October 2005
Vol. 4, No. 5

What's Inside

Mentorship Program

At the 28th Annual Meeting & Workshops the SCA will introduce a Mentorship Program. This program will match selected SCA member residents, fellows and junior investigators who have authored an abstract accepted for presentation at the SCA Annual Meeting with a mentor. On Saturday, April 29, 2006, those selected for this program will meet with their mentor to discuss research goals and objectives and future academic plans at a special SCA mentorship session. Following this session, investigators along with their mentors will be invited to attend a reception. The mentors will be experienced academic anesthesiologist volunteers drawn from the SCA leadership.

SCA member residents, fellows and junior investigators submitting an abstract for the 28th Annual Meeting who wish to be considered for this program should check the appropriate box on the online abstract submission application found on SCA's website (www.scahq.org).

Society of Cardiovascular Anesthesiologists
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What's Online (www.scahq.org)

October 2005 Newsletter

Call for Nominations

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

☑ **Board of Directors (2 positions)** 3-year term

In order to nominate a member, please forward to Dr. Gravlee, 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, 2006. The slate of candidates for Board of Directors will appear on the SCA's website (www.scahq.org). Eligible SCA members will have 45 days to cast their online votes.

Literature Reviews

Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: Implications on operative outcome.

Habib RH, Zacharias A, Schwann TA, et al. *Crit Care Med* 2005; 33:1749-1756.

Reviewed by Michael H. Wall, MD
University of Texas Southwestern Medical Center at Dallas
Dallas, TX

Abstract: This retrospective review studied 1,760 patients undergoing isolated coronary artery bypass grafting using cardiopulmonary bypass between 1995-1996 and 2002-present. The pump was primed with plasmalyte and 250 mL of 20% mannitol. Cold blood cardioplegia and systemic normothermia (in 98% of cases) was used. Primary renal outcome variables were 1) %ΔCr, 2) %ΔCr clearance (calculated from Cockcroft-Gault equation), 3) renal injury (%ΔCr > 50%) and 4) acute renal failure (ARF) as defined by the Society of Thoracic Surgeons. In addition, mortality, length of hospital stay (LOS) and re-admission rates were evaluated. The independent variables were lowest hematocrit (Hct), cardiopulmonary bypass time (TCPB) and intra-operative packed red blood cell (PRBC) transfusion. The data was analyzed using multivariate and propensity analysis. Lowest Hct, TCPB and pre-CPB Cr were 22 ± 4.6%, 94 ± 35min and 1.01 ± 0.23 mg/dL. The overall %ΔCr was 24 ± 57%, ARI occurred in 285 (16%) patients and ARF occurred in 89 (5.1%) patients. Intra-operative PRBC transfusion was used in 21.9% of all patients.

The authors found that %ΔCr ($p < 0.001$) and ARF ($p < 0.001$) has a dose dependent association to lowest Hct (risk increases with Hct < 22-24%). Also, this risk was increased if the TCPB > 90min or pre-op Cr > 1.2 gm/dL. Furthermore, PRBC transfusion was associated with increased renal dysfunction ARI was significantly associated with increased mortality and LOS.

Comments: The excellent discussion section of this article, and the editorial by Spiess[1] should be required reading for all of us who give blood transfusions.

Briefly, this study is consistent with several other studies that have shown associations between lowest Hct's on-pump and increased mortality, LOS and morbidity (including lung dysfunction, increased neurologic events, renal dysfunction and cardiac dysfunction). This study is the first that shows transfusion (probably given to prevent or treat a low Hct) actually is associated with worsening renal function. This presents a major daily clinical problem. Habib, et al and Spiess[1] thoroughly discuss theoretical reasons as to why transfusion may actually worsen outcomes (including problems with 2, 3, DPG, increasing free iron, decreased tissue oxygenation following PRBC transfusion, abnormalities in RBC shape and deformability, inflammatory and immunosuppressant properties of PRBC's). Habib, et al and Spiess[1] stress the importance of intra-operative blood conservation, modification/miniaturization of CPB circuits and the urgent need for large prospective randomized trials of transfusion in patients undergoing cardiac surgery. Until these trials are completed, we will continue to struggle with the frequent question: to transfuse or not to transfuse?

