

December 2006

Vol. 5, No. 6

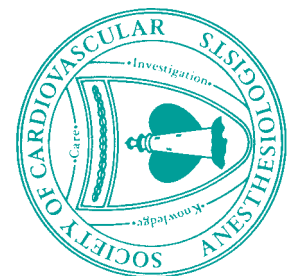
# What's Inside

Website Table of Contents	page 2
President's Message	page 3
Meeting Review	page 4
Drug & Innovation Update	page 5
Literature Reviews	page 6

# Society of Cardiovascular Anesthesiologists

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# What's Online ([www.scahq.org](http://www.scahq.org))

## December 2006 Newsletter

- Calendar of Future Meetings (Web Only)

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- Meeting Review: 10th Annual ICCVA Meeting

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- President's Message: Positive affiliations

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- Literature Reviews
  - Prognostic significance of multiple previous percutaneous coronary interventions in patients undergoing elective coronary artery bypass surgery.
  - A novel antidote-controlled anticoagulant reduces thrombin generation and inflammation and improves cardiac function in cardiopulmonary bypass surgery.
  - Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control?
  - Methylene blue added to a hypertonic-hyperoncotic solution increases short-term survival in experimental cardiac arrest.

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- Drug & Innovation Updates
  - Levosimendan: The Next Dobutamine?

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- Order the SCA Echo DVD Monograph online

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- Password-Protected Area for Members

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- Acknowledgement of Industry Support

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- Fellowship Listings

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

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- Job Postings

## Call for Nominations

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

- President-Elect – 2-year term
- Secretary/Treasurer – 2-year term
- Board of Directors (2 positions) – 3-year term
- Nominating Committee member (2 positions) – 2-year term
- Continuing Medical Education Committee (CME) member (2 positions) – 2-year term

The deadline for nominations is January 8, 2007. The slate of candidates for Board of Directors, Nominating Committee members and CME Committee members will appear on 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 Montreal, April 23, 2007.

10th Annual Comprehensive Review  
& Update of Perioperative Echo

## Clinical Decision Making in the Cardiac Surgery Patient

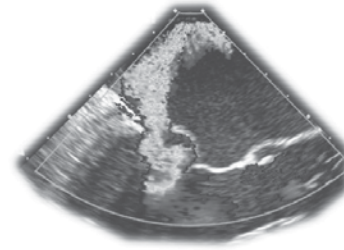
**BASIC**

February 5 – 7, 2007

**ADVANCED**

February 8 – 10, 2007

Sheraton San Diego Hotel & Marina  
San Diego, CA



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

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## SCA ANNUAL MEETING & WORKSHOPS

April 21 - 27, 2007

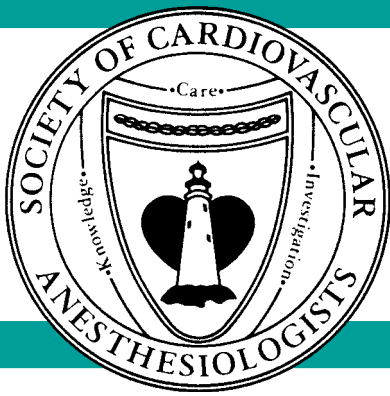
Palais de congrès de Montréal  
Montreal, Quebec, Canada

### WORKSHOPS INCLUDE:

TEE Review Courses

Professional Development in Education Skills:  
Learning to be a Better Educator

Challenging Cases from the Real World: The Adult with  
Congenital Heart Disease



# NEWSLETTER

2209 Dickens Road • Richmond, VA 23230-2005 • (804)282-0084 • [sca@societyhq.com](mailto:sca@societyhq.com)

December 2006

## President's Message

### Positive affiliations enhance our visibility & influence

One of the continuing issues in fostering the development of SCA to be the premier resource for cardiothoracic and vascular anesthesiologists is that of our relationship with others. Now more than ever, we are continually being approached, both as individuals and as a society, to join ranks with others or facilitate membership with other groups. The "dynamic tension" is whether such affiliation promotes greater strength and progress, or whether it dilutes our voice and influence. It is my view that the vast majority of the time, affiliations which are fostered and developed with enlightened self-interest, greatly enhance our visibility, our influence, and our ability to function professionally, both as individuals and as a group.

#### **Our Journal: *Anesthesia & Analgesia***

From the time of our first affiliation with the International Anesthesia Research Society (IARS) and its journal in 1993, there has been a continuing debate at the SCA Board regarding the wisdom of this affiliation and whether or not we should pursue the option of having our "own" journal. Each time our contract comes up for renewal (this happens next in December 2007) a lively debate ensues on the future of our affiliation.

