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What's Inside

Society of Cardiovascular Anesthesiologists
2209 Dickens Road • Richmond, Virginia 23230-2005

SCA
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Richmond, VA 23230-2005

What's Online (www.scahq.org)

August 2006 Newsletter

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 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). 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.

SCA BREAKFAST PANEL AT THE ASA ANNUAL MEETING

Saturday, October 14, 2006
Chicago, IL

Racial and Gender Outcome Differences in CV Anesthesia & Medicine

Moderator: Solomon Aronson, MD, FASE

Outcomes in Women

Nancy A. Nussmeier, MD

Outcomes in African Americans

John E. Ellis, MD

Outcomes in Canada

Davy C.H. Cheng, MD, MSc, FRCPC

Tickets are $15 each and are available through the ASA.

NEWSLETTER

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

President's Message

New Faces in SCA Leadership Positions

It is my pleasure to introduce to you our newly-elected Board members, as well as some new Committee Chairs chosen by members of the Executive Committee. We are fortunate to have so many capable, interested, and dedicated members willing to serve the society, and I encourage each and every one of you to get involved as well. You can email me at james.ramsay@emoryhealthcare.org, or Heather Spiess at heather@societyhq.com.

New Board Members

Nancy Nussmeier and Bob Savage both completed their terms as elected members of the board this year, and both intend to stay active in the society. Nancy is co-chair of our Philanthropy Task Force, and Bob will be helping define a task force looking into standards for anesthesia in places like the cardiac catheterization laboratory. Both Nancy and Bob have done a great job and it has been a real pleasure to have them on the Board.

Our two newly-elected board members are Linda Shore-Lesserson and Gregg Hartman. Linda has been an active member of SCA for sixteen years, and is no stranger to the board having attended most of our meetings over the last four years in her capacity as Scientific Program Vice Chair and Chair. She is Associate Professor and Chief, Division of Cardiothoracic Anesthesiology, at the Montefiore Medical Center in New York. Linda has presented papers, lectured, and been a panelist at many SCA meetings including the Annual, CPB and Echo meetings. She was a member of the Education Committee and then chaired that committee until it merged with the Scientific Program Committee. She is one of the original committee members investigating ACGME accreditation of cardiovascular fellowships, is a Liaison Editor for our journal, *Anesthesia & Analgesia*, and a member of the Editorial Board of the *Journal of Cardiothoracic and Vascular Anesthesia*. She is also a member of the task force appointed to create the cardiovascular track at the ASA Annual Meeting.

Gregg Hartman is Professor of Anesthesiology at Dartmouth Hitchcock Medical Center in Lebanon, New Hampshire. He has been a member of the Society for almost 16 years and has served as a speaker at several SCA Annual Meetings as well as the Echo Meeting. He is currently a Co-Director of our Annual Comprehensive Review & Update of Perioperative Echo meeting; he has served in this role since 2004. Like Linda, Gregg has also attended a number of our Board meetings in his capacity as co-director of our Echo meeting. Before being elected to the Board Gregg was elected to a two-year term on the Nominating Committee from 2003-2005. He has recently been appointed to the National Board of Echocardiography Perioperative TEE examination committee.

New Committee Chairs

Scott T. Reeves, MD
Chair, Scientific Program Committee

Scott has served as vice-chair with Linda Shore-Lesserson, and now succeeds Linda as the Chair of the committee which organizes our Annual Meeting. He is Chair and Professor, Department of Anesthesia and Perioperative Medicine at the Medical University of South Carolina. Scott has been a member of the SCA since 1994 and has served on the Society's Education Committee, Certification for Perioperative Transesophageal Echocardiography Task Force, Economics Task Force, and Nominating Committee. He has chaired numerous SCA Workshops, spoken at multiple Comprehensive Review of Intraoperative Echo Meetings and has served as an abstract reviewer for a number of years as well.

Robert N. Sladen, MD
Chair, International Committee

Rob Sladen has been a member of the SCA since 1980, and has contributed to many of our meetings over the years. Rob succeeds Bel Russell as the International Committee Chair, and will be collaborating with many individuals outside of North America to plan a "satellite" meeting at the World Congress in South Africa in 2008. Rob is Professor and Vice-Chair, and Chief of the Division of Critical Care, in the Department of Anesthesiology at the College of Physicians and Surgeons of Columbia University, New York. He has served on the SCA's Scientific Program Committee (1990-2, 2002-6) and International Committee (1998-2002), and in conjunction with Manny Fontes has organized the panel on Critical Care Medicine at our Annual Meeting for the last several years. Rob is a past-president of the American Society of Critical Care Anesthesiologists.

James G. Ramsay, MD
President, 2005-2007

Bryant A. Murphy, MD
Chair, Membership Committee

Bryant succeeds Uday Jain as the new Chair of our Membership Committee. He is a staff anesthesiologist at Cape Fear Valley Medical Center in Fayetteville, NC and is partner in Cumberland Anesthesia Associates. A member of the SCA since 1998, he served as a member of the Membership Committee prior to enthusiastically accepting the position of Chairman. He also served for several years as a facilitator for PBLDs at the Annual Meetings.