Reference

1. Spiess BD. Choose one: Damned if you do/damned if you don't! *Crit Care Med* 2005; 33:1871-4.

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SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS
Care · Knowledge · Investigation

NEWSLETTER

P.O. Box 11086 • Richmond, VA 23230-1086 • (804)282-0084 • sca@societyhq.com October 2005

President's Message

James G. Ramsay, MD
President, 2005-2007

SCA and the International Community of Cardiovascular Anesthesiologists

Before speaking of our society's many efforts to work with the international community, on behalf of the SCA board I wish to extend my heartfelt sympathy and compassion to all those affected by hurricane Katrina. In addition I would like to recognize the many efforts and sacrifices made by our members in the stricken states; I know of many examples of heroic medical work by these members, many of whom have had their lives turned upside down by the catastrophe.

The SCA website now has a special temporary job section, as a service to those who may wish to find temporary positions while their own hospitals are closed. While only SCA members may list positions, anyone with Internet access can view the temporary positions available around the country. Also, our website has access information for two organizations helping to coordinate the relief effort.

SCA is an International Society

While most of our members live in North America and most of our activities occur on this continent, the SCA is an international society. Nearly 20% of our members (excluding residents) live outside the United States, and 14% live outside of North America. In conjunction with local societies we have co-sponsored nine very successful international meetings, some of which have been "satellite" meetings held near in time and place with the World Congress of Anesthesiologists meetings. In 2006 we are co-sponsoring the 10th International Congress of Cardiothoracic & Vascular Anesthesia in Prague, Czech Republic (August 27-30, 2006; http://www.iccva2006.cz). The Chair of our International Committee, Bel Russell, has been working closely with Karel Cvachovec, President of the Czech Society of Anesthesiology and Intensive Care Medicine, to plan an outstanding scientific program with cardiovascular and thoracic experts from around the world.

Our most recent international meetings have been in Tel Aviv (Israel), Quebec City (Canada), Santiago (Chile), and Istanbul (Turkey). In each instance the SCA has provided starter or "seed" money to help get the planning process underway, and then followed with major time and energy contributions by members of our International Committee to help plan the meetings. In some instances the "seed" money has been returned to the SCA when the meeting was financially successful. We view these meetings as an important part of our mission, and strongly urge our members from all countries to consider attending. As you can see, these meetings take place in interesting locations where you can combine business with pleasure.

While our three meetings held annually in North America and these international meetings provide excellent educational and "networking" opportunities for our members, there are many anesthesiologists around the world who do not have the resources to attend. In particular, few members from developing countries can afford the combined costs of meeting registration, travel, and accommodation. We have made several attempts to bring the SCA expertise to cardiovascular anesthesiologists who may have difficulty in attending our meetings. At our 22nd Annual Meeting in Orlando, Florida, we put on a TEE workshop in Spanish, organized by my former colleague Luis Michelson. While those who attended were very positive in their evaluations, the cost of coming to and staying in Orlando was still excessive for most Latin American anesthesiologists (the target audience); the attendance was disappointing.

SCA Teaching Outreach to Developing Countries

A few years ago Zbigniew Wojciechowski and Bruce Spiess developed the concept of a "Teaching Outreach" for developing countries. The SCA board endorsed this concept, and we allocated funds to send SCA members to "host" countries for outreach projects in 2001 and 2003 (alternate years from International Meetings). While we made an attempt to publicize this program, our efforts proved to be ineffective and we did not have any applicants. My hope is this newsletter message will reach members in developing countries (or perhaps members in more developed countries who have "connections" with developing countries), and they will contact the SCA office or me directly – we would very much like to continue to offer this program.