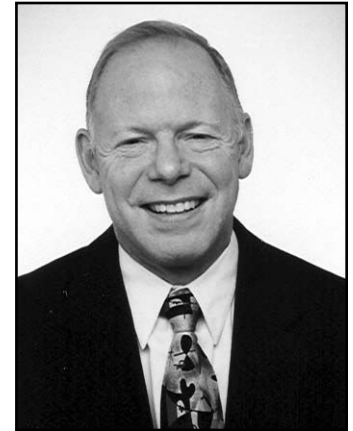
I believe the choice of *Anesthesia & Analgesia* as our journal was a very wise one. Over the years we have shaped the society's section of the journal, and under the talented leadership of our Editor Steve Shafer, Associate Editor Chuck Hogue, and Section Editor Marty London the quality, diversity, and appeal grow with every issue. We benefit from the wisdom and knowledge of the entire Editorial Board of *Anesthesia and Analgesia*, the resources of the oldest journal in the specialty, and our "journal within a journal" section is available to the more than 20,000 subscribers worldwide. Our members, most of whom do not have a 100% practice of cardiothoracic anesthesiology, benefit from exposure to articles and reviews covering the entire spectrum of anesthesiology practice and research. The IARS recognizes the importance of SCA to its success, and consults with our Board on issues important to the journal as a whole. At the same time as having a premiere spot for our own subspecialty in the print and electronic media, we are better integrated into the greater world of anesthesiology because we have chosen *Anesthesia & Analgesia* to be our journal.

#### **The National Board of Echocardiography (NBE) and the American Society of Echocardiography (ASE)**

Readers of the newsletter will recall the history of the creation of the NBE in 1996 by a joint venture of the SCA and ASE. Society members such as Dan Thys, Jack Shanewise, and Stan Shernan to name a few, have worked closely with our cardiology colleagues to recognize the expertise of cardiac anesthesiologists in perioperative echocardiography. We now share a certification organization and process with these colleagues, an unusual development for two very separate specialties of medicine. The bylaws of the NBE assure strong representation from our own subspecialty; in fact SCA past president Dan Thys is the current president of NBE. The ASE endorsed the SCA's echocardiography meeting when it was originally put together by Sol Aronson and Bob Savage, and has

continued to do so over the years.

In 2008 the NBE will begin to sponsor an annual lecture at this highly successful meeting entitled "The Arthur E. Weyman MD Lecture," in honor of the founding president of the NBE. The ASE is introducing a special introductory membership program for SCA members, and we are working to move forward with this society with other joint ventures. Who could doubt the benefits to our members and anesthesiology as a whole, from being recognized by the community of cardiologists as expert, certified perioperative echocardiographers?



*James G. Ramsay, MD  
President, 2005-2007*

#### **American Heart Association (AHA)**

Through the active participation and lobbying by SCA President-Elect Christina Mora Mangano and several others, the Council of the AHA formerly known as "Cardiovascular Surgery" is now called "Cardiovascular Surgery and Anesthesia." The annual supplement to *Circulation* on cardiac surgery, formerly edited by a cardiac surgeon, will now be co-edited by a surgeon and anesthesiologist, the first being Jerrold Levy. As a result of participation at the Council by Christina, Jerrold, and others, council chair Loren Hiratzka came to a recent SCA board meeting to encourage cardiovascular anesthesiologists to participate in the AHA and to apply for the generous grants available for cardiovascular research. There is also a Council on Cardiopulmonary, Perioperative and Critical Care where members such as Deb Schwinn and Simon Body have ably represented our specialty. The word "perioperative" was inserted in this council name as the result of Deb's efforts. Our members have been invited to participate in the creation and approval of important guidelines such as the recently completed Guidelines for the Management of Patients with Valvular Heart Disease, and the updated Guidelines on Perioperative Cardiovascular Evaluation of the Patient with Cardiac Disease (currently under review). Our collaboration with surgeons and cardiologists at the AHA better integrates the cardiac anesthesiologist into the world where we live – the world of cardiac care, rather than just the operating room.

My view is we have a great deal to contribute to the field of cardiovascular care, and this is best done through pursuing affiliations with our own colleagues in anesthesiology as well as surgeons and cardiologists. We do not live in a vacuum, and our "customers" are these colleagues as well as our patients. In addition to making our contributions to knowledge and care known outside our subspecialty, we have a great deal to learn from our peers and related specialties. Our lives are richer and more interesting because of these affiliations. I challenge you to reach out to those in your own institution, and make similar affiliations to those your society is striving for nationally and internationally.



