

August 2004

Vol. 3, No. 4

## What's Inside

Website Table of Contents	page 2
Call for Nominations	page 2
Grants Awarded for 2004	page 2
President's Message: Growing Pains	page 3
Literature Reviews	page 4
Drug and Innovation Review	page 8

### Fellow/Faculty Recruitment Reception October 25, 2004 • Las Vegas, Nevada

The purpose of this reception will be for potential cardiac anesthesia fellows and faculty to meet with representatives from cardiothoracic fellowship and academic programs currently recruiting for faculty positions. In addition members of the SCA Board of Directors will be available to answer questions about the SCA. For more information on attending this reception, please contact the SCA at (804)282-0084 or [sca@societyhq.com](mailto:sca@societyhq.com).

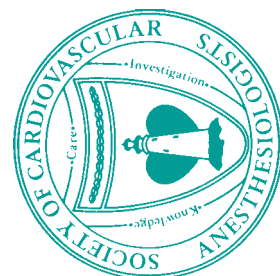
# Society of Cardiovascular Anesthesiologists

P.O. Box 11086 • Richmond, Virginia 23230-1086

© 2004 Society of Cardiovascular Anesthesiologists

Non Profit  
U.S. POSTAGE  
PAID  
Permit #1430  
RICHMOND, VA

SCA  
P.O. Box 11086  
Richmond, VA 23230-1086



# What's Online (www.scahq.org)

## August 2004 Newsletter

- Calendar of Future Meetings (Web Only)

---

- The SCA Welcomes Three New Board of Directors

---

- President's Message: Growing Pains

---

- Literature Reviews
  - A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit
  - A Validated Prediction Model for All Forms of Acute Coronary Syndrome: Estimating the Risk of 6-month Post Discharge Death in an International Registry

---

- Drug and Innovation Reviews
  - Report on Meeting of the American Institute of Ultrasound in Medicine, May 2004
  - Selective Pulmonary Vasodilators for Pulmonary Hypertension

## Password Protected Area for Members

## Acknowledgment of Industry Support

## Fellowship Listings

*Anesthesia & Analgesia* Link (official journal of the SCA)

## Job Postings

---

### Annual Meeting & Workshops

---

May 14–18, 2005  
Baltimore Convention Center  
Baltimore, MD

**Beginning September 15, 2004, SCA will be accepting abstracts online at [www.scahq.org](http://www.scahq.org) for its 2005 Annual Meeting. Deadline for abstract submission is November 1, 2004.**

---

### Comprehensive Review of Intraoperative Echo

---

February 14–19, 2005  
Sheraton San Diego Hotel & Marina  
San Diego, CA

---

### Update on Cardiopulmonary Bypass

---

March 13–18, 2005  
Snowmass Conference Center  
Snowmass, CO

## Call for Nominations

Dr. Roger Moore, Chair of the Nominating Committee, has announced that nominations are being sought for the following positions:

- |  |             |
|--|-------------|
| <input checked="" type="checkbox"/> <b>President-Elect</b>   | 2-year term |
| <input checked="" type="checkbox"/> <b>Secretary/Treasurer</b>                                       | 2-year term |
| <input checked="" type="checkbox"/> <b>Board of Directors (2 positions)</b>                          | 3-year term |
| <input checked="" type="checkbox"/> <b>Nominating Committee member (2 positions)</b>                 | 2-year term |
| <input checked="" type="checkbox"/> <b>Continuing Education Committee (CME) member (2 positions)</b> | 2-year term |

**In order to nominate a member, please forward to Dr. Moore, PO Box 11086, Richmond, VA 23230-1086, the following:**

- A letter of nomination
- Two letters from Society members seconding the nomination
- A "willingness to serve" statement from the nominee

The deadline for nominations is January 10, 2005. The slate of candidates for Board of Directors, Nominating Committee members and CME Committee members will appear on the SCA's website ([www.scahq.org](http://www.scahq.org)). Eligible SCA members will have 45 days to cast their online votes. The slate of candidates for President-Elect and Secretary/Treasurer will appear in the SCA Newsletter with elections taking place at the Annual Business Meeting in Baltimore, May 16, 2005.

## The SCA is pleased to announce that the following 2004 grants have been awarded:

### 2004 SCA STARTER GRANTS

#### Wolfgang Steudel, MD

University of Colorado Health Sciences Center  
*Cyclosporine Pretreatment to Decrease Ischemia- Reperfusion Injury and to Improve Organ Survival after Heart Transplantation*

#### Jacob Raphael, MD

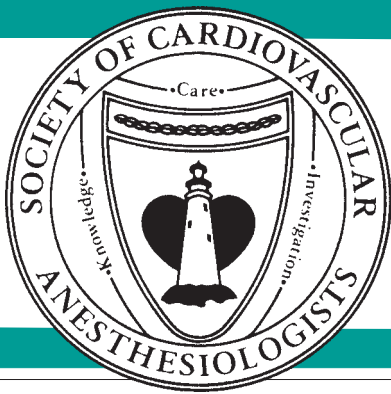
Hadassah University Medical Center, Jerusalem  
*Mechanisms of Ischemic Preconditioning: A Potential Role of the Hypoxia Inducible Factor 1 in a Rabbit Model of Regional Myocardial Ischemia*

#### Ian Welsby, MD

Duke University Medical Center  
*Combination Anticoagulation Better Suppresses Thrombin Generation and Improves Outcome after Cardiac Surgery*

[www.scahq.org](http://www.scahq.org)

Visit the website for the Members' Only section and updates on future meetings



# NEWSLETTER

P.O. Box 11086 • Richmond, VA 23230-1086 • (804)282-0084 • [sca@societyhq.com](mailto:sca@societyhq.com)

August 2004

## President's Message

### Growing Pains

An anesthesiologist from a small city (population approximately 50,000) recently called to seek advice about a problem his group is facing. His group covers both hospitals in this city, each of which has a cardiac surgery program. The same cardiac surgery group covers both hospitals. Each hospital has two cardiac surgical operating rooms available exclusively to these cardiac surgeons, and each hospital does about 250 cardiac cases per year, hence averaging about 1 cardiac case per hospital per scheduled workday, and 0.5 cardiac cases per operating room per workday. His group is expected to staff as many as two rooms at each hospital each day, whether or not all four rooms are used that day. The cardiac surgeons perform very few noncardiac procedures in these rooms, and the hospitals dare not place noncardiac cases in the heart rooms for fear of invoking the surgeons' wrath. Since the two hospitals are competitors, neither one wishes to run the risk of a "use it or lose it" insistence that the surgeons use their allocated OR time more efficiently. To add insult to injury, the cardiac surgeons now are pressing the hospital administrations and the anesthesia group to provide anesthesiologists who have expertise in transesophageal echocardiography (TEE) for each of those four ORs on each cardiac case.

Driven substantially by interventional cardiologists' needs for cardiac surgical back up and by variability in state-by-state Certificate of Need processes, the past two decades have seen considerable growth in the number of hospitals offering cardiac surgery. Over the past decade, the American cardiac surgical caseload held fairly steady at approximately 600,000 cases per year (through 2002 at least). One source indicates that 62% of cardiac surgical programs in Pennsylvania have an annual cardiac surgical volume of less than 100 cases (Cardiovascular Roundtable, The Advisory Board Co., Washington, DC, 2004). The highly influential Leapfrog Group suggests an annual minimum hospital volume of 450 cases for CABG alone, although that number has provoked much controversy. Medium-sized communities take great pride in being able to provide a full range of cardiac services locally, to the point that towns in Ohio with populations of 20-30,000 persons now

support cardiac surgical programs. If pressed about the need, a typical response is, "We serve a referral base of over 100,000 people." My guess is that, if one added up the referral bases of all the hospitals making such claims, the inferred population of the US would exceed that of China and India combined.