Asociación Latinoamericana de Anestesiólogos Cardiotorácicos ("ALACTO")

Last month I had the pleasure and honor of attending the first meeting of the Latin American Society of Cardiovascular Anesthesiologists, or "ALACTO." Dr. Jose Sanchez from Lima is the President of this new society, and he was a very effective advocate for this first meeting held in Cusco, Peru. There were more than 60 anesthesiologists present, representing almost all the middle and South American countries. The Secretary of the society is Ricardo Gerenstein, a former Argentinian now living and practicing in Florida. In addition to organizing TEE workshops for the attendees, Ricardo very graciously translated my two lectures into Spanish "on the spot," allowing me to communicate with the mostly Spanish speaking audience. Both Drs. Sanchez and Gerenstein are SCA members in good standing. They and their colleagues from the various Latin American countries were very gracious hosts. The attendees at this first ALACTO meeting were enthusiastic at the prospect of forming ties with the SCA. I believe we should support their developing society, perhaps more as a "Teaching Outreach" as described above than as an international meeting. Their next meeting in August 2006 is planned to be in Cartagena, a beautiful resort city on the coast of Colombia. It certainly seems more realistic that North American SCA members travel to these meetings, than the other way around. I invite any members with an interest in this society to go to their (Spanish language) website, www.alacto.com. In addition, the SCA board will discuss how we might support ALACTO in their future meetings.

I encourage any member with ideas or proposals to foster increased interactions with cardiovascular anesthesiologists outside of North America to contact Heather Spiess at our society office, or to contact Bel Russell or me directly.

NEWSLETTER

Literature Reviews

Continued from page 2

Increased prothrombotic state lasting as long as one month after on-pump and off-pump coronary surgery.

Parolari A, Mussoni L, Frigerio M, et al. *J Thorac Cardiovasc Surg* 130:303-308, 2005

Reviewed by Mark A. Chaney, MD
University of Chicago
Chicago, IL

Abstract Excerpt: This study investigated whether the activation of coagulation, fibrinolysis, and endothelium occurring during the first postoperative month after on-pump coronary artery bypass surgery differs from that after off-pump coronary artery bypass grafting. Thirty-five patients undergoing coronary surgery were randomized to undergo on-pump (n = 18) or off-pump (n = 17) coronary artery bypass grafting. Blood samples were collected prior to surgery and up to one month after surgery. Prothrombin fragment F1.2, thrombin-antithrombin complex, and D-dimer increased after surgery and were persistently higher than preoperative values as late as 30 postoperative days in both on-pump and off-pump groups. Higher levels of these variables were detected after on-pump surgery relative to off-pump surgery only at the time point after termination of cardiopulmonary bypass (fragment F1.2 and thrombin-antithrombin complex) or from bypass end to eight postoperative days (D-dimer). Fibrinogen levels decreased after surgery and then increased in parallel in both groups to eight days after surgery. The von Willebrand factor level increased postoperatively in both groups and returned to baseline 30 days after surgery; it was higher after on-pump surgery from bypass end to eight postoperative days. Soluble vascular cell adhesion molecule one was increased significantly from baseline in both groups 30 days after surgery, with no difference between groups. The investigators conclude that patients undergoing off-pump cardiac surgery showed protection against activation of coagulation and fibrinolysis and against endothelial injury only during the intraoperative period, which was followed by the development of a prothrombotic pattern comparable to that of patients undergoing on-pump cardiac surgery, lasting at least as late as 30 days after surgery.