John F. Butterworth, IV, MD
Chair, Publications Committee

John Butterworth is the R. K. Stoelting Professor and Chairman of the Department of Anesthesia at Indiana University. A member of SCA since 1987, he has reviewed scientific abstracts for the annual meeting for many years and has been a frequent contributor to the annual meeting. He has served on the editorial board of the SCA's journal, *Anesthesia & Analgesia* since 2000 and on the Publications Committee since

Continued on page 8

NEWSLETTER

Literature Reviews

Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: First clinical application in humans

Michael M.H. Cheung MB, ChB, MRCP, Rajesh K. Kharbanda MD, PhD, Igor E. Konstantinov MD, PhD, Mikiko Shimizu MD, Helena Frndova Meng, Jia Li MD, PhD, Helen M. Holtby MD, Peter N. Cox MD, Jeffrey F. Smallhorn MD, FRCP, Glen S. Van Arsdell MD, and Andrew N. Redington MD, FRCP; *Journal of the American College of Cardiology* 2006;47(11):2277-82.

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

Objectives and background: The authors conducted a randomized controlled trial of the effects of remote ischemic preconditioning (RIPC) in children undergoing repair of congenital heart defects. RIPC reduces injury caused by ischemia/reperfusion (I/R) in distant organs. Cardiopulmonary bypass (CPB) is associated with multi-system injury. The authors hypothesized that RIPC would modulate injury induced by CPB.

Methods: Children undergoing repair of congenital heart defects were randomized to RIPC or control treatment. RIPC was induced by four 5-min cycles of lower limb ischemia and reperfusion using a blood pressure cuff. Measurements of lung mechanics, cytokines, and troponin I were made pre- and postoperatively.

Results: Thirty-seven patients were studied. There were 20 control patients and 17 patients in the RIPC group. The mean age and weight of the RIPC and control patients were not different (0.9 ± 0.9 years vs. 2.2 ± 3.4 years, p = 0.4; and 6.9 ± 2.9 kg vs. 11.5 ± 10 kg, p = 0.06). Bypass and cross-clamp times were not different (80 ± 24 min vs. 88 ± 25 min, p = 0.3; and 55 ± 13 min vs. 59 ± 13 min, p = 0.4). Levels of troponin I postoperatively were greater in the control patients compared with the RIPC group (p = 0.04), indicating greater myocardial injury in control patients. Postoperative inotropic requirement was greater in the control patients compared with RIPC patients at both 3 and 6 h (7.9 ± 4.7 vs. 10.9 ± 3.2, p = 0.04; and 7.3 ± 4.9 vs. 10.8 ± 3.9, p = 0.03, respectively). The RIPC group had significantly lower airway resistance at 6 h postoperatively (p = 0.009).

Conclusions: This study demonstrates the myocardial protective effects of RIPC using a simple noninvasive technique of four 5-min cycles of lower limb ischemia and reperfusion. These novel data support the need for a larger study of RIPC in patients undergoing cardiac surgery.

Comments: Ischemic preconditioning (IPC) is an innate protective mechanism that markedly reduces I/R injury in most human tissues. Despite the protective effects of IPC, routine use has not become widely accepted, because it is limited by the need to induce ischemia in the target organ, a process that itself may induce dysfunction and that is clearly inappropriate for global myocardial protection. RIPC was first described as a transient ischemia of the left circumflex territory and was shown to reduce the effects of subsequent potentially lethal ischemia in the left anterior descending artery territory in dogs. Further studies in rodent models demonstrated that ischemia of the kidney and intestine may induce myocardial protection. Although providing proof of principle, none of these studies has particular relevance to protection against I/R injury in the clinical setting. The authors first demonstrated the clinical effectiveness of RIPC in this study. They used a simple protocol of transient limb ischemia provided protection against myocardial and pulmonary I/R injury, and also modulated the systemic inflammatory response in children undergoing open-heart surgery. One of the obvious advantages of this technique of RIPC is its non-invasive nature and ease of application. Furthermore, in contrast to local IPC, the effects of transient skeletal muscle ischemia are relatively benign and there are no myocardial dysfunction, risk of arrhythmia, low cardiac output, or secondary organ injury. Additionally, the "non-local" effect of RIPC may afford more widespread protection against I/R injury and the CPB-induced systemic inflammatory response. Although this study was done in pediatric population, it can also be applied to adult open-heart surgery.

Clinical and hemodynamic comparison of 15:2 and 30:2 compression-to-ventilation ratios for cardiopulmonary resuscitation.

Yannopoulos D, Aufderheide TP, Gabrielli A, Beiser DG, McKnite SH, Pirrallo RG, Wigginton J, Becker L, Vanden Hoek T, Tang W, Nadkarni VM, Klein JP, Idris AH, Lurie KG. *Crit Care Med*. 2006 May;34(5):1444-9.