## OFFICERS

### President

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Christina Mora Mangano, MD

### Secretary/Treasurer

Steven N. Konstadt, MD

### Immediate Past President

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*Canadian Representative*

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Glenn P. Gravlee, MD

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Christopher E. Troianos, MD

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### Ethics

Richard L. Wolman, MD

### International

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Theodore A. Alston, MD

Philip E. Greilich, MD

Hong Liu, MD

Feroze Mahmood, MD

Mohammed M. Minhaj, MD

Komal Patel, MD

## Meeting Review:

# 10th International Congress of Cardiothoracic and Vascular Anesthesia

It is a great pleasure for me as a Member of the Local Organizing Committee to write a report about the 10<sup>th</sup> International Congress of Cardiothoracic and Vascular Anesthesia (ICCVA) which was being held at the Hilton Hotel in Prague, Czech Republic between August 27 and 30, 2006. The Congress was jointly organized by the Society of Cardiovascular Anesthesiologists (SCA) and the Czech Society of Anesthesiology and Intensive Care Medicine (CSARIM). It was attended by a total of 569 people from 54 countries which included 486 registered delegates, 45 exhibitors and 38 accompanying persons.

The theme of the Congress, "The changing face of cardiothoracic and vascular anesthesiology", promised an attractive programme. The Faculty consisting of 84 members worked hard to fulfil the expectations of attendees. These speakers presented altogether 89 lectures in two parallel sessions. In addition, there were two late afternoon specials, industrial symposia (Bayer and Abbott) and industry supported sessions/lectures (Organon, Haemoscope, Linde and Novo Nordisk), industrial exhibits, transesophageal echocardiography workshop and poster exhibition comprising 111 posters.

It is not possible to mention all the highlights of the Congress and not to omit one at such a small space in this article. There were many stars but let me present my personal view. The Opening Ceremony in the evening of Sunday, August 27 was started by welcome speeches of Professor George Silvay, Mount Sinai Hospital, New York, USA, Honorary President of the Congress, Professor James G. Ramsay, President of the SCA and Professor Karel Cvachovec, Charles University, Prague, Czech Republic, President of the Local Organizing Committee and President of the CSARIM. Czech historian of architecture Zdeněk Lukeš then introduced to the numerous audience Prague's modern architectural monuments, especially in art nouveau. His presentation illustrated with a plenty of slides was very interesting for foreigners whom provided a suggestion what to see in Prague as well as for local people who realized which architectural treasures they are passing by every day without registering them. After the Welcome Cocktail the Faculty spent three hours cruising on the Vltava river through the illuminated Prague and seeing in reality some of the buildings mentioned before, such as The Dancing House by Frank Owen Gehry and Vlado Milunič.

The actual scientific programme began on Monday quite early in the morning with the session titled "Approach to challenging cardiac surgical patients" chaired by George Silvay and Hans-Joachim Priebe. Maria Galati, USA, spoke about anesthesia benchmarks and Joachim Radke, Germany, about ethics and money in anesthesia and intensive care. This ethical and financial framework was supplemented by Benjamin Drenger, Israel talking about standardization of perioperative assessment and Solomon Aronson, USA, who fully explained the problem of ischemic mitral regurgitation. Both of these topics often entail ethical and financial burden.

The parallel programme line during the whole Monday morning was devoted to the thoracic anesthesia and dealt with anesthesia technique for esophagectomy, lung ventilation, separation and injury in thoracic surgery. The Monday afternoon sessions addressed the issues of echocardiography in cardiac surgery, ventricular assist devices – their indications and management, organ protection as well as blood transfusion with their risks or alternatives.

Late afternoon special on Monday was presented by Professor Hans-Joachim Priebe, the Past President of the European Society of Anesthesiology. In his lecture he summed up the current situation with perioperative beta-blocker therapy, which was already in 2002 designated as one of 11 specific practices with sufficient clinical-based evidence for patient safety. However, in the light of recently published studies (2005, 2006) he recommended waiting for results of a large trial proving beta-blockers' effectiveness and safety, such as the POISE (PeriOperative ISchemic Evaluation) study, before a widespread use of these drugs on ordinary surgical wards can be implemented.