When new cardiac surgical programs open, I have often been amazed at how little thought goes into planning anesthesia coverage for this service. The expansion of cardiovascular surgery programs has therefore strained anesthesia groups, which now must cover many cardiac surgical programs that have relatively small caseloads. The surgeons typically receive carte blanche cooperation from the hospitals, and the anesthesia groups are expected to provide the coverage. Since the daily caseload is unpredictable and the coverage is expected 24/7, many groups have understandably decided that the most efficient way to cover cardiac cases is to ask most of their practitioners to perform anesthesia for cardiac cases. Groups recognize that there simply are not enough fellowship-trained, TEE-qualified cardiovascular anesthesiologists to cover the hearts. Even if there were, the economics wouldn't compute. If a hospital averages 1 cardiac case per operating room (OR) per day, and if this generates average gross revenue of \$1,200 per case (central Ohio reality), this yields \$300,000 in gross revenue per year, assuming 250 working weekdays per year. Assuming conservative 8% overhead and 15% benefits costs, net annual revenue available for physician compensation becomes \$231,000 for this OR. Further assuming that it takes 1.15 full-time-equivalents (FTEs) to staff this OR every day (e.g., vacation, meetings, post-call days), this yields a net annual revenue available for physician compensation of \$201,000 per FTE. I don't know about your situation, but we can't recruit cardiac (or any) anesthesiologists for that amount in the Midwest. Consequently, our colleagues in small-city USA are being asked to take one for the "team." Further, they are being asked to provide hot-and-cold running CV anesthesiologist/echocardiographers for ORs that likely generate less than \$100,000 in physician salary per FTE



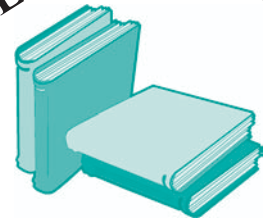
*Glenn P. Gravlee, MD*  
*President, 2003-2005*

per year. The numbers don't work, regardless of whether a group supervises CRNAs/AAs or provides all-physician anesthesia for its heart cases.

The coverage situation becomes even more complex when anesthesiologists are expected to provide expert TEE coverage either on demand or routinely on all cardiac cases, which seems to be increasingly desired. TEE is a skill that requires extensive dedicated training and experience beyond what can be reasonably expected of the "occasional" cardiac anesthesiologist. Medicolegal considerations come into play if the anesthesiologist is expected to make calls about the suitability of a mitral valve for repair (vs. replacement) or of the adequacy of a valve repair after it is performed. Cardiologists increasingly resist coming to the ORs to provide this service because - Guess what? - it is not cost-effective for them to do so.

What should our small-city colleagues do? Cardiac surgeons and hospitals need to understand that a competitive anesthesiologist marketplace does not permit anesthesia groups to accommodate gross inefficiency. The USA has a shortage of anesthesiologists, yet anesthesiologists have too often failed to avail themselves of the leverage afforded by the short supply. If we can't drive the OR engine now, surely we'll never be able to do so. If we fail to insist on a reasoned approach, then when a hospital opens its doors to premiere its state-of-the-art small-volume cardiac surgical

*Continued on page 4*



## REVIEW

### A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit.

The SAFE Study Investigators. *N Engl J Med* 2004; 350: 2247-56.

**Reviewer:** Michael H. Wall, MD  
*University of Texas Southwestern Medical Center at Dallas*  
*Dallas, TX*

**Abstract Excerpt:** This multi-centered, randomized, double-blinded trial evaluated 28-day mortality of a heterogenous population of ICU patients resuscitated with 4% albumin versus normal saline.

Patients admitted to 16 closed ICU's in Australia and New Zealand between November 2001 and June 2003 who needed fluid resuscitation to maintain or increase intravascular volume were eligible for inclusion in this study. (Patients following cardiac surgery, liver transplantation or burns were excluded). Six thousand, nine hundred, ninety-seven patients were randomized (according to institution and presence or absence of trauma) then received specially manufactured "masked" 500 cc bottles and infusion sets. The amount and rate of administration was determined by each clinician. Maintenance fluids, replacement fluids, nutrition, blood products, monitoring (CVP vs. PAC) and all other aspects of patient care were not controlled. The primary outcome variable was 28-day mortality. There were many secondary outcome variables including: new organ failures, duration of ventilation, etc. There were no differences in baseline characteristics between groups except the CVP was higher in the albumin group ( $9.0 \pm 4.7$  mmHg vs.  $8.6 \pm 4.6$  mmHg). About 44% of the patients in both groups were admitted to the ICU from the emergency room or hospital floor and 42% from the operating room. Patients in the albumin group received less fluid on day one and two ( $1183 \pm 973$  cc vs  $1565 \pm 1536$  and  $602 \pm 892$  cc vs  $954 \pm 11484$  respectively). The albumin group had higher serum albumin levels on day 1-4 and received more blood (about  $\frac{1}{4}$  unit over days 1-4) than the saline group. On days 1-4 there was no difference in MAP between groups but the CVP was higher (by about 1 mmHg) in the albumin group. HR was lower only on day one in the albumin group ( $88 \pm 20$  bpm vs.  $90 \pm 21$  bpm).

There were no significant differences in 28-day mortality, mechanical ventilation, ICU or hospital stay, new single or multiple organ failures between groups. Subgroup analysis showed a trend toward improved outcome in trauma pa-

program, we may as well accept the role of the red carpet. Yes, we CAN insist upon efficiency in the use of OR resources, because the hospital and surgeons most often can't replace us with sufficiently qualified anesthesiologists at an affordable price. If the volume justifies one room, tell the administrator that you'll staff one room. If he or she wants more, show him the economics using your own reimbursement figures. If he persists, ask him to show you the money. Inefficiency hurts him as much as it hurts you, and most hospitals can ill afford to sustain a cardiac surgical program on one case per OR per day. Hospital administrators may assume that this "loss leader" is justifiable because it will increase the overall volume of their cardiac services product line. They might be correct about that, in which case compensating you for the inefficiency should become an accepted line-item on the hospital's "cost of doing business" budget.

If the one fellowship-trained, TEE-certified anesthesiologist our small-city group has can't cover two hospitals and four ORs at once (Slacker!), then the anesthesia group must explain to the cardiac surgical group that they cannot provide TEE routinely for CABGs - at least not yet - and that they may need to stagger their elective valve procedures on alternate days at the two hospitals. Heaven forbid that the need for subspecialized cardiac anesthesia care should impact surgeons' scheduling practices! Another viable possibility is to work together with cardiology on joint TEE coverage or on a transition plan while further anesthesiology TEE expertise is being recruited or obtained internally through additional training.

This group's experience underscores an increasingly clear reality: Anesthesiology TEE competency is becoming the expected standard for anesthesiologists who practice in the heart rooms. Obtaining and maintaining this competency will require more than occasional appearances in a cardiac room. We should embrace this emerging standard, and we should also use it as a means to gain respect and concessions as needed.