Comments: Use of cardiopulmonary bypass is associated with activation of several metabolic pathways and cellular components leading to a systemic inflammatory response. While this extensive physiologic response has mainly been documented in the early postoperative period, some studies have revealed a marked activation of the hemostatic, thrombotic, and inflammatory systems that persists for several weeks following surgery. Previous studies in patients undergoing cardiac surgery have revealed a marked activation of the coagulation-fibrinolytic system lasting several weeks, perhaps accounting for the increased thrombotic complications that frequently occur during the postoperative period. The early period after cardiac surgery is characterized by the highest rates of myocardial infarction, cerebrovascular accident, and bypass graft occlusion, all occurring within the first few postoperative months. Over the past decade, the use of off-pump cardiac surgery has increased dramatically, in hopes of avoiding the known detrimental physiologic effects of cardiopulmonary bypass (neurologic dysfunction, pulmonary dysfunction, renal dysfunction, hematologic abnormalities, activation of systemic inflammatory response, etc.). The clinical advantages of off-pump versus standard on-pump cardiac surgery, however, are still controversial. It is also unclear whether cardiopulmonary bypass is the main cause of the postoperative inflammatory and procoagulant responses that occur following cardiac surgery. Recent studies have shown that surgical trauma alone may cause activation of the systemic inflammatory response. Thus, these investigators attempted to determine whether activation of coagulation and fibrinolysis differed between patients undergoing off-pump cardiac surgery and on-pump cardiac surgery. Because graft occlusion mainly occurs during the first postoperative month, thrombotic variables were assessed up to one month after surgery.

These investigators found that patients undergoing off-pump cardiac surgery demonstrate a persistent activation of coagulation and of fibrinolytic pathways that lasts up to 30 days following surgery. However, these potentially detrimental physiologic effects are somewhat delayed (in contrast to immediate detrimental findings in patients undergoing on-pump cardiac surgery). These findings suggest that avoidance of cardiopulmonary bypass may protect from the early postoperative appearance of a prothrombotic state yet does not prevent the increases in prothrombotic and endothelial injury markers that occur during the later postoperative period. These findings also indicate that the early phase prothrombotic state may be initiated by cardiopulmonary bypass and the later phase prothrombotic state may be ascribable to the inflammatory reaction induced by general surgical trauma.

Evidence indicating definitive clinical advantages of either technique of myocardial revascularization is currently lacking, and the differences between on-pump and off-pump techniques in terms of clinical outcomes are controversial. However, these findings indicate that the off-pump technique may protect against pro-oxidant, proinflammatory, and pro-thrombotic activation during the immediate postoperative period. However, during midterm follow-up, whatever surgical strategy is adopted, a significant prothrombotic activation (with endothelial dysfunction) occurs and persists for weeks following surgery. These findings (in addition to other investigations) indicate the need to reevaluate antithrombic treatment in patients undergoing both on-pump and off-pump cardiac surgery.

Characterization of beta3-adrenoceptors in human internal mammary artery and putative involvement in coronary artery bypass management.

Bertrand Rozec MD, Sabrina Serpillon, PhD; Gilles Toumaniantz, PhD; Camille Sèze, MSc; Yohann Rautureau, PhD; Olivier Baron MD, Jacques Noireaud, PhD and Chantal Gauthier, PhD. *Journal of the American College of Cardiology* 2005; 46 (2): 351-9

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

Objectives and Background: The aim of the present study was to analyze whether beta3-adrenoceptors (β_3-ARs) were effectively present and functional in the human internal mammary artery (IMA). The beta1- and beta2-adrenoceptors classically mediate the relaxant effects of catecholamines in the vessels. In vitro and in vivo studies performed in various animal species described vasodilating effects due to activation of a third beta-ARs subtype (β_3).

Methods: Reverse transcription-polymerase chain reaction analysis, Western blot experiments, and pharmacological studies were carried out in human IMA samples harvested from 27 patients undergoing coronary bypass surgery(CABG).

Results: The β_3-ARs messenger ribonucleic acid and protein were detected in intact IMA, but were absent in endothelium-free samples. This finding was confirmed by immunohistochemical experiments. In organ baths, a β_3-AR agonist, SR 58611A, induced an endothelium-dependent relaxation of phenylephrine-precontracted IMA rings. This vasodilation was not modified by β_1/β_2-AR antagonists, but was greatly altered in the presence of L-748,337, a selective human β_3-AR antagonist. Moreover, the inhibition of nitric oxide (NO) synthases abolished β_3-adrenergic vasodilation, suggesting the involvement of a NO-signaling pathway.