Reviewers: Ala Nozari, MD, PhD;
Theodore A. Alston, MD, PhD
Harvard Medical School

Abstract: In its most recent revision of the ACLS guidelines, the American Heart Association recommends a compression-to-ventilation ratio of 30:2 for the resuscitation of victims of circulatory arrest, from infants to adults. It is difficult to design clinical trials in order to fine-tune resuscitation strategies, so controlled laboratory tests with experimental animals are important. Yannopoulos et al. describe a pig model that supports the 30:2 ratio and also supports their ingenious airway device as an aid to resuscitation.

The animals were subjected to 6 min of no-flow ventricular fibrillation followed by 10 min of closed-chest CPR with a compression-to-ventilation ratio of 15:2 or 30:2. An impedance threshold valve was added to the breathing circuit in both groups after 6 min of CPR (12 min of ventricular fibrillation). The impedance threshold valve is designed to impede inspiration of gas during elastic recoil of chest and, hence, to increase the negative intrathoracic pressure and the venous return to the heart. The acid-base status, cerebral and cardiovascular hemodynamics were monitored or calculated in all animals. The authors found significantly improved diastolic blood pressure, coronary perfusion pressure, and common carotid blood flow in the animals randomized to 30:2 compression-to-ventilation ratio. End tidal CO2 was greater in the 30:2 CPR group, but arterial pH did not differ between the groups. Most importantly, the authors report successful return of spontaneous circulation in 6 of 9 animals in the 30:2 CPR group, versus 1 of 9 in the control group.

In human studies, the authors evaluated fatigue and quality of CPR for 5 min of 15:2 or 30:2 on a recording manikin. No differences were observed between the groups in the quality of CPR performance.

Comments: The rationale for the 30:2 compression-to-ventilation ratio is to ensure delivery of longer series of uninterrupted chest compressions. Uninterrupted sequential chest compression generates better vital organ blood flow, and hence improves the chance of successful resuscitation. The Yannopoulos paper demonstrates improved hemodynamics and survival with a 30:2 ratio and no significant adverse effects on the respiratory parameters.

A survival rate of 67% after 10 min of cardiac arrest without pressors or other aids to improve the blood flow generated by chest compressions is impressive. Even though successful restoration of spontaneous circulation has been reported in animal models of CPR after longer arrest times, pharmacological or mechanical techniques have always been used to improve vital organ blood flow. In fact, without pressors or other mechanical aids in the current study, only 1 of 9 animals survived after 10 min of 15:2 CPR. The significance of the difference between the groups was corroborated by hemodynamic and biochemical differences during CPR.

The authors not only decreased the ventilations per compression, they also applied an experimental inspiratory impedance valve to the airways of the animals. The valve improved hemodynamics with either compression:ventilation ratio. The valve is simple and portable and applies an impedance of -40 cm H2O pressure during chest recoil after each chest compression. It can be used with either an endotracheal tube or else with a well fitting face mask. By inhibiting airway gas entry during elastic recoil of the chest, it improves the effect of negative intrathoracic pressure on venous return. It is likely that future ACLS guidelines will commend the use of the "inspiratory threshold device" in resuscitation.

Dynamic quantitative echocardiographic evaluation of mitral regurgitation in the operating department.

Alijandro G MD, Vicky Souliere MD, Andre Y Denault MD et al. *J Am Soc Echocardiogr* 2006; 19 140:146

Reviewers: Feroze Mahmood, MD;
Robina Matyal, MD
Beth Israel Deaconess Medical Center
Harvard Medical School, Boston, MA

Introduction: The intraoperative assessment of mitral regurgitation (MR) is complicated by the altered loading conditions and is often underestimated. Generally the assessment of MR in the operating room (OR) is performed by semi-quantitative methods such as Doppler color jet area (CJA), which is affected by instrument settings as well as the morphology of the regurgitant jet. This study was done to compare the preoperative and intraoperative transesophageal echo (TEE) findings using more objective quantitative methods such as Proximal Isovelocity Surface Area (PISA) method of MR assessment.

Methods: Patients who were 18 years or older and presenting for coronary revascularization or mitral valve surgery due to isolated MR without any other pathology were enrolled in the study. Patients with mitral stenosis, prior mitral surgery, aortic valve disease of more than mild severity and ruptured papillary muscles were excluded.

Baseline TEE examination was performed under conscious sedation and studies were recorded for off line analysis. A baseline intraoperative TEE examination was performed after induction of general anesthesia (GA) and placement of invasive monitoring lines prior to incision and MR severity was graded. Then the systolic blood pressure was gradually elevated to preoperative levels and MR assessment done again. The MR assessment was done by a single experienced echocardiographer using similar TEE machine as the preoperative TEE exam and instrument settings. The mechanism of MR was diagnosed on the basis of Carpentier's classification.