Glenn P. Gravlee, MD  
*SCA President*

### OFFICERS

#### President

Glenn P. Gravlee, MD

#### President-Elect

James G. Ramsay, MD

#### Secretary/Treasurer

Christina Mora Mangano, MD

#### Immediate Past President

Roger A. Moore, MD

### BOARD OF DIRECTORS

George E. Burgess, III, MD

David J. Cook, MD

Martin J. London, MD

Jonathan B. Mark, MD

Robert J. Marino, MD

Nancy A. Nussmeier, MD

Gary W. Roach, MD

Robert M. Savage, MD

Jack Shanewise, MD

C. David Mazer, MD,

*Canadian Representative*

### COMMITTEE CHAIRPERSONS

#### Allied Health Liaison

Laurie Davies, MD

#### Bylaws and Procedures

Steven R. Young, MD

#### Economics

Steven N. Konstadt, MD

#### Electronic Communications

Gary W. Roach, MD

#### Ethics

Richard L. Wolman, MD

#### Governmental Affairs

Joseph S. Savino, MD

#### International

Isobel Russell, MD, PhD

#### Membership

Uday Jain, MD, PhD

#### Newsletter

Mark A. Chaney, MD

#### Nominating

Roger A. Moore, MD

#### Publications

David J. Cook, MD

#### Research

Nancy A. Nussmeier, MD

#### Scientific Program

Linda Shore-Lesserson, MD

### NEWSLETTER COMMITTEE

Mark A. Chaney, MD, Chair

K.W. Tim Park, MD, Vice Chair

Albert Cheung, MD

Hong Liu, MD

Feroze Mahmood, MD

Andrew D. Maslow, MD

E. Andrew Ochroch, MD

Michael H. Wall, MD

tients who were resuscitated with saline, and patients with sepsis who were resuscitated with albumin. However, the authors commented that further large prospective studies of these subgroups need to be done. The authors concluded "albumin and saline should be considered clinically equivalent treatments...." and the choices of resuscitation fluid include clinician preferences, safety and cost.

**Comments:** The crystalloid vs colloid debate surrounding fluid resuscitation rages on. Two published meta-analyses came to different conclusions regarding albumin or fluid resuscitation in the ICU – one showed a 6% increase in the risk of death in ICU patients given albumin, the other showed no significant difference in death rate. However, both meta-analyses were limited by small inadequately powered studies. This important trial was the first specifically designed and adequately powered to prospectively evaluate mortality in ICU patients, and overall they found no difference in 28-day mortality. The trends toward improved outcomes in subgroups with trauma (particularly trauma without head injury) resuscitated with saline and sepsis resuscitated with albumin will have to be prospectively evaluated. A similar trial needs to be done in patients undergoing elective cardiac surgery. Until these additional trials are done the debate will continue!

### Effects of Perioperative Central Neuraxial Analgesia on Outcome After Coronary Artery Bypass Surgery: A Meta Analysis.

Liu SS, Block BM, Wu CL. *Anesthesiology* 2004; 101: 153-161.

### An Epidural Hematoma in an Adolescent Patient After Cardiac Surgery (Case Report).

Rosen DA, Hawkinberry DW, Rosen KR, et al. *Anesth Analg* 2004; 98:966-969.

**Reviewer:** Mark A. Chaney, MD  
*University of Chicago*  
*Chicago, IL*

Use of regional anesthetic techniques in patients undergoing cardiac surgery, while seemingly increasing in popularity, remains extremely controversial, prompting numerous Editorials by recognized experts in the field of cardiac anesthesia.<sup>1-4</sup> All cardiac anesthesiologists should be aware of two recent publications that may help one assess the risk:benefit ratio when contemplating utilizing regional anesthetic techniques in patients undergoing cardiac surgery.

In the first, a meta-analysis by Liu and associates published in *Anesthesiology* assessed effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery. These authors, via MEDLINE and other databases, searched for randomized controlled trials in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass. Fifteen trials enrolling 1,178 patients were included for thoracic epidural anesthesia analysis and seventeen trials enrolling 668 patients were included for intrathecal analysis. Thoracic epidural techniques did

not affect incidences of mortality or myocardial infarction yet reduced risk of dysrhythmias (atrial fibrillation and tachycardia), reduced risk of pulmonary complications (pneumonia and atelectasis), reduced time to tracheal extubation, and reduced analog pain scores. Intrathecal techniques did not affect incidences of mortality, myocardial infarction, dysrhythmias, or time to tracheal extubation and only modestly decreased systemic morphine utilization and pain scores (while increasing incidence of pruritus). These authors conclude that central neuraxial analgesia does not affect rates of mortality or myocardial infarction following coronary artery bypass grafting yet is associated with improvements in faster time until tracheal extubation, decreased pulmonary complications and cardiac dysrhythmias, and reduced pain scores. However, the authors also note the majority of potential clinical benefits offered by central neuraxial analgesia (earlier extubation, decreased dysrhythmias, enhanced analgesia) may be reduced and/or eliminated with changing cardiac anesthesia practice using fast-track techniques, use of beta adrenergic blockers or amiodarone, and/or use of NSAIDs or COX-2 inhibitors. These authors also note that the risk of spinal hematoma due to central neuraxial analgesia in patients undergoing full anticoagulation for cardiopulmonary bypass remains uncertain.

In the second, the first ever case report of an epidural hematoma associated with a thoracic epidural catheter inserted in a patient prior to cardiac surgery was published in *Anesthesia and Analgesia*. This 18-year-old male had a thoracic (T9-T10) epidural catheter uneventfully inserted following induction of general anesthesia (patient had intense fear of needles) immediately prior to initiation of cardiopulmonary bypass for aortic valve replacement surgery. Three hours elapsed from instrumentation to systemic heparinization. The entire intraoperative course and immediate postoperative course were uneventful (tracheally extubated soon after surgery, ambulating without difficulty on the first postoperative day). Forty-nine hours following surgery, intravenous heparin therapy was initiated (prosthetic valve thromboprophylaxis). Fifty-three hours following surgery, alteplase (thrombolytic drug) was used to flush a dysfunctional intravenous catheter. Within two hours of intravenous alteplase administration, the patient reported intense back pain while ambulating. At this point, the epidural catheter was removed. The activated partial thromboplastin time assessed at this time (during catheter removal) was 87.4 seconds (normal range 24.8 – 37.3 seconds). The patient was also thrombocytopenic at this time. Upon catheter removal, the patient experienced sudden onset of numbness and weakness distal to T9. Intravenous heparin was discontinued, a computed tomographic scan was inconclusive, requiring a magnetic resonance imaging scan, which revealed an epidural hematoma. Five hours from the onset of neurologic symptoms, the patient underwent surgical evacuation of the hematoma (which extended from the T8 to T11 levels). Intraoperatively, intravenous methylprednisolone (30 mg/kg) was administered, followed by an infusion (5.4 mg/kg/hr) which was continued for 72 hours. Twenty-four hours

postlaminectomy, the patient demonstrated mild residual lower extremity motor and sensory deficits. Six weeks later, his neurological examination had returned to normal. The authors note the factors affecting coagulation in this patient (heparin, alteplase, thrombocytopenia) that likely led to hematoma formation and theorize that removing the catheter may have increased bleeding, further compounding the problem.

Use of regional anesthetic techniques in patients undergoing cardiac surgery remains extremely controversial. One of the main reasons such controversy exists (and likely will continue for some time) is that the numerous clinical investigations regarding this topic are suboptimally designed and utilize a wide array of disparate techniques preventing clinically useful conclusions all can agree on.<sup>1-6</sup> The recent publications by Liu and associates (meta analysis regarding clinical outcome) and Rosen and associates (first case report of epidural hematoma), while not able to definitively settle all issues, help to shed additional light on this controversial topic.

