4]

Inadequate heparinization as the cause of the prothrombotic state in

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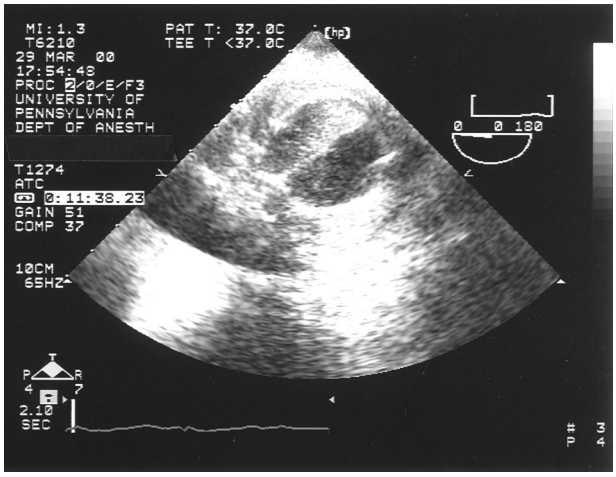

Fig. 1. Short axis view of descending aorta with transesophageal echocardiography, showing aortic graft lumen filled with thrombus.

this case is extremely unlikely, given that our standard DHCA protocol was followed and given the DHCA experience at our institution. It is more likely that the prothrombotic state was multifactorial in etiology: disseminated intravascular coagulation triggered by hypothermic cardiopulmonary bypass, the antifibrinolytic action of aprotinin, neutralization of heparin, and the presence of transfused functional platelets. The presence of hemostatic aortic graft material in this case was Hemashield (Boston Scientific), which, although hemostatic, has not been associated with acute intravascular thrombosis.[9,10] The mechanism of this fatal thoracic aortic thrombosis is unclear.

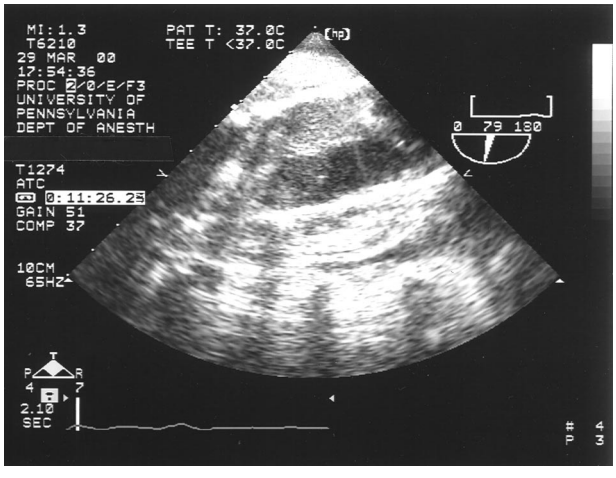

Fig. 2. Long axis view of descending aorta with transesophageal echocardiography, showing aortic graft lumen filled with thrombus.

Fatal thrombosis has been reported in adult DHCA; the antifibrinolytic, however, was not aprotinin but aminocaproic acid.[11] This syndrome has also been reported in pediatric cardiopulmonary bypass; the antifibrinolytic was aprotinin.[12]

Therefore, our case is the first reported case of fatal thrombosis in an adult undergoing DHCA in the presence of aprotinin despite adequate heparinization. Despite adequate heparinization, this syndrome is still possible in cardiovascular surgery necessitating cardiopulmonary bypass, regardless of antifibrinolytic or patient age. Further hypothesis-driven perioperative research is required to understand and prevent this uncommon but important complication associated with antifibrinolytic therapy.

John G. T. Augoustides, M.D.,* **Judy Lin, B.A., Andrew J. Gambone, B.A., Albert T. Cheung, M.D.** * Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. yiandoc@hotmail.com

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