Semiquantitative methods used for MR assessment were CJA measurement, pulmonary venous flow assessment (PW), vena contracta measurement and the PISA method for quantitative assessment (Table I).

Results: A total of 25 patients were enrolled. Sixteen patients were in sinus rhythm and nine were in atrial fibrillation (AF). Ten patients were classified as having organic MR, 13 were classified as having functional MR (10 with ischemic MR and three with annular dilatation). Mean baseline ejection fraction (EF) 40+/- 12% for functional MR and 53+/- 9% for organic MR. The mean time delay between the preoperative intraoperative TEE assessment was 3.8 days.

Blood pressure varied significantly amongst the three time periods ($p < .001$). Maximal regurgitant jet velocity decreased with GA and returned to baseline with phenylephrine boluses. Heart rate was significantly lower under GA as compared with preoperative level and did not increase with phenylephrine infusion.

The assessment of MR during those three time periods is as shown in table II.

The severity of MR decreased with induction of GA regardless of the method of assessment. There was no difference in severity of MR during different time points when measured with the PISA method alone suggesting that it is least susceptible to be altered by loading conditions. However the variations in other hemodynamic parameters such as heart rate and filling pressures were not associated with change in the severity of MR.

Discussion: Intraoperative assessment of mitral regurgitation is a complicated subject. Preoperative transthoracic echo (TTE) and intraoperative TEE have shown only modest correlation.[1] Similarly pre-cardiopulmonary bypass TEE examination leads to a change in the management plan regarding mitral valve surgery in a significant number of patients.[2] The severity of MR is known to decrease under GA.[3-5] The exact cause of the reduction in severity is not known. Reduction on severity of MR is especially more pronounced in patients in which the regurgitation is due to inadequate leaflet coaptation (annular dilatation/ventricular dilatation), and does not seem to decrease in severity if the regurgitation is due to a flail leaflet.[4] However, gradual increase in afterload with phenylephrine infusion has been demonstrated in the past to increase MR severity.[5]

In the present study, both semiquantitative and quantitative methods were used for assessment of MR,[6] yet there were significant limitations in the study. Nine out of 25 patients were in atrial fibrillation, in whom the assessment of mitral regurgitation is even more complicated due to variability of the heart rate, contractility and the pulmonary venous inflow patterns are unreliable. Similarly, as reported by the authors, there was a significant reduction in the heart rate in all the patients. This could have accounted for reduction of MR in those patients who were being operated for ischemia. The authors did not report the preoperative/intraoperative dimensions of the left ventricle that could also account for a more optimal geometric alignment of the papillary muscles and thus leading to a better coaptation of the leaflets.[4] The time delay between the preoperative and intraoperative TEE was approximately three days, and no information is available on the preoperative filling pressures at the time of baseline TEE examination.

But this study does stress the importance of assessment of mitral valve as part of a "mitral valve apparatus" and assessment of regurgitation severity with multiple quantitative and semi-quantitative means. Also, the impact of altered loading conditions must always be considered when making a diagnosis regarding mitral valve surgery. Similarly, increased preload/afterload and rate rhythm and contractility to provoke mitral regurgitation should be considered when there is discordant data.

References and tables are on www.scahq.org

Continued on page 6

Inhaled nitric oxide decreases infarction size and improves left ventricular function in a murine model of myocardial ischemia-reperfusion injury.

Hataishi R, Rodrigues AC, Neilan TG, Morgan JG, Buys E, Shiva S, Tambouret R, Jassal DS, Raher MJ, Furutani E, Ichinose F, Gladwin MT, Rosenzweig A, Zapol WM, Picard MH, Bloch KD, Scherrer-Crosbie M. *Am J Physiol Heart Circ Physiol*. 2006 Jul;291(1):H379-84. Epub 2006 Jan 27.

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

Abstract: Inhaled nitric oxide gas (NO) selectively dilates blood vessels in the ventilated regions of the lung. The free radical itself is rapidly scavenged by hemoglobin, so systemic vascular resistance is preserved despite powerful pulmonary vascular dilation. However, blood elements passing through the lungs may react with NO there and then carry pharmacological effects to the heart and other organs. It is probably for this reason that an impressive cardiac benefit of inhaled NO is seen in this mouse model of cardiac ischemia-reperfusion.

Anesthetized mice underwent left anterior descending coronary occlusion for 30 to 120 min. Starting 20 min before reperfusion, the mice inhaled 0-80 ppm NO and supplemental oxygen. After recovery from anesthesia, the NO was continued in air for 24 h. Infarct size was assessed histologically, and functional assessment included echocardiography.

Although 20 ppm NO did not significantly reduce infarct size, infarcts were roughly halved in area by 40 or 80 ppm NO. Accordingly, the mice treated with inhaled NO exhibited a relatively small increase in left ventricular end diastolic volume and a relatively small decrease in ejection fraction.