#### References:

1. Mora Mangano CT: Risky business (editorial). *J Thorac Cardiovasc Surg* 125: 1204-1207, 2003.
2. Schwann NM, Chaney MA: No pain, much gain? (editorial). *J Thorac Cardiovasc Surg* 126: 1261-1264, 2003.
3. Gravlee GP: Epidural analgesia and coronary artery bypass grafting: the controversy continues (editorial). *J Cardiothorac Vasc Anesth* 17: 151-153, 2003.
4. Castellano JM, Durbin CG: Epidural analgesia and cardiac surgery: worth the risk? (editorial). *Chest* 2000; 117: 305-307
5. de Leon-Casasola OA: When it comes to outcome, we need to define what a perioperative epidural technique is (editorial). *Anesth Analg* 2003; 96: 315-318
6. Rosenquist RW, Birnbach DJ: Epidural insertion in anesthetized adults: will your patients thank you?(editorial). *Anesth Analg* 2003; 96: 1545-1546

### A Validated Prediction Model for all Forms of Acute Coronary Syndrome: Estimating the Risk of 6-Month Post Discharge Death in an International Registry

Eagle KA, Lim MJ, Dabbous OH, et al. *J Am Med Assoc* 2004; 291:2727-33

**Reviewer:** KW Tim Park, MD  
*Beth Israel Deaconess Medical Center*  
*Boston, MA*

**Background:** The acute coronary syndrome (ACS) is comprised of conditions ranging from unstable angina to both non-ST-segment elevation and ST-segment elevation myocardial infarction (NSTEMI and STEMI). In order to help with clinical decision making, prediction models on outcome after ACS have been developed. Pre-

*Continued on page 6*

vious risk-prediction models for outcome after ACS were developed from large randomized clinical trials and focused on in-hospital mortality, and their generalizability to risk prediction in the average clinical setting has been questioned.<sup>1-6</sup> The current study sought to develop a prediction model of all-cause 6-month mortality after all types of ACS in patients similar to those encountered in routine clinical practice.

**Methods:** The Global Registry of Acute Coronary Events (GRACE) is a multinational registry of patients admitted with ACS at 94 hospitals in 14 countries. To be entered in the registry, the patient had to be >18-years-old, admitted with a presumptive diagnosis of ACS, and had one of the following: ECG changes consistent with ACS, serial increases in serum cardiac markers, and/or documentation of coronary artery disease (CAD). The qualifying ACS must not have been precipitated by significant noncardiovascular comorbidity such as acute anemia or hyperthyroidism. At discharge, all cases were categorized as unstable angina, NSTEMI, or STEMI. At ~ 6 months post discharge, patients were followed up to ascertain their vital status. The primary endpoint was all-cause mortality within 6 months of discharge. Using patients' baseline demographics, comorbidities, symptoms and signs at presentation, in-hospital treatments and procedures, a prediction model was developed in all patients enrolled in GRACE between April 1, 1999 and March 31, 2002 (n=17,142), using stepwise Cox proportional hazards regression. Then, the model was tested in a validation cohort of consecutive patients enrolled in GRACE between April 1, 2002 and December 31, 2003 (n=7,638).

**Results:** The overall follow-up rate in the development cohort was 87.5% (n=15,007) for death. The development cohort of patients was 65 ± 13 in age and 67% men. Fifty-eight percent had hypertension and prior or current smoking history, 24% had diabetes mellitus, 32% had a history of MI, 46% had hyperlipidemia, and 10% had a history of congestive heart failure (CHF). Forty-three percent were on aspirin, 25% on angiotensin converting enzyme inhibitors, 31% on β-blockers, 25% on oral nitrates, 23% on statins, and 21% on calcium channel blockers. By stepwise Cox proportional hazards regression, nine predictors for the 6-month mortality were identified: age per 10-year increase above 40, history of MI, history of CHF, increase in heart rate, decrease in systolic pressure, elevated serum creatinine, elevated cardiac enzymes, ST-segment depression, and no in-hospital percutaneous coronary intervention (PCI). Based on the model's variable coefficients, these prediction variables were given weighted scores. When the model was then applied to the validation cohort, the model performed well in all forms of ACS with a c statistic of at least 0.70.

**Discussion and Comments:** As the authors of the study point out, previous prediction models developed from large clinical trials are robust for the specific endpoints in the population in which

they were developed. Many ACS trials, however, used combined endpoints that included need for revascularization and this variable is influenced so much by local practice style and availability of a cardiac catheterization laboratory. This has limited the generalizability of the previous models. Another limitation of previous models has been the arbitrary distinction between NSTEMI and STEMI, even though it has been shown that in-hospital mortality is similar whether the ST segment deviation is elevation or depression.<sup>7</sup> The current model developed from GRACE utilized an unambiguous end-point of all-cause 6-month mortality and is equally robust for all forms of ACS, including unstable angina, NSTEMI, and STEMI. Furthermore, patients enrolled in the registry are consecutive patients admitted with ACS and are population-based, rather than study protocol-based. Therefore, this model may be more generalizable than previous models. While the model is quite generalizable, the model does not account for all possible predictors — e.g., the authors did not consider socioeconomic factors.

Another notable factor about the current model is that it is applicable to patients who are discharged alive after being admitted with ACS. It may thus be applicable to patients presenting for major noncardiac surgery after a prior admission with ACS. Current ACC/AHA guidelines on preoperative cardiac evaluation consider all forms of ACS within a month of the surgery as a major clinical predictor, whereas history of stable angina or MI > 1 month is considered an intermediate clinical predictor.<sup>8</sup> The current study suggests that as far as mortality is concerned, one may need to make distinctions among different forms of ACS with whose history a patient may be coming to a major noncardiac surgery. For example, a 55-year-old without prior history of MI or CHF, presents with unstable angina, but is well managed with systolic pressure > 140 and resting heart rate < 70 bpm. His serum creatinine is 1.0 and he has no cardiac enzyme elevations. His symptoms are resolved with PCI. He would get a score of 54 on this model, with an associated 6-month predicted mortality of < 1%. On the other hand, a 75-year-old with prior history of CHF rules in for an MI with ST depression and enzyme elevation. His systolic pressure drops to 90's and his resting heart rate was in 100's before being controlled with β-blockade. He also has a serum creatinine of 2 mg/dl. His score on this model would be 186, with an associated 6-month predicted mortality of about 30%. The implications for perioperative mortality and cardiac morbidity for these two hypothetical patients, though both have ACS and a major clinical predictor, cannot be the same. This study calls for a study to develop a perioperative post-ACS prediction model that takes into account different forms of ACS.