Tuesday morning started with another fixed star of cardiac anesthesia, namely epidural and spinal anesthesia for cardiac surgery. After Hugo van Aken, Germany, who spoke about the impact of epidural anesthesia on organ function, Beyhan Bakkaloğlu, Turkey, offered a six-year experience with 487 patients undergoing off-pump revascularizations and recommended the technique either for MIDCABs or for OPCABs with contraindications to general anesthesia. Richard Kowalewski, Canada, then presented his unique concept of high spinal anesthesia using hyperbaric bupivacaine 15-20 mg with opioids supplemented by light general anesthesia. His vast experience includes more than 9000 patients now. In the next session "Approach to challenging cardiac surgical and vascular patients" Martin Střiteský, Czech Republic, advocated the "awake" approach (sole epidural) to cardiac surgery performed with cardiopulmonary bypass.

In parallel to regional anesthesia Helfried Metzler, Austria, gave an extensive rationale for a sound

# Levosimendan: The Next Dobutamine?

Mark A. Chaney, MD  
University of Chicago

Dobutamine, a traditional beta-receptor agonist, is perhaps the most commonly used agent in the world to increase myocardial contractility. However, distinct clinical disadvantages exist when using this class of drugs (tachycardia, arrhythmia, increased myocardial oxygen demand). While phosphodiesterase inhibitors (milrinone) increase myocardial contractility without initiating tachycardia or increasing myocardial oxygen demand, this class of drugs is also associated with distinct clinical disadvantages (arrhythmia, sometimes excessive systemic vasodilation). Levosimendan, a member of a new class of drugs – calcium sensitizers – may offer substantial clinical advantages over traditional beta-receptor agonists and phosphodiesterase inhibitors by increasing myocardial contractility without initiating tachycardia or arrhythmia nor increasing myocardial oxygen demand or excessive systemic vasodilation.

Traditional beta-receptor agonists increase formation of intracellular cAMP whereas phosphodiesterase inhibitors prevent cAMP breakdown. Increased intracellular cAMP (from both classes of drugs) increases calcium current into myocytes to increase myocardial contractility. In contrast, levosimendan increases the sensitivity of myofilaments to calcium (increases myocardial contractility) without alteration of intracellular calcium levels. Potential clinical benefits of levosimendan include increased myocardial contractility (without increased intracellular calcium levels), vasodilation (coronary, systemic, pulmonary), and no effects on myocardial oxygen demand nor arrhythmogenesis. The most common adverse effects are headache and mild hypotension.

Clinical research experience has been accumulating with levosimendan. In patients with severe low-output heart failure, intravenous levosimendan has improved hemodynamic performance more effectively than dobutamine (fewer serious side effects, lower mortality). Several trials have validated the safety and efficacy of levosimendan as an inotropic agent. Several promising human studies on levosimendan usage in cardiac surgery have also been published, suggesting the drug may be

useful in low-output states after cardiac surgery. The available evidence suggests that levosimendan enhances cardiac performance and reduces left ventricular afterload following cardiopulmonary bypass in patients with normal preoperative left ventricular function. Also, in addition to being effective in postoperative rescue therapy for patients with difficult weaning from cardiopulmonary bypass, elective preoperative initiation of levosimendan in patients with high perioperative risk or compromised left ventricular function appears to reduce catecholamine requirements, need for mechanical circulatory support, and duration of critical care.

In summary, levosimendan is a positive inotropic drug with vasodilating properties that has been extensively investigated in experimental studies and that is also increasingly the subject of clinical trials. To date, clinical experience with the drug is encouraging because it combines several beneficial actions that differ considerably from other cardiostimulant drugs. Levosimendan increases myocardial contractility without increasing intracellular calcium concentration, does not increase myocardial oxygen demand, does not increase heart rate, does not impair myocardial relaxation, improves coronary blood flow, reduces preload and afterload, and may also exert anti-ischemic actions. Initial clinical studies have revealed beneficial effects on short- and long-term survival compared with standard inotropes. The drug is associated with a low incidence of adverse effects when used in appropriate amounts. These encouraging preliminary results with levosimendan suggest that the drug may perhaps replace the more commonly utilized traditional beta-receptor agonists and phosphodiesterase inhibitors when one wants to increase myocardial contractility.

Please see  
[www.scahq.org](http://www.scahq.org)  
for newsletter articles with full references

## ICCVA, from page 4

approach to patients with recently introduced coronary stents who can bring much trouble in everyday practice.

Basic Transesophageal Echocardiography (TEE) Workshop took place on Tuesday afternoon. Moderated by Jack Shanewise, USA, all speakers presented a comprehensive description how to efficiently master TEE in the perioperative period to the numerous audience that gave up other attractive parallel sessions like “Deep hypothermic circulatory arrest” or “Grown-up congenital heart disease”. At this time all over the world TEE is steadily shifting from cardiologists’ to anesthesiologists’ and intensivists’ hands.