The mechanism of the NO protection does not seem to involve transport of NO itself to the heart. For instance, inhaled NO failed to increase myocardial levels of cyclic-GMP. Instead, neutrophils are implicated in the mechanism. NO decreased myocardial infiltration by neutrophils. Furthermore, an antibody depleting neutrophils reduced infarct size in a manner not further enhanced by NO.

Comments: Inhaled NO was introduced as a miracle drug, dramatically rescuing certain newborns from otherwise fatal pulmonary hypertension without the need for dangerous extracorporeal ventilation of the blood. The drug continues to effect miracles in many settings. For instance, the drug often obviates the need for highly invasive mechanical assist devices for right heart failure. Most of the indications for inhaled NO therapy are highly specialized. This mouse paper suggests that a large number of coronary patients may greatly profit from prompt and simple access to this the intriguing agent.

The authors are quick to point out that, unlike nitroglycerin and other systemic "nitrovasodilators," inhaled NO can be very easily administered with relative safety in nearly any clinical situation. Vocabulary issues aside, let us hope that this heart-saving action of inhaled NO applies, as Steinbeck anticipated, to mice and men.

Pathophysiological processes underlying emotional triggering of acute cardiac events.

Strike PC, Magid K, Whitehead DL, Brydon L, Bhattacharyya MR, Steptoe A. *Proc Natl Acad Sci USA* 2006 Mar 14;103(11):4322-7.

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

Abstract: Every time comedian Redd Foxx became angry or disappointed, he would histrionically clutch his chest and announce that he was joining his departed wife. The humor depended on the grim plausibility of a lethal reaction to emotional stress. Though negative emotions are long suspected to prompt acute coronary events, the phenomenon is difficult to examine with high scientific control. Researchers from University College London interviewed 34 men after they had survived a myocardial infarction or a bout of unstable angina. Fourteen of the patients reported acute negative emotion in the 2-hour period before onset of symptoms. Examples included "arguments with neighbors, family conflict, anniversaries of bereavements," and, a good one, "frustrating commuting." About a year later, in comparison with the rest of the patients, the fourteen exhibited markedly increased platelet aggregation when blood was sampled soon after deliberate psychological stress.

There were two experimental stresses. One was a challenge to identify target color words printed over incongruous colors on a computer screen. This challenge of trying to push the right buttons on the computer increased systolic blood pressure and cardiac index (calculated from finger pulse pressure recordings) in both groups of patients. There is a lesson there. The computer stressor was followed by a public speaking challenge that further increased blood pressure and cardiac index. Those cardiovascular indices were slower to recover after the "emotional" group was stressed.

Peripheral venous blood samples were citrated and incubated with color-tagged antibodies against various cell surface antigens. Flow cytometry then quantified leukocyte-platelet, monocyte-platelet, and neutrophil-platelet aggregates. The results are striking. The patients who did not identify an emotional trigger for their coronary event did not exhibit an increase in platelet aggregates in response to experimental stress. The patients for whom an emotional stress may have triggered a coronary event exhibited a significant rise in circulating aggregates during experimental stress, and the rise peaked at 30 minutes after the experimental stress.

The authors conclude that "some patients with coronary artery disease may be particularly susceptible to emotional triggering of acute coronary syndrome because of heightened platelet activation in response to psychological stress, coupled with impaired hemodynamic poststress recovery."

Comments: The difficulty in achieving perfect isolation of variables in a clinical study of this subject is obvious. When possible, aspirin and beta-blockers were withheld for experimental testing. However, both drugs were continued more often in the emotion-triggered patients. This limitation of the study does not seem to quantitatively explain the impressive platelet differences found between the two groups.

Leukocyte-platelet aggregates form when platelets are stimulated to move leukocyte-binding P-selectin molecules from intracellular alpha granules to the platelet surface. This measure of platelet activation is plausibly connected to coronary thrombosis, but the connection is, of course, hypothetical in this study.

Interestingly, our hospitals are no doubt emotionally stressful for our cardiovascular patients.

Effect of clopidogrel premedication in off-pump cardiac surgery are we forfeiting the benefits of reduced hemorrhagic sequelae?

Kapetanakis EI, Medlam DA, Petro KR, Haile E, Hill PC, Dullum MK, Bafi AS, Boyce SW, Corso PJ. *Circulation*. 2006 Apr 4;113(13):1667-74. Epub 2006 Mar 27