Conclusions: Those results demonstrated the presence of β_3-ARs in the endothelial layer of human IMA. The present work highlights the role of β_3-ARs in vasomotor control of IMA and opens new fields of investigation in coronary bypass graft management, heart failure, and hypertension.

Comments: The development of IMA grafting is the most remarkable achievement in coronary artery surgery in the past two decades. It has a superior graft patency and increased long-term survival compared with saphenous vein grafts. However, the development of IMA malperfusion syndrome is a critical complication of CABG (1.9% and up to 20% after primary coronary bypass and reoperation, respectively) and can have devastating effects on the outcome of a cardiac operation leading to a perioperative increase in morbidity and mortality. The etiology of the syndrome is multifactorial, but a spasm of the graft has been frequently suggested. The vasoconstriction can be evoked by several stimuli such as mechanical trauma, nerve stimulation, and vasoconstrictor substances. Circulating sympathomimetic substances are considered as possible spasmogenic agents. It is, therefore, essential to treat and to prevent the vasospasm. The authors used complementary approaches of molecular biology, biochemistry, and pharmacology to show the presence of functional endothelial β3-ARs to be responsible for a vasodilation involving the NO pathway in the human IMA. The development of a third generation of beta-blockers with vasodilating properties resulting from a β3-AR agonistic effect might constitute an interesting new method of investigation. Combined with other studies, the present findings highlighted the potential role of β3-ARs in blood flow regulation, especially in the flow regulation in IMA. By opening the new field of concerning the involvement of β3-ARs in human cardiovascular physiopathology, we expect to see a greater improvement in IMA malperfusion syndrome and better outcome of CABG operation.

Aprotinin reduces bleeding and blood product use in patients treated with clopidogrel before coronary artery bypass grafting.

Gabriella Lindvall, MD; Ulrik Sartipy, MD; Jan van der Linden, MD, PhD. *Annals of Thoracic Surgery* 2005;80:922-7

Reviewed by Mohammed M. Minhaj, MD
University of Chicago
Chicago, IL

Abstract: This study was a retrospective review of the use of aprotinin in patients who had emergent coronary artery bypass graft (CABG) surgery and had been on clopidogrel within five days of surgery. Of the 33 patients whose records were reviewed, 18 patients received full dose aprotinin regimens while 15 did not (these 15 served as the control group). Full dose aprotinin was as follows: Two million KIU before surgery, 500,000 KIU during the operation, and an additional two million KIU during cardiopulmonary bypass (CPB) as part of the CPB priming solution.

The two groups were similar with respect to baseline characteristics and operative data (anesthetic/CPB management, surgical techniques employed, etc). Mean postoperative bleeding was 710 mL in the aprotinin group vs. 1210 mL in the control group (p=0.004). Additionally, the aprotinin group received significantly fewer blood transfusions, platelet transfusions, and fewer blood products overall vs. the control group. There were only three reoperations, all of which occurred in the control group. Based on these results the investigators determined that aprotinin use in patients on clopidogrel significantly reduces blood loss, administration of blood products and reoperations.

Comments: The use of clopidogrel (an irreversible platelet inhibitor) has risen dramatically since its introduction in the late 1990's. It has been shown to be beneficial in patients with significant coronary artery disease, especially those with unstable angina and is routinely used post percutaneous coronary interventions to prevent thrombotic events and their sequelae. Additionally, patients with peripheral vascular disease and ischemic strokes may also benefit from its use. Unfortunately, the effects of clopidogrel can last 5-10 days even after cessation of the drug, making its anti-platelet function detrimental in a perioperative setting as in emergent cases it cannot be held adequately in advance.. Indeed, studies have demonstrated that patients on aspirin and clopidogrel have increased blood loss and requirements for transfusion when CABG surgery.