## References:

1. Krumholz HM, Chen J, Wang Y, et al. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation* 1999; 99:2986-92
2. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9461 patients. *Circulation* 2000; 101:2557-67
3. Morrow DA, Antman EM, Giugliano RP, et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet* 2001; 358:1571-5
4. Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an international trial of 41,021 patients. *Circulation* 1995; 91:1659-68
5. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *J Am Med Assoc* 2000; 284:835-42
6. Rathore SS, Weinfurt KP, Gross CP, Krumholz HM. Validity of a simple ST-elevation acute myocardial infarction risk index: are randomized trial prognostic estimates generalizable to elderly patients? *Circulation* 2003; 107:811-6
7. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003; 163:2345-53
8. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery – Executive Summary: a report of the ACC/AHA task force on practice guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) *J Am Coll Cardiol* 2002; 39:542-553

## A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators. *N Engl J Med* 2004;350:2247-2256 (accompanying editorial by Cook D. *N Engl J Med* 2004;350:2294-2296)

**Reviewer:** Bernhard Riedel, MBChB, MMed, FCA, FAHA  
The University of Texas  
M. D. Anderson Cancer Center  
Houston, TX

**Background:** It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) significantly affects patient outcome.<sup>1-7</sup> The absence of adequately powered randomized, controlled trials, and the conflicting results of meta-analyses examining how the choice of crystalloid or colloid solution and of albumin-containing or albumin-free fluid

affects survival in critically ill patients<sup>1-3,7</sup> have left many clinicians unsure about the effect of albumin-containing fluids on survival in critically ill patients. To address this uncertainty, the Saline versus Albumin Fluid Evaluation (SAFE) Study tested the hypothesis that when 4% albumin is compared with 0.9% sodium chloride (normal saline) for intravascular-fluid resuscitation in patients in the ICU, there is no difference in the 28-day rate of death from any cause.

**Methods:** Adult patients admitted to closed, multidisciplinary ICUs of 16 academic tertiary hospitals in Australia and New Zealand between November 2001 and June 2003 were assessed for eligibility for the study. Eligible patients were those whom the treating clinician judged to require fluid administration to maintain or increase intravascular volume, with this decision supported by the fulfillment of at least one objective criterion (e.g., heart rate >90 beats per minute, a systolic blood pressure <100 mm Hg). Patients admitted to the ICU after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded. Eligible patients were randomly assigned to receive either 4% albumin or normal saline in a double-blind fashion. Randomization, using a minimization algorithm, was centrally accessed through a secure internet-based Web site, and stratified according to institution and according to whether there was a diagnosis of trauma on admission to the ICU. The allocated study treatment was used for all fluid resuscitation in the ICU until death, or discharge, or until 28 days after randomization. The administration of maintenance fluids, specific replacement fluids, enteral or parenteral nutrition, and blood products, as well as the monitoring of central venous pressure, pulmonary-artery catheterization, and all other aspects of patient care were performed at the discretion of the treating clinicians. The primary outcome measure was death from any cause within 28 days after randomization. Secondary outcome measures were the survival time during the first 28 days, the proportion of patients who had new organ failure, the duration of mechanical ventilation, the duration of renal-replacement therapy, and the duration of the ICU and hospital stay. The trial was designed to detect a 3% difference in absolute mortality rates between the two groups from an estimated baseline mortality rate of 15% at a power of 90%.

**Results:** Of the 6,997 patients who underwent randomization, 94.7 percent were enrolled with the use of the provision for delayed consent, 3,497 were assigned to receive albumin and 3,500 were assigned to receive saline. Compliance was excellent; more than 97 percent of patients received their assigned fluid. Information on vital status 28 days after randomization was unavailable for 67 patients (1.0%). Patients randomly assigned to receive albumin received significantly less study fluid during the first four study days, with an overall ratio of volume of albumin to volume of saline administered approximating 1:1.4. Thereafter, there were no differences between the two groups with regards to volume of study fluids administered.

There were 726 (20.9%) deaths in the albumin group, as compared with 729 (21.1%) deaths in the saline group (relative risk of death, 0.99; 95% CI, 0.91 to 1.09;  $P=0.87$ ). At 28 days, 111 patients in the albumin group (3.2%) and 87 patients in the saline group (2.5%) remained in the ICU (relative risk, 1.27; 95% CI, 0.96 to 1.68;  $P=0.09$ ). There were no significant differences with regards to the mean ( $\pm$ SD) number of days spent in the ICU ( $6.5\pm 6.6$  vs.  $6.2\pm 6.2$  days;  $P=0.44$ ), days spent in hospital ( $15.3\pm 9.6$  vs.  $15.6\pm 9.6$  days;  $P=0.30$ ), days of mechanical ventilation ( $4.5\pm 6.1$  vs.  $4.3\pm 5.7$  days;  $P=0.74$ ), or days of renal-replacement therapy ( $0.5\pm 2.3$  vs.  $0.4\pm 2.0$  days;  $P=0.41$ ) between the albumin group and the saline group, respectively. The number of patients with new single- or multiple-organ failure was similar in the two groups ( $P=0.85$ ).

In a subgroup analyses of patients with trauma, 13.6% (81/596) patients assigned to receive albumin compared with 10.0% (59/590) patients assigned to receive saline died (relative risk, 1.36; 95% CI, 0.99 to 1.86;  $P=0.06$ ). This difference in the relative risk of death was due to the greater number of patients with trauma and an associated brain injury who died after random assignment to albumin as opposed to saline: 24.5% (59/241) patients assigned to receive albumin compared with 15.1% (38/251) patients assigned to receive saline (relative risk, 1.62; 95% CI, 1.12 to 2.34;  $P=0.009$ ). Among patients who had trauma without brain injury, there was no difference between the groups in terms of mortality.

In a subgroup analysis of patients with severe sepsis, 30.7% (185/603) of patients assigned to receive albumin compared with 35.3% (217/615) of patients assigned to receive saline died (relative risk, 0.87; 95% CI, 0.74 to 1.02;  $P=0.09$ ).

**Discussion and Comments:** The SAFE Study investigators concluded that in a heterogeneous population of critically ill patients who require fluid resuscitation that the use of 4% albumin or normal saline for intravascular volume resuscitation resulted in equivalent rates of 28-day mortality from any cause. Rates of secondary outcomes—survival time, organ dysfunction, the duration of mechanical ventilation, the duration of renal-replacement therapy, and the length of stay in the intensive care unit and in the hospital—were also similar. These results challenge some polarized convictions and fail to support the results of the Cochrane Injuries Group Albumin Reviewers' meta-analysis, which suggested that the use of albumin was associated with an increased mortality rate among critically ill patients.<sup>1</sup>

In the context of the overall results, what do the subgroup analyses suggest? Given that the study had insufficient power to detect small but important differences in mortality among the pre-defined subgroups, cautious interpretation of these findings is warranted. Patients with traumatic brain injury constituted only 7% of the study population, and the excess number of deaths in the albumin group was only 21. Accordingly, the trend, in the albumin treated group, toward increased mortality among patients with brain

injury associated with trauma and toward reduced mortality among patients with severe sepsis requires further investigation by specifically designed and appropriately powered studies.

This study by the Australian and New Zealand Intensive Care Society Clinical Trials Group heralds a new era in critical care. The SAFE study,<sup>8</sup> a large, simple, randomized, concealed, blinded trial that examined a ubiquitous intervention in the intensive care unit: intravenous fluid—one of the most fundamental and contentious issues in critical care, was commendably conducted, carefully analyzed, and transparently reported. As a consequence this study, by using multidisciplinary implementation strategies and Web-based management and by demonstrating excellent protocol adherence in thousands of patients, has raised the bar for future trials. The SAFE Study is not only a landmark trial; it is also a milestone for the discipline of critical care medicine.<sup>9</sup>

From the perspective of clinical practice, some clinicians will point to the overall absence of harm associated with albumin in the SAFE Study and use it on the basis of pathophysiological rationale and favorable trends in selected studies. Others will conclude that without proof of benefit, routine use of albumin is hard to justify; for similar clinical outcomes at a lower cost, crystalloids may suffice in most circumstances. Additional influences will include patient-specific conditions, clinicians' preferences, perceptions regarding safety of biologic fluids, availability, and cost. The affair with albumin in the intensive care is not over.<sup>9</sup>

References:

1. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. *BMJ* 1998; 317:235-40.
2. Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999; 27:200-10.
3. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; 135:149-64.
4. Cook D, Guyatt G. Colloid use for fluid resuscitation: evidence and spin. *Ann Intern Med* 2001; 135:205-8.
5. Whether albumin therapy improves or worsens survival of critically ill patients is not known. *Ann Intern Med* 2001; 135:S-25.
6. Boldt J. New light on intravascular volume replacement regimens: what did we learn from the past three years? *Anesth Analg* 2003; 97:1595-604.
7. Bunn F, Alderson P, Hawkins V. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev* 2003; CD001319.
8. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247-56.
9. Cook D. Is albumin safe? *N Engl J Med* 2004; 350:2294-6.