Reviewer: Mohammed Minhaj, MD
University of Chicago

Abstract: The use of clopidogrel reduces the incidence of thrombotic complications after percutaneous coronary revascularization procedures. However, because of the irreversible platelet inhibition that clopidogrel causes, patients subsequently undergoing surgical revascularization are at increased risk of bleeding complications and transfusion requirements. The purpose of this study was to determine if clopidogrel administration led to increased hemorrhagic complications (hemostatic reexploration, transfusion requirements, morbidity, etc.) in patients undergoing off-pump coronary artery bypass grafting (CABG). Off-pump surgery was selected because of the proposed benefits in reducing hemorrhagic complications versus traditional CABG surgery utilizing cardiopulmonary bypass (CPB). One thousand, five hundred, seventy-two patients who had isolated off-pump CABG surgery were identified and their perioperative course examined retrospectively. Of these 1,572 patients 281 (17.9%) did and 1,291 (82.1%) did not receive clopidogrel prior to their operation. The group receiving clopidogrel had a five times higher likelihood of hemostatic reoperations, a 60% increase in the odds of receiving packed cell transfusions and a 2.5 times higher likelihood of platelet transfusion. Clopidogrel patients also had a higher median length of hospital stay. The mortality rate was not significantly different. The authors conclude that clopidogrel administration in the cardiology suite increased the risk for hemostatic reoperation and requirements for blood products perioperatively

for patients subsequently undergoing off-pump CABG surgery.

Comments: Proponents of off-pump CABG surgery cite decreased transfusion requirements as one of the benefits when off-pump surgery is compared to more traditional CABG utilizing CPB. However, the authors of this study demonstrate this potential benefit is mitigated by the use of clopidogrel preoperatively, as these patients required increased blood product transfusions and surgical reexplorations. It should be noted that the retrospective nature of the study presents limitations, one of which is that physicians were not blinded to the use of clopidrogel in patients and therefore may have had a bias towards more blood product (especially platelet) transfusions. However, this should have had no bearing on the differences seen in surgical reexploration.

These results pose a dilemma for physicians involved in caring for these patients. The benefits of clopidogrel, coupled with its relatively low side effect profile, have led to widespread use by everyone from internists to emergency room physicians in patients thought to be experiencing myocardial ischemia. While the majority of these patients may not need surgical revascularization, those that do may end up requiring more transfusions and their inherent risks (infection, transfusion reactions, etc.), as well as surgical procedures. The authors suggest that perhaps administration of clopidrogel be delayed until it is certain which type of intervention patients will undergo. This, however, may not be realistic. An accompanying Editorial notes that the majority of patients do not go on to have surgical intervention; thus, withholding clopidrogel in all patients may lead to increased risk (Bavry AA, Lincoff AM: Is clopidrogel cardiovascular medicine's double-edged sword? *Circulation*, 2006 Apr 4;113(13):1638-1640). The Editorial also proposes that patients who have received clopidrogel should perhaps have their surgery delayed for five days when possible, or withhold the drug when surgical intervention seems likely rather than withholding it in all patients. This recommendation however, has its own drawbacks, namely not all patients can have their surgery delayed safely with medical management, and not all patients are easily pre-identified as being destined for surgical management.

Previous studies have demonstrated that clopidrogel is associated with increased bleeding risks, but these were mostly in patients undergoing surgery associated with CPB. This is the first study to demonstrate the increased risk of hemorrhagic complications in off-pump CABG surgery in patients on clopidrogel, something many of us have experienced anecdotally. From an anesthesiologist's perspective, we usually inherit the patient who has already received clopidrogel as we are not present during the initial evaluation and/or treatment of most of these patients. However, we can participate in discussion with the cardiologists and surgeons regarding optimal surgical timing for these patients to reduce the use of blood products, possibly avoiding complications associated with increased transfusions, and continue to judiciously allocate our limited blood product resources.

Drug & Innovation Updates

Ranolazine: A new class of anti-ischemic medication

Andrew Maslow, MD
Rhode Island Hospital
Brown University Medical School
Providence, RI

Prevention and treatment of myocardial ischemia involves multiple therapeutic avenues directed at improving coronary blood flow and reducing myocardial oxygen demand (MVO_2). The latter includes reductions of cardiac preload, afterload, contractility, and rate, while maintaining adequate forward flow and pressure. More recently, attention has been directed toward improving the efficiency of the heart muscle itself, especially during times of increased MVO_2, and/or relative reductions in oxygen supply.[1-3] Specifically, these medications (ranolazine, perhexiline, trimeazidine, etomoxir) alter substrate utilization for the generation of high-energy phosphates (ATP) in the mitochondria.

Mitochondria, which account for almost 50% of the heart muscle cell volume, generate ATP from the oxidation of stored sugars and fat. While the latter is a more efficient storage of substrate, the former provides greater production of ATP per mole of oxygen used. Therefore, any treatment that increases glucose oxidation should improve the efficiency of the heart muscle to make energy, especially during conditions of reduced oxygen delivery.[1-3] While at rest (low MVO_2), energy production is mainly due to oxidation of fatty acids. However, during moderate to heavy exercise, a normal increase in glucose oxidation occurs. For patients with reduced oxygen supply, a greater use of glucose utilization over fatty acids may improve muscle efficiency and, therefore, pump function. Ranolazine is a relatively new anti-anginal medication which inhibits fatty acid oxidation and subsequently results in increased oxidation of glucose.[1-3] In addition, it has minimal beta 1 and 2 adrenergic receptor blockade and mild antiarrhythmic properties.[4,5] These benefits occur without affecting cardiac loading conditions or the rate-pressure product.[4] Improvement in cardiac efficiency without affecting hemodynamics has potential clinical benefits, especially for the perioperative patient, for which significant hemodynamic changes usually occur as a result of anesthetic medications, perioperative blood loss, and fluid shifts.