The use of aprotinin in cardiac surgery has been well documented to reduce blood loss and postoperative bleeding. This agent is a serine protease inhibitor with platelet preservation activity on CPB. While not without risks, rarely anaphylaxis can occur especially on repeat administration, the use of aprotinin has been recently shown to possibly decrease neurological morbidity as well as its positive effects on hemostasis.

This study demonstrated that patients exposed to clopidogrel within five days of surgery who received a full dose regimen of aprotinin were three times less likely to require blood products, had less perioperative bleeding and lower rate of reoperation. This is important for many reasons including economical (fewer operations/blood products) as well as from a resource standpoint (with the blood product shortage seen on a routine basis).

A potential drawback, which the authors addressed as well, was the nature of the study being retrospective not allowing for randomization of patients. There may have been some underlying patient characteristics (e.g. baseline platelet function) that could have altered the results. Additionally the relatively small sample size could affect results.

Overall, the study does have impressive results, even with these reservations and hopefully a prospective trial (which the authors alluded to which may be forthcoming) will serve to validate their preliminary results.

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Secondary tricuspid regurgitation or dilatation: Which should be the criteria for surgical repair?

Dreyfus GD, Corbi PJ, Chan KMJ, Bahrami T. *Ann Thorac Surg* 79:127-132, 2005.

Reviewed by Mark A. Chaney, MD
University of Chicago

Abstract: Secondary tricuspid dilatation may or may not be accompanied by tricuspid regurgitation (TR). Tricuspid dilatation can be objectively measured whereas TR can vary according to preload, afterload, and right ventricular function. This investigation attempted to determine whether surgical repair of the tricuspid valve based on tricuspid dilatation rather than TR could lead to potential benefits. In 311 patients undergoing mitral valve repair, the tricuspid valve was examined. Tricuspid annuloplasty was performed only if the tricuspid annular diameter was greater than twice the normal size (≥70 mm) regardless of the grade of regurgitation. 163 patients (52%) received mitral valve repair alone and 148 patients (48%) received mitral valve repair plus tricuspid annuloplasty. There was no difference between the two groups with regard to hospital mortality and actuarial survival rate (up to 10 years follow-up). However, the New York Heart Association functional class was significantly improved in patients receiving tricuspid annuloplasty. Furthermore, TR increased by more than two grades in 48% of patients not receiving tricuspid annuloplasty and in only 2% of patients receiving tricuspid annuloplasty ($p<0.001$). These investigators conclude that remodeling annuloplasty of the tricuspid valve based on tricuspid dilatation improves functional status irrespective of the grade of regurgitation. Considerable tricuspid dilatation can be present even in the absence of substantial TR, and is an ongoing disease process that will, with time, lead to severe TR.

Comments: "Secondary" TR associated with mitral valve disease is thought by many to decrease or even disappear following surgical correction of mitral valve disease. This concept has been widely accepted and influences current surgical practice regarding management of TR (most attack the primary lesson - the mitral valve - and leave the tricuspid valve alone). This clinical investigation reveals that this may not be the correct path to take.

Knowledge of the pathophysiologic processes that lead to TR is important. The tricuspid annulus is a component of both the tricuspid valve and the right ventricle. For TR to occur, the tricuspid annulus, and hence the right ventricle, has to be dilated (excluding overt leaflet dysfunction). If the tricuspid annulus and right ventricle are not dilated, there is very low probability that TR can occur. Furthermore, dilatation of the tricuspid annulus is only possible in its anterior and posterior aspects (corresponds to the free wall of the right ventricle). In addition to tricuspid dilatation, three important factors determine whether TR occurs: preload, afterload, and right ventricular function. Thus, significant TR may not be detected echocardiographically despite considerable pathology of the tricuspid valve. Thus, the absence of TR or the presence of only mild TR does not mean that the tricuspid orifice is free of any abnormality such as tricuspid annular dilatation. Considerable tricuspid dilatation may not always result in pronounced TR at a given time. Such undetected and untreated TR may influence functional capacity of patients and lead to subsequent progression of TR.