## Report on Meeting of the American Institute of Ultrasound in Medicine, May 2004

Joseph Savino, MD

*Chair, Committee on Governmental Affairs*

I represented the SCA at the meeting of the AIUM at the Ritz-Carlton in Pentagon City, Virginia on April 22 and 23, 2004. The following is a brief review of topics discussed that might interest the membership of the SCA:

The two-day session was conducted with formal lectures followed by break out sessions. Attendance included representatives from the American Society of Echocardiography (Drs. John Gorscan and Randy Martin), American Society of Anesthesiologists (Drs. Chang and Porembka - CCM), National Board of Echocardiography (Dr. Edward Gaiser), American College of Surgery as well as professional societies representing radiologists, sonographers, urologists, and obstetricians and gynecologists. In addition, groups representing industry were present, including SonoSite, Philips, GE, Seimans, and others.

The major topic of discussion was the development of Compact Ultrasound. The key message was Compact US would grow and dominate the industry in the next decade with miniaturization of all components. Movement to silicon transduction (cMUTS) (semiconductor based) rather than conventional piezoelectric elements was forthcoming. Miniaturization would not hamper the continued development in 3-D technology and tissue characterization. AIUM discouraged and in fact asked that the term 'Hand Held Ultrasound' be abandoned, as it did not accurately characterize the technology.

After a brief history of ultrasound, the program rapidly progressed to defining the growing market of Compact Ultrasound and miniature technology. Compact US systems are not necessarily more inexpensive than conventional platform systems. 2003 Compact US consisted of 2% of United States sales with an annual growth of 6%. The technology is moving toward PC based systems, facilitated visualization, wireless transmission, and digital storage.... a PDA type system was envisioned.

Compact US systems are becoming available as 'fully featured systems' as well as limited capability (only 2 D). The world market of Ultrasound users is 40% Radiology, 25% Cardiology,

20% Ob-Gyn, 5% Vascular, and 10% other. The market has grown in the past decade from \$10M (diagnostics only), to currently \$160M (diagnostics and procedural) to a projected \$1B by 2010 (diagnostics, procedural and imaging physicals). A significant portion of the 'procedural applications' of compact US are being performed by anesthesiologists in placement of central lines and guidance for nerve blocks.

The Ultrasound industry (Seimans, Philips, SonoSite, GE) voiced a clear imperative to take a new direction in their product development. Traditionally, industry has focused on a technology driven R&D strategy: develop new technologies (hardware and software) and seek out applications (e.g. AQ technology developed by Hewlett Packard, color kinesis, etc.). At this session, AIUM and industry suggested that future development should focus on 'service'... making it easier to perform, read and archive ultrasounds.

Two hours were devoted on the education of ultrasound providers. The general sense was that standardization was a sound idea, but most agreed that standardization of education would be done at a subspecialty level rather than having a global standardization process across all ultrasound disciplines. Breakout sessions were devoted on education, research/technology, clinical service, and reimbursement:

**Education:** Poor standardization exists across the disciplines (eg cardiac ultrasound versus prostate ultrasound versus renal ultrasound). It was emphasized that an effort to take Ultrasound out of the hands of clinicians (eg urologists doing prostate US) would not be in patients' best interest. However, should the family practitioner be doing prostate US as a screening tool? Currently there is little in regulatory control of such applications. Encouraged activities included introduction into medical school curricula, sonography training programs, and anatomy simulation. Europe and Asia have dedicated ultrasound training programs for medical students. It is a required course. Simulation of anatomy was considered an unexplored area: use of echo to teach gross anatomy, functional anatomy to medical students. Accreditation was discussed very briefly.

**Research/Technology:** most of the discussion focused on miniaturization and growth. R&D strategy was expected to change with increasing focus on defined service lines. Discussion lead to the request for outcomes research to determine if and how ultrasound makes a difference. The internal jugular vein IJV cannulation research done by cardiovascular anesthesiologists (US guided cannulation of the internal jugular vein) was offered as an example of clinical investigation that is directed at outcome and safety. With the projected increase in US, the issue of bio-effects was brought up but quickly set aside as it was determined not to be a major issue and not a focus of the meeting.

**Reimbursement:** A very difficult problem to determine if payors will pay for compact US. Will insurers pay for using US to cannulate the IJV? or to perform a nerve block? The questions were essentially unresolved.

**Clinical Service:** Continued growth of US in procedures and new growth in imaging physicals is anticipated. Cost barriers that would blunt this growth include hardware, training, and likelihood of very limited incremental reimbursement. The use of ultrasound as an entertainment tool was strongly discouraged. Apparently, there are malls in the United States where for \$100 someone takes an ultrasound of your fetus and gives you a picture. In contrast, exploring the use of ultrasound as a screening tool was advocated. The patient evaluation in the near future might include a medical history and a physical examination using various tools and instruments that a clinician carries with them: stethoscope, otoscope, and a compact ultrasound machine.

## Selective Pulmonary Vasodilators for Pulmonary Hypertension

Andrew Maslow, MD

*Rhode Island Hospital  
Providence, RI*

The low pressure compliant pulmonary vascular system offers little resistance to right ventricular ejection and provides a large surface area for gas exchange. This is largely due to the effects of nitric oxide (NO) and prostacyclin (PGI<sub>2</sub>) released from the pulmonary vascular endothelium and alveolar macrophages.<sup>1-5</sup> Activation of guanylate and adenylate cyclase by NO and PGI<sub>2</sub> respectively, increases intracellular cyclic-guanosine monophosphate (cGMP) and adenosine monophosphate (cAMP). These secondary messengers activate protein kinases, which reduces calcium influx, dephosphorylates myosin light chains, and promotes vascular relaxation.<sup>1-7</sup> Both NO and PGI<sub>2</sub> depress platelet and inflammatory cell function activation and aggregation, and proliferation, all of which are responses to stress, hypoxemia, and disease. Normal cellular suppression reduces chemical mediators from the pulmonary endothelium cells (endothelin-1; subtype ET<sub>A</sub>), platelets (thromboxane, serotonin), and inflammatory cells (cytokines, interleukins 1 and 6, and tumor necrosis factor) which counter the effects of NO and PGI<sub>2</sub> and cause pulmonary vascular constriction and remodeling resulting in pulmonary hypertension.