During clinical trials, the oral administration of ranolazine increased exercise capacity in patients with chronic heart failure and/or a history myocardial ischemia. This is either due to superior anti-ischemic properties and/or the minimal effect on systemic hemodynamics.[6-7] Similar benefits were seen in patients with hypertrophied hearts.[8] Ranolazine may also possess antiarrhythmic effects similar to those of amiodarone.[5] In rat hearts subject to ischemia and then reperfusion, the administration of ranolazine reduced fatty acid oxidation, increased glucose oxidation, increased the amount of ATP formed, and reduced the accumulation of fatty acid intermediates, lactate, and tissue acidosis.[3,9-11]

During intravenous therapy in a dog model of heart failure (coronary microembolization), increases in left ventricular ejection fraction (27-36%), left ventricular dp/dt (1712- 1900 mmHg/sec), and stroke volume (20-26 cc/beat) were observed.[12] There were no changes in heart rate nor systemic blood pressure.[12] In normal dogs, there was no clinical effect.[12] When compared to dobutamine, both medications improve cardiac function while only dobutamine is associated with an increase in MVO_2.[13] In another ischemia model, a bolus of ranolazine, followed by an infusion, reduced the size of the myocardial infarct by 33% and troponin leak, when compared to saline.[10]

Reported adverse effects after prolonged oral administration occur in up to 29% of patients.[7] These include asthma-like symptoms (12.3%), dyspepsia (4.5%), nausea (3.9%), constipation (3.6%), palpitations (2.6%), and dizziness (1.3%).[7] Ranolazine's effects on gluconeogenesis, glycolysis, and increases in fatty acid stores may, in theory, alter insulin resistance (this has not yet been investigated). Others have reported an increased incidence of tissue dysplasia and colonic tumors in mice, perhaps cautioning administration of ranolazine in patients with a history of colonic polyps, previous colon cancer, or current malignant cancer (potential for drug-related increase in tumor burden).[14]

Although ranolazine has been used clinically in oral form in non-surgical patients with histories of chronic angina and/or congestive heart failure, its intravenous administration and short-term benefits may find its way to the surgical patient. The shift from fatty acid oxidation to glucose oxidation and improved oxygen utilization without affecting the rate-pressure-product may help improve hemodynamic stability while providing protection against perioperative ischemia. In addition, administration prior to cardiopulmonary bypass may attenuate "post-pump" dysfunction by improving substrate utilization and by reducing fatty acid intermediates and tissue acidosis.[9] These potential perioperative benefits have yet to be studied.

Drug & Innovation Update continued from page 7

References are on www.scahq.org

Heparin-Induced Thrombocytopenia

Devin Trousdale, MD
Philip E. Greilich, MD, FAHA
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The incidence of heparin-induced thrombocytopenia (HIT) in patients undergoing cardiovascular surgery is as high as 2.0% and appears to be rising.[1] While thrombocytopenia following cardiac surgery is common and up to 50% of patients develop heparin antibodies, only a fraction will develop HIT syndrome.[2] Unfortunately, when HIT does occur it is associated with a 40-80% incidence of thrombosis and a mortality rate of 28%.[2]

HIT is a transient, yet recurring, IgG antibody-mediated response directed against the platelet factor four (PF-4)-heparin complex.[2] It is more likely to occur with high dose, unfractionated heparin (UFH), but can occur with any exposure.[3] The onset can be less than one day if a previous heparin exposure has occurred within 30 days.[1,2] The risk of HIT can be lowered, but not eliminated, with the use of low molecular weight heparin.[2] HIT may continue for days to weeks, even after heparin discontinuation.[1,2] Sequelae include arterial/venous thrombosis,[1,2] skin lesions at heparin injection sites, or severe acute systemic reactions.[4] The most common presentation following cardiac surgery is a >50% drop in the peak postoperative platelet count 5-10 days after surgery.[2,3]

The diagnosis of HIT is made using both clinical and serologic findings. The most common test is the PF-4/heparin polyanion enzyme immunoassays.[5] Recently, Warkentin has proposed the use of a scoring system to help establish the pre-test probability for HIT, which takes into account degree and timing of thrombocytopenia, extent of thrombosis and cause of platelet decrease (Table 1, website) to guide treatment while laboratory results are pending.[5] A high clinical score indicates that HIT is highly likely (>80%) and avoidance of heparin exposure is warranted. Conversely, a low clinical score suggests the probability of HIT is low (<5%) and use of low molecular weight heparin or UFH would be reasonable if anticoagulation is indicated. The impact of laboratory testing has its greatest impact when the clinical risk score is moderate. In this range, physician judgment dictates which actions would be most appropriate pending the results of laboratory testing. Periodic reassessment of the HIT clinical score is critical as the clinicopathological picture evolves. If the diagnosis of acute HIT is made, then avoidance of all heparin exposure and treatment is indicated. Platelet transfusion should be avoided and used only in extreme situations after heparin has been discontinued for several hours.[4]