Tuesday’s Late Afternoon Special followed after sessions like HITT (Heparin-induced thrombocytopenia and thrombosis) symposium sponsored by Organon and parallel and provocative “Advanced age – acceptable risk or contraindication for surgery?” Per Johansson, Denmark, introduced the audience into a new era of transfusion medicine, i.e. hospitalwide thromboelastography (TEG). His results deserve congratulation.

For Wednesday there were four sessions left – “Nitric oxide, its use and misuse”, “SIRS and challenge of bleeding”, “New drugs” and “Anesthesiologic management of operations on thoracic aorta.”

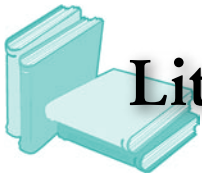
Traditional Gala Dinner took place on Tuesday at Žofin Palace situated on a small island on the river Vltava just in front of the National Theatre

and viewing Prague Castle opposite. Thanks to a pleasant weather it was a nice opportunity to enjoy good meal among colleagues and friends from all over the world together with one of the nicest views in Prague.

At the conclusion, it is necessary to warmly thank all the presenters for their comprehensive and attractive lectures, chairpersons for a valuable discussion as well as to all the poster authors for their effort in presenting the interesting results of their research. Highly appreciated is also the support granted by all the partners such as Abbott, Arrow International, Organon, Bayer Health Care, Hameoscope, Linde and Novo Nordisk.

The organizers supported logistically by Congress organizer Guarant International did their best to prepare a high-quality, friendly and perhaps and hopefully a long time remembered meeting in a pleasant place in the heart of Europe. I believe they were successful. The next International Congress of Cardiothoracic and Vascular Anesthesia will take place down south at Cape Town, South Africa in 2008. Let us wish to see ourselves all there together, even with those who really wanted to come to Prague and unfortunately, due to various reasons, could not. Goodbye in Cape Town.

Michal Horáček, MD, DEAA  
[michal.horacek@fnmotol.cz](mailto:michal.horacek@fnmotol.cz)



# Literature Reviews

## Prognostic significance of multiple previous percutaneous coronary interventions in patients undergoing elective coronary artery bypass surgery.

M, Leyh R, Massoudy P, et al. *Circulation* 2006;114[suppl I]:I441-I447.

### Reviewer

Mohammed Minhaj, MD  
Assistant Professor  
Department of Anesthesia and Critical Care  
University of Chicago Hospitals

### Abstract Excerpt

There is a question of whether multiple percutaneous coronary interventions (PCI) lead to increased perioperative risk during coronary artery bypass graft surgery (CABG). This study compared 2626 consecutive patients undergoing first-time isolated CABG (group 1) to 360 patients who had single PCI (group 2) and 289 patients who had multiple PCI sessions (group 2) prior to CABG. Statistical analysis revealed that multiple PCI sessions prior to CABG was associated with increased in-hospital mortality and major adverse cardiac events (MACEs). The authors conclude that patients with a history of multiple PCI sessions prior to CABG were at increased perioperative risk of morbidity and mortality.

### Reviewer's Comments

The number of patients undergoing PCI has risen dramatically in recent years and as techniques and experience have improved, more complicated lesions and multiple stenting procedures are being performed on patients. However, PCI is not effective in all patients, and despite multiple interventions, some of these patients present for surgical revascularization after stenting procedures. This study is the first to identify that patients who have had multiple PCI sessions are at risk for increased perioperative mortality and major adverse cardiac events (including perioperative myocardial infarction and low cardiac output syndrome). Multiple theories are postulated, including more coronary endothelial injury secondary to stent placement, compromised collateral blood flow secondary to multiple stent placement, and increased surgical difficulty with respect to more distal anastomoses on target vessels (targets need to be distal to stent placement) where vessel diameter may be smaller.

There are several limitations to this study. First, it is retrospective in design and the results may be influenced by bias. Most patients also had bare-metal stents, not drug-eluting stents. Additionally, all results are from a single medical center, and therefore results may not be applicable to all institutions. There is also no evidence of increased stent thromboses in patients undergoing previous PCI. Finally, there were some statistical differences between groups. Ejection fractions were similar, but patients with multiple PCI sessions had more previous myocardial infarctions and hyperlipidemia than their counterparts who had had no previous PCI. Neither one of these factors through multivariable and univariable analyses were found to be statistical risk factors for worse outcomes, however.