Pulmonary hypertension (PHTN) is defined as a mean pulmonary artery pressure (mPAP) > 25 mmHg at rest or > 30 mmHg with exercise. Alternatively, PHTN can be defined by a pulmonary vascular resistance (PVR) > 2-3 Wood units or > 200 - 300 dynes s<sup>-1</sup> cm<sup>-5</sup>. The microcellular development of PHTN is complex, involving platelet activation and aggregation, pulmonary vascular smooth muscle and endothelial cell proliferation, endothelial cell dysfunction, and activation and influx of inflammatory mediators. These cause acute and chronic changes of the pulmonary vascular architecture resulting in vasoconstriction, pulmonary 'vascular remodeling' and subsequent PHTN.

Causes of perioperative of PHTN include hypoxemia, acidosis, inflammation, hypothermia, changes in sympathetic stimulation, and pulmonary endothelial dysfunction. These lead to cel-

lular activation and aggregation, release of vasoconstrictors, and a reduction of NO and PGI<sub>2</sub>.<sup>1-4</sup> Hypoxic pulmonary vasoconstriction (HPV) reduces blood flow to poorly oxygenated alveoli, and shifts blood toward oxygenated alveoli. Although this improved matching of ventilation and perfusion is initially protective, persistent HPV results in PHTN and vascular remodeling. Pulmonary endothelial dysfunction is a contributor to PHTN seen after cardiopulmonary bypass.<sup>1-4</sup>

Regardless of its cause or onset, PHTN results in varying degrees of pulmonary dysfunction, and/or right heart dysfunction. Transient changes are usually managed by supporting the respiratory and cardiovascular systems, however if severe and/or allowed to continue, cardiopulmonary failure develops, increasing mortality. There is increasing emphasis on the need to diagnose PHTN, assess the severity and reversibility, and administer therapy to improve function and prevent exacerbations. This is best illustrated in the cardiac transplant patient with preoperative PHTN. Preoperative assessment predicts the reversibility of PHTN to prevent RV failure due to the acute increase of RV afterload to the donor heart.

Management of PHTN includes treatment of its cause, correction of metabolic abnormalities (hypothermia, acidosis), reduction of the sympathetic response, anticoagulation, and, for acute cases, support of the cardiopulmonary systems. The latter often involves a combination of oxygen therapy, mechanical ventilation when necessary, and manipulation of cardiac (especially the right heart) loading conditions. While a balance is sought between too much and too little preload, a reduction in RV afterload (pulmonary vasodilation) and maintenance of right coronary perfusion are desirable.

Available pulmonary vasodilators can be categorized by selectivity, by pharmacologic class, and by route of administration. Medications either directly or indirectly (NO donors; nitroglycerin (NTG); sodium nitroprusside (SNP)) stimulate adenylyl or guanylyl cyclase, or inhibit hydrolysis of cAMP or cGMP (phosphodiesterase inhibitors (PDEi)). Sympathetic agonists (epinephrine) and prostaglandins (PGE<sub>1</sub>, PGI<sub>2</sub>) activate adenylyl cyclase, and/or inhibit platelet function and cellular activation (PGI<sub>2</sub>). Nitric oxide is the only therapy approved by the FDA for inhalation (INO) administration, and only for treatment of near-term newborns with acute lung injury and persistent pulmonary hypertension.

Since its identification as endothelium-derived relaxing factor (EDRF) in 1987 and the delineation of its role in biology by 1998, nitric oxide has been extensively studied allowing establishment of guidelines.<sup>1-7</sup> Although FDA approval is limited for newborns with PHTN, INO has been administered safely to both pediatric and adult patients with PHTN. Inhaled NO (1-40 parts per million (ppm)) causes selective pulmonary vasodilation, inhibition of the function, adhesion and activation of inflammatory cells and platelets, inhibition of cell proliferation, and reduction in intrapulmonary shunt.<sup>1-3</sup> Reductions in mPAP and PVR are proportional to the severity of PHTN and associated with improvement

in right heart function, and increases in cardiac output.<sup>5-8</sup> Dilation of pulmonary vessels associated with alveoli delivering the NO results in improved matching of ventilation and perfusion and reduction in intrapulmonary shunt.<sup>5-8</sup> Although clinical benefits have been demonstrated across a wide range of patients, a 20-30% hyporesponse rate has been described, and the benefit for patients with chronic obstructive lung disease is not clear, perhaps due to abnormal airways.<sup>1-7</sup>

The absence of systemic vasodilation after inhalation of NO is the result of rapid binding to hemoglobin to form methemoglobin. Serum methemoglobin levels in cardiac surgical patients have been reported on average 1.9%.<sup>5-8</sup> High doses (> 500 ppm) result in platelet dysfunction, pulmonary alveolar edema and hemorrhage, alveolar hyperplasia, hypoxemia, depletion of pulmonary surfactant, pulmonary accumulation of inflammatory cells, and death due to acute respiratory failure.<sup>5-8</sup> Rapid discontinuation of INO may lead to rebound PHTN and severe respiratory failure. NO can be cytotoxic and cause DNA damage.<sup>1-8</sup> In light of these adverse effects, guidelines recommend continued analysis of NO and NO<sub>2</sub> (bi-product of NO breakdown) concentrations, repeated calibration of the gas monitors, and use of certified tanks and delivery systems.<sup>6</sup> Current OSHA recommendations recommends places limits on exposure to 8 hours for doses of 25 ppm.<sup>5,6</sup>

Practical problems with the delivery of INO exist. The necessary specific equipment costs 3,000 dollars for the first day and 125 dollar/hour thereafter.<sup>8</sup> An analysis of 17 adult cardiac surgical patients with PHTN recorded an average cost of 6,417 dollars for a mean administration of 30.2 hours per patient.<sup>8</sup> Since a specific delivery system is required INO is not readily available like other vasoactive medications at our disposal.

Alternative pulmonary vasodilators include intravenous NTG, SNP, prostaglandins (PGE<sub>1</sub>, PGI<sub>2</sub>) and PDEi, which are known to dilate both the pulmonary and systemic circulations.<sup>1-4,9-11</sup> Schmid et al compared inhaled NO (40 ppm) to intravenous PGE<sub>1</sub> (0.1 ug/kg/min) and intravenous NTG (3-5 ug/kg) in 14 cardiac surgical patients with postoperative PHTN. All three medications reduced mPAP and PVR, while only INO and PGE<sub>1</sub> increased cardiac index.<sup>11</sup> While PGE<sub>1</sub> and NTG reduced mean systemic arterial pressure, INO produced selective dilation of the pulmonary circulation.<sup>11</sup> Other data report the need for high dose norepinephrine (> 1-2 ug/kg/min) in more than 50% of patients receiving intravenous prostaglandin.<sup>1,9,10</sup> In contrast to INO, intravenous NTG and PGE<sub>1</sub> increase intrapulmonary shunt.<sup>1,9,11,12</sup>

Data have demonstrated selective pulmonary vasodilator effect of inhaled NTG, SNP, PGI<sub>2</sub>, PGE<sub>1</sub>, and PDEi (milrinone PDEi III; Zaprinast PDEi V).<sup>1-7</sup> Benefits include reductions in mPAP, PVR, increases in cardiac output, and reductions in intrapulmonary right to left shunting without reductions in systemic arterial pressure.<sup>1-3,12-17</sup> Compared to INO, these medications are as efficacious and easier to prepare and administer using simple nebulizers.