After confirming the diagnosis, treatment beyond heparin discontinuation may be necessary. Recommendations include: 1) UFH (intraoperatively only) for those with a history of HIT, but who are currently PF-4/heparin EIA negative; 2) delay surgery for those who have subacute (normal platelet count, positive PF-4/heparin EIA) or acute HIT for 100 days or until they become seronegative; 3) for urgent or emergent surgery for patient with confirmed diagnosis or moderate to high suspicion of HIT, administer direct thrombin inhibitors (bivalirudin, lepirudin) or UFH with an antiplatelet agent.[6-8] Additional antiplatelet medications can be administered as necessary either alone or in combination.

None of the commercially available direct thrombin inhibitors (lepirudin, argatroban, bivalirudin) (Table 2, website) are FDA-approved as an alternative (to heparin) for use in cardiovascular surgery. Most clinicians prefer the use of bivalirudin, based on its favorable pharmacokinectic properties (t ½ ≈ 25 min) and on an emerging literature suggesting that it is a safe and effective alternate to heparin during percutaneous coronary interventions (PCI) and on- and off-pump cardiac surgery.[4,9] Lepirudin is approved for the treatment of acute HIT, yet can be problematic, as it has a longer half-life (t ½ ≈80 min) and is immunogenic (repeat doses are not recommended)[2,10,11] Argatroban is also approved for the treatment of acute HIT and as an alternate to heparin during PCI and non-cardiac surgery (vascular).[2,10]

Platelet hyperactivity plays in a central role in the development of HIT syndrome. As such, the use of antiplatelet agents are included in the treatment of patients with a history of HIT.[4] UFH can be used safely with infusions of potent antiplatelet agents (tirofiban or epoprostenol) in patients with both acute and subacute HIT.[6-8]

The inherent risk and complexity of managing patients with non-heparin anticoagulants during cardiac surgery suggests that each center should establish an institutional protocol using as few agents as possible. Bilvarudin has been administered during cardiac surgical procedures.[9] For on-pump cases, dosing recommendations are 1 mg/kg bolus, followed by a 2.5 mg/kg/hr infusion.[9,12] Fifty milligrams are added to pump prime. Repeat doses of 0.1-0.5 mg/kg are administered to maintain a target ACT ≥2.5 times baseline. The infusion continues until 15 minutes before cardiopulmonary bypass separation. Lower doses are employed for renal impairment. Although ECT monitoring is preferred, the use of the kaolin ACT appears to provide acceptable results.[9,12] Of the direct thrombin inhibitors, bivalirudin has the shortest half-life due to enzymatic cleavage (slowed with hypothermia)[2,9] and renal excretion, the latter of which can be increased with forced diuresis and ultrafiltration.[13]

In summary, the approach to patients with HIT includes initial confirmation or likelihood of HIT followed by elimination of heparin from all sites when appropriate. Then, based on the clinical picture, the decision to treat HIT with direct thrombin inhibitors and/or other antiplatelet medications can be made given the clinical score (platelet count, evidence of thrombosis, etc) and serological findings. Future work is needed to develop accurate monitors of direct thrombin inhibitors plasma levels and methods to reduce residual activity.[13,14]

President's Message continued from page 3

2004. John succeeds David Cook who served as chair of the committee for four years.

Glenn P. Gravlee, MD
Chair, Bylaws Committee

Glenn is of course familiar to you all as our immediate Past-President. Glenn has shown an interest (and aptitude!) in bylaws issues over the last several years, and has graciously agreed to serve as successor to Steve Young who was our Bylaws Committee chair (in fact, functionally he was the Bylaws Committee) for five years. Glenn has just moved to Denver where he is Professor and Director of Education in the Anesthesiology Department at the University of Colorado Denver and Health Sciences Center. Glenn has been a member of SCA since 1980, and his past SCA activities of note include: Chair, Allied Health Liaison Committee; Vice Chair and Chair, Education Committee; member of the Fellowship Accreditation Task Force; Chair, Continuing Medical Education (CME) Committee; member of the Board of Directors; Secretary/Treasurer; President-Elect; and President. As immediate Past-President Glenn serves as Chair of the Nominating Committee, and he is also co-chair (with Nancy Nussmeier) of the Philanthropy Task Force. I know Glenn would like to find some SCA members who might have an interest in Bylaws issues!

Congratulations to all our new elected and appointed leaders, and thank you to all those who have served their terms (many of whom served multiple terms)!