Overall, this study confirms what many practitioners probably have already known: patients with multiple PCI sessions have higher perioperative risk. Proving this with data may lead to patients and practitioners opting for earlier CABG rather than repeated PCI sessions for patients at risk for multiple revascularization attempts. Additionally, as the scope of our practice changes, and more of our CABG patients have previous PCI sessions, we need to be even more vigilant in attempting to reduce perioperative risks for these patients. Finally, with the rise of drug-

eluting stents being used, patients who have had these placed need to be evaluated for surgical outcomes after CABG.

## A novel antidote-controlled anticoagulant reduces thrombin generation and inflammation and improves cardiac function in cardiopulmonary bypass surgery.

Nimjee SM, Keys JR, Pitoc GA, Quick G, Rusconi CP, Sullenger BA. *Mol Ther.* 2006 Sep;14(3):408-15. Epub 2006 Jun 9.

### Reviewers:

Nicholas M. Barrett, University College Cork  
Theodore A. Alston, MD, PhD, Harvard Medical School

### Abstract:

In the beginning were heparin and protamine, and they were good. Yet, we eternally strive for more nearly perfect pharmacology. Researchers at Duke and Regado Biosciences demonstrate that little pieces of artificially synthesized RNA can replace the anticoagulant from pig intestines and the reversal agent from fish parts.

The researchers screened a large battery of RNA fragments for ability to bind to and inhibit clotting factor 9a. A particular 35-base oligonucleotide dubbed 9.3tC seems suitable for clinical development. Accordingly, anesthetized piglets were subjected to cardiopulmonary bypass with 9.3tC as the anticoagulant.

The 12 animals received either 9.3tC (0.5 mg/kg) or else heparin (300 unit/kg) for cardiopulmonary bypass achieved via median sternotomy. The pumps were primed with blood from donors receiving the same anticoagulant as the bypass animal. During a crossclamp time of 30 min, the animals received cardioplegia solution and were systemically cooled to 30°C. Rewarming and bypass were continued for 30 min after the crossclamp was removed.

The heparinized animals achieved ACT values of about 500 sec while, of note, the RNA-treated animals achieved values of about 300 sec. Furthermore, the aPTT values were much higher in the heparin group. However, no thrombi were found in any circuits. Furthermore, thrombin generation, as measured by blood levels of fragment F 1+2, was dramatically reduced in the RNA group. Interleukins 1B and 6 were also lower in the RNA group.

Part of the beauty of RNA molecules raised to bind to enzymes is that antidotes are easily synthesized. The researchers synthesized a 35-base strand of largely complementary sequence to 9.3tC. The complementary molecule, termed 5-2C for now, binds tightly to 9.3tC much as complementary DNA strand form double helices. Anticoagulation by 9.3tC was nicely reversed by 5.2C (5 mg/kg). Furthermore, MAP and CO were better preserved during RNA reversal of RNA than during protamine reversal of heparin.

### Comments:

Jack Szostak, awarded a 2006 Lasker prize, was one of the first scientists to recognize that small pieces of RNA could be artificially engineered to bind to nearly any selected target molecule. From aptus (Latin for "to fit"), he coined the term "aptamer" for these target-binding polymers of nucleic acid. There are countless pharmacological targets for which aptamers can be constructed, and Watson-Crick base-pairing considerations permit the ready preparation of aptamer antidotes for aptamer drugs.

A DNA-based aptamer against thrombin had permitted uneventful experimental cardiopulmonary bypass, and now an RNA-based inhibitor of factor 9a shows good promise. Aptamers are touted to have little or no antigenicity, and they will hopefully prove free of allergic problems resembling heparin-induced thrombocytopenia or catastrophic protamine reactions. If an aptamer against a single coagulation factor does come to clinical fruition as an anticoagulant for CPB, though, it seems that an activated clotting time lower than that demanded of heparin will have to

Continued on page 7

be demanded of the aptamer. Any new anticoagulant will have its own required ACT value or will require a different clotting assay altogether.

It is interesting to wonder what new side-effects might be encountered with new drugs. For instance, the purine loads from aptamer drugs might trigger gout. Perhaps the purines would inhibit immunosuppression by mycophenolate in heart transplantation. Despite this speculation, aptamers will very likely enter the pharmacopoeia. Other interesting targets for aptamers in development include complement C5 and neutrophil elastase.

### Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control?