Of these alternatives, inhaled prostacyclin (Epoprostenol, Prostacyclin, Flolan) or its derivative (Iloprost) have been studied more extensively. Data reports selective reductions in PVR, and mPAP within minutes of its administration, which may last up to one hour or longer.<sup>1-7</sup> Inhaled PGI<sub>2</sub> has compared favorably to INO regarding improved right heart function, reductions in mPAP, PVR, and decreased intrapulmonary shunt.<sup>1-3,12,13,15,16</sup> Reduction of mPAP and PVR range from 15-40% of baseline along with up to 10% increases in cardiac index.<sup>1-3,12-16</sup> Dosing varies from single inhaled doses of 15-20 ug to continuous doses of 2-70 ng/kg/min using simple nebulizers.<sup>1,12-16</sup> Intravenous, and not inhaled, administration is associated with reductions in systemic blood pressure, flushing, headache, jaw pain, and diarrhea.<sup>13-15</sup> Preparation of inhaled prostacyclin, supplied as a powder, requires mixing with saline and/or glycine, the latter of which has been associated with excess moisture in the gas sampling tubing and, in one case, obstruction of the expiratory valve of the breathing circuit.<sup>15</sup>

Compared to INO, inhaled PGI<sub>2</sub> is significantly less expensive and easier to deliver.<sup>8,15</sup> For 126 patients who received inhaled prostacyclin for a mean of 45.6 hours, the cost was 35,878 dollars (150 dollars/day). If INO were administered instead of PGI<sub>2</sub> the total study cost would have been 717,564 dollars (125 dollars/hour), a difference of 681,686 dollars.<sup>8,15</sup>

Alternatively, inhaled milrinone and nitroglycerin have also resulted in similar selective reductions of mPAP, PVR and intrapulmonary shunt.<sup>16,17</sup> Combining inhaled milrinone and PGI<sub>2</sub> resulted in an additional 5-8% improvement in cardiac indices than either medication alone, without reduction in systemic blood pressure.<sup>16</sup> Both nitroglycerin and milrinone are mixed in saline and may be simpler, safer, and cheaper alternatives.

Prophylactic administration of continuous nebulized prostacyclin during 90 minutes of CPB was compared to an untreated CPB group (CPB without PGI<sub>2</sub>).<sup>18</sup> Significant benefits of the study group included lower post CPB mPAP, preservation of pulmonary endothelial function and reactivity, and improved oxygenation.

The indications for inhaled pulmonary vasodilators are not known since they are considered experimental (i.e. not FDA approved). However, on-going experience and continued data collection will further delineate the role of inhaled selective pulmonary vasodilators, alone or in combination, for the treatment of PHTN, especially when complicated by hypoxemia, and/or right heart failure. Alone or in combination with other therapies, inhaled selective pulmonary vasodilators offer unique benefits for patients with PHTN and secondary dysfunctions. Although effects may be transient, they may last long enough to treat acute increases in mPAP, or exacerbations of chronic PHTN during the perioperative period. Continued research will likely result in greater acceptance and approval for the

*Continued on page 10*

use of these inhaled alternatives to NO. Newer therapies will be more specific for abnormalities in ion channels, endothelin receptors, the inflammatory system, and causes of cellular proliferation.<sup>1-4</sup>

The alternatives to INO discussed above meet the needs of the perioperative intensivist in that they can be prepared and administered with relative ease at a significant cost reduction, and would be at our disposal '24/7'.

References:

1. Lowson S: Inhaled alternatives to Nitric Oxide. *Anesthesiology* 2002;96:1504-1513.
2. Blaise G, Langleben D, Hubert B: Pulmonary arterial hypertension. *Anesthesiology* 2003;99:1415-1432.
3. Fischer LG, Aken HV, Burkle H: Management of pulmonary hypertension: Physiologic and pharmacologic considerations for anesthesiologists. *Anesth Analg* 2003;96:1603-1616.
4. Tsai BM, Wang M, Turrentine MW, Mahomed Y, Brown JW, Meldrum DR: Hypoxic pulmonary vasoconstriction in cardiothoracic surgery: basic mechanisms to potential therapies. *Ann Thorac Surg* 2004;78:360-368.
5. Body SC, Hartigen PM, Shernan SK, Formanek V, Hurford WE: Nitric oxide: Delivery, measurement, and clinical applications. *J Cardiothorac Vasc Anesth* 1995;9:748-763.

6. Steudel W, Hurford WE, Zapol WM: Inhaled nitric oxide: Basic biology and clinical applications. *Anesthesiology* 1999;91:1090-1121.
7. Haddad E, Lawson SM, Johns RA, Rich GF: Use of inhaled nitric oxide perioperatively and in intensive care patients. *Anesthesiology* 2000;92:1821-1825.
8. Maxey TS, Smith CD, Kern JA, Tribble CG, Jones DR, Kron IL, Crosby IK: Beneficial effects of inhaled nitric oxide in adult cardiac surgical patients. *Ann Thorac Surg* 2002;73:529-533.
9. Vincent JL, Carlier E, Pinsky MR, Goldstein J, Naeije R, Lejeune P, Brimmiouille S, Leclerc JL, Kahn RJ, Primo G: Prostaglandin E<sub>1</sub> infusion for right ventricular failure after cardiac transplantation. *J Thorac Cardiovasc Surg* 1992;103:33-39.
10. D'Ambra MN, LaRaia PJ, Philbin DM, Watkins WD, Hilgenberg AD, Buckley MJ: Prostaglandin E<sub>1</sub>: A new therapy for refractory right heart failure and pulmonary hypertension after mitral valve replacement. *J Thorac Cardiovasc Surg* 1985;89:567-572.
11. Schmid ER, Burki C, Engel MHC, Schmidlin D, Tornic M, Seifert B: Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. *Anesth Analg* 1999;89:1108-1115.
12. Pappert D, Busch T, Gerlach H, Lewandowski K, Radermacher P, Rossaint R: Aerosolized prostacyclin versus inhaled nitric oxide in children with severe acute respiratory distress syndrome. *Anesthesiologist* 1995;82:1507-1511.
13. Langer F, Wihelm W, Tscholl D, Schramm R, Lausberg H, Wendler O, Schafers H-J: Intraoperative inhalation of the long-acting prostacyclin analog iloprost for pulmonary hypertension. *J Thorac Cardiovasc Surg* 2003;126:874-875.
14. Zwissler B, Welte M, Messmer K: Effects of inhaled prostacyclin as compared with inhaled nitric oxide on right ventricular performance in hypoxic pulmonary vasoconstriction. *J Cardiothorac Vasc Anesth* 1995;9:283-289.
15. De Wet CJ, Affleck DG, Jacobsohn E, Avidan MS, Tymkew H, Hill LL, Zanaboni PB, Moazami N, Smith JR: Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. *J Thorac Cardiovasc Surg* 2004;127:1058-1067.
16. Haraldsson A, Kieler-Jensen N, Ricksten S-E: The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. *Anesth Analg* 2001;93:1439-1445.
17. Yurtseven N, Karaca P, Kaplan M, Ozkul V, Tuygun AK, Aksoy T, Canik S, Kopman E: Effect of nitroglycerin inhalation on patients with pulmonary hypertension undergoing mitral valve replacement surgery. *Anesthesiology* 2003; 99:855-858.
18. Fortier S, DeMaria RG, Lamarche Y, Malo O, Denault A, Desjardins F, Carrier M, Perrault LP: Inhaled prostacyclin reduces cardiopulmonary bypass-induced pulmonary endothelial dysfunction via increased cyclic adenosine monophosphate levels. *J Thorac Cardiovasc Surg* 2004;128:109-116.

## Society of Cardiovascular Anesthesiologists

# 2005 Meetings