Don Poldermans, MD, PhD, Jeroen J. Bax, MD, PhD, Olaf Schouten, MD, Aleksandar N. Neskovic, MD, PhD, Bernard Paelinck, MD, PhD, Guido Rocci, MD, PhD, Laura van Dortmont, MD, PhD, Anai E.S. Durazzo, MD, PhD, Louis L.M. van de Ven, MD, PhD, Marc R.H.M. van Sambeek, MD, PhD, Miklos D. Kertai, MD, PhD, Eric Boersma, PhD for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo Study Group

Journal of the American College of Cardiology 2006 Sep 5; 48(5):964-9

#### Reviewer:

Hong Liu, MD, UC Davis Health System, Sacramento, CA

#### Abstract:

The purpose of this study was to assess the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate (HR) control scheduled for major vascular surgery. Treatment guidelines of the American College of Cardiology/American Heart Association recommend cardiac testing in these patients to identify subjects at increased risk. This policy delays surgery, even though test results might be redundant and beta-blockers with tight HR control provide sufficient myocardial protection. Furthermore, the benefit of revascularization in high-risk patients is ill-defined. Methods and results: All 1,476 screened patients were stratified into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (3 risk factors). All patients received beta-blockers. The 770 intermediate-risk patients were randomly assigned to cardiac stress-testing (n = 386) or no testing. Test results influenced management. In patients with ischemia, physicians aimed to control HR below the ischemic threshold. Those with extensive stress-induced ischemia were considered for revascularization. The primary end point was cardiac death or myocardial infarction at 30-days after surgery. Testing showed no ischemia in 287 patients (74%); limited ischemia in 65 patients (17%), and extensive ischemia in 34 patients (8.8%). Of 34 patients with extensive ischemia, revascularization before surgery was feasible in 12 patients (35%). Patients assigned to no testing had similar incidence of the primary end point as those assigned to testing (1.8% vs. 2.3%; odds ratio [OR] 0.78; 95% confidence interval [CI] 0.28 to 2.1; p = 0.62). The strategy of no testing brought surgery almost 3 weeks forward. Regardless of allocated strategy, patients with a HR <65 beats/min had lower risk than the remaining patients (1.3% vs. 5.2%; OR 0.24; 95% CI 0.09 to 0.66; p = 0.003). Conclusions: Cardiac testing can safely be omitted in intermediate-risk patients, provided that beta-blockers aiming at tight HR control are prescribed.

#### Comments:

65 million Americans have cardiovascular disease and approximately 100,000 of the 600,000 per year in the United States who undergo cardiac surgery and 1.5 million of the 30 million who undergo non-cardiac surgery suffer perioperative cardiovascular morbidity resulting in 50,000 myocardial infarctions and 20,000 deaths a year at a cost exceeding \$20 billion annually. The mortality rate for coronary artery surgery is 3.2%.

The risk of death for non-cardiac surgery after CABG is 1.5%. The risk of non-cardiac without CABG is 3%. So, the combined total risk (3.2% (CABG) + 1.5% (non-cardiac after CABG)) is still higher than 3% (risk of non-cardiac without CABG).

Beta-blocker therapy has become an essential part of the medical treatment of patients with acute coronary syndromes, also a major cause of perioperative adverse outcome. Two randomized trials showed that perioperative beta-blocker therapy was associated with an improved outcome in high-risk surgical patients. A recent large retrospective observational study, evaluating the effect from 663,635 surgical procedures confirmed the benefit of beta-blocker in those with increased risk. These promising results were questioned by a recent meta-analysis of 8 randomized clinical trials evaluating a total number of 1,152 patients. This meta-analysis showed only a nominal statistically significant effect of beta-blockers for the composite end point of 30-day cardiovascular mortality, nonfatal MI, and nonfatal cardiac arrest (relative risk 0.44; 95% CI 0.20 to 0.97). Two more recently completed studies failed to show a favorable effect of beta-blockers. In the POBBLE (Perioperative Beta-Blockade) trial metoprolol failed to improve 30-day cardiovascular outcome in 97 low-risk vascular surgery patients; those with a history of ischemic heart disease were excluded. The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, involving 921 patients with diabetes undergoing non-cardiac surgery, failed to show that metoprolol significantly reduced the risk of death and cardiac complications after a median follow-up of 18 months. A potential factor that might explain these conflicting study outcomes is a difference in dosing and HR control. Beta-blockers reduce HR and myocardial contractility and, subsequently, myocardial oxygen demand. To exert the optimal beneficial effect, dose adjustments for HR control are important. This study confirmed these findings, because tight HR control was clearly associated with an improved outcome. The authors in this study believe that for a proper interpretation of the perioperative cardiac protective effect of beta-blockers, the effect on HR control needs to be taken into account.

### Methylene blue added to a hypertonic-hyperoncotic solution increases short-term survival in experimental cardiac arrest.

Miclescu A, Basu S, Wiklund L.

Crit Care Med. 2006 Nov;34(11). Epub 2006 Sep 5.

#### Reviewers:

Nicholas M. Barrett, University College Cork

Theodore A. Alston, MD, PhD, Harvard Medical School

#### Abstract:

Methylene blue is not just for methemoglobinemia anymore. The blue dye sometimes improves circulation in "dire" situations. Accordingly, researchers in Uppsala report a benefit of methylene blue as an aid to resuscitation from cardiac arrest.

Fifty-nine anesthetized piglets (approximately 25 kg), divided into three groups, were electrically subjected to ventricular fibrillation. After 12 minutes of untreated cardiac arrest, chest compressions and ventilation with 100% O<sub>2</sub> were initiated. The animals received arginine vasopressin and one of three other intravenous therapies: isotonic saline alone (55 ml/kg/hr), hypertonic saline/dextran (7.5%/6%) alone (10 ml/kg/hr), or hypertonic saline/dextran with methylene blue (10ml/kg/hr and 7.5 mg/kg/hr, respectively). Countershocks were attempted after 8 minutes of resuscitation, and, if necessary, intravenous epinephrine was administered.

The hypertonic saline/dextran group fared better than the isotonic saline group (survival of 12/19 versus 9/20 in the 4 hour experiments).

However, methylene blue saline/dextran fared even better than isotonic saline (survival of 16/20 versus 12/19,  $p = .03$ ). Early hemodynamics were best in the methylene blue group. Jugular venous levels of neuronal protein S-100 $\beta$ , early jugular venous levels of inflammatory 15-keto-dihydro-PGF<sub>2 $\alpha$</sub> , and systemic levels of myocardial troponin and creatine kinase were lowest with methylene blue.

**Comments:**

The tricyclic methylene blue molecule was the first of the phenothiazine chemicals. It was synthesized by Heinrich Caro in 1876 as an aniline-derived dye for textiles. It faded too fast for commercial success in the fabric industry, but it made much history as a histochemical stain, invaluable biochemical reagent, and multipurpose medical therapeutic. Its pharmacological use began in the 1890s when Paul Ehrlich (Nobel 1908) discovered the dye to have useful antimalarial activity. It was thereby probably the first synthetic antimicrobial drug to have reasonable efficacy and safety when used systemically. In the 1920s it proved a dramatic antidote for cyanide poisoning. Tested against many other poisons, it miraculously reversed toxic methemoglobinemia, and this property is the main reason why the drug is well-known to benzocaine-using anesthesiologists today. However, the drug is full of other surprises. For instance, it helps to reverse symptoms of cyclophosphamide-induced encephalopathy and, exotically, those of Jamaican ackee fruit poisoning.

Robert Furchgott, Louis Ignarro, and Ferid Murad each mentioned methylene blue in their 1998 Nobel speeches on the discovery of nitric oxide as the Endothelium-Derived (and drug-derived) Relaxing Factor of

blood vessels. The reagent was useful to them as an antagonist of nitric oxide (<http://nobelprize.org>). The antagonism probably involves many mechanisms. For instance, methylene blue inhibits NO synthetase, reacts directly with NO, generates superoxide molecules (which react rapidly with NO), and inhibits guanylate cyclase (the vessel-relaxing receptor for NO).

Consequently, methylene blue therapy has proven salutary in a number of states of pathologically low systemic vascular resistance. For instance, Francis Schneider (Strasbourg) found the drug to sometimes dramatically help to reverse hypotension in septic shock. Similarly, the drug has been helpful in cases of profound "vasoplegia" following cardiopulmonary bypass, and it may have value in the treatment of protamine reactions. It can help in some cases of anaphylactic shock, and it has helped to treat hypotension related to lithium toxicity, ACE inhibition, and hemodialysis.

It is interesting that our drug armamentarium in cardiovascular anesthesiology includes inhaled NO and nitroglycerin as potentially life-saving sources of NO and methylene blue as a potentially life-saving antagonist of NO. It may be necessary to pharmacologically modulate physiological balance by pressure in either direction.

One caveat about this seminal paper in the use of methylene blue as an aid to resuscitation from electrically-induced fibrillatory arrest is that the experimental animals had normal coronary arteries. It will be interesting to see if the nitroglycerin antagonist is also helpful in the setting of ischemically-induced arrest. If so, we will have a new clinical indication to give a blue drug to a blue patient.

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