Current practice regarding management of secondary TR (focuses on assessment of TR severity, advocates treatment of primary lesion alone) may be incorrect. For example, treatment of the mitral lesion alone does not correct tricuspid dilatation nor does it affect preload or right ventricular function. As tricuspid annular dilatation seems to be the underlying mechanism regarding nonorganic TR, it may be a more reliable indicator of tricuspid valve pathology compared with TR. Successful treatment of secondary tricuspid valve pathology may necessitate the correction of tricuspid annular dilatation in addition to mitral valve surgery. This has been these investigators' practice during the last twelve years. In 311 patients undergoing mitral valve surgery, the tricuspid valve was surgically evaluated irrespective of the grading of the preoperative TR. The tricuspid annular diameter was directly measured from the anteroseptal commissure to the anteroposterior commissure using a supple ruler. Patients with a tricuspid annular dimension greater than or equal to 70 mm (twice the normal size) underwent a remodeling tricuspid annuloplasty. They prospectively recorded all patient data to determine if tricuspid valve repair for secondary tricuspid valve dilatation (irrespective of TR severity) improves outcome.

This clinical study involving more than 300 patients, some of whom were followed up for more than ten years, indicates that tricuspid annuloplasty performed at the time of mitral valve surgery improves functional capacity and may prevent progression of TR severity. However, the authors acknowledge that the "threshold" size to correct tricuspid dilatation requires further study and perhaps lesser degrees of tricuspid dilatation should also be corrected. What we, as cardiac anesthesiologists, should take away from these findings is that there is little or no correlation between tricuspid dilatation and TR and that tricuspid dilatation is more reliable than TR when assessing secondary tricuspid valve disease. Interestingly, in this study, significant TR was not detected for the majority of patients receiving remodeling tricuspid annuloplasty during the preoperative assessment despite an annular diameter of greater than twice normal. 88% of these patients demonstrated grade 0 or 1 TR at preoperative echocardiographic assessment. Thus, there was no correlation between TR and tricuspid dilatation. Furthermore, the aim of treating tricuspid annular dilatation at the same time that mitral valve surgery is performed is to prevent future progression to symptomatic TR.

Stem cells in the dog heart are self-renewing, clonogenic, and multipotent and regenerate infarcted myocardium, improving cardiac function.

Linke A, Muller P, Nurzynska D, Casarsa C, Torella D, Nascimbene A, Castaldo C, Cascapera S, Bohm M, Quaini F, Urbanek K, Leri A, Hintze TH, Kajstura J, Anversa P. *Proc Natl Acad Sci USA*. 2005 Jun 21;102(25):8966-71. *Epub* 2005 Jun 10.

Reviewed by Theodore A. Alston, MD, PhD
Assistant Professor
Harvard Medical School

Abstract: The ability of myocardium to re-grow in large mammals is demonstrated. About one cardiac stem cell is present for each 18,000 myocytes in the adult dog heart. The stem cells carry surface antigens that facilitate cell isolation. For instance, cells can be tagged with fluorescent antibodies for cell sorting. The cells can also be collected with antibodies attached to magnetic microbeads. The stem cells lack cardiac actomyosin but can be stimulated to grow in vitro into multicellular clones of cardiomyocytes, endothelial cells, and vascular smooth muscle cells. Stimulants included the so-called hepatocyte growth factor as well as insulin-like growth factor one. These test tube tricks prompted an exciting experiment in vivo.

The two growth factors achieved tissue regeneration in experimental myocardial infarction. Dogs underwent implantation of sonomicrometric crystals into the left ventricle in order to facilitate serial measurements of regional cardiac performance. Four hours after a left anterior descending artery occlusion, the growth factors were injected into the border zone of the infarct. After another 4 hours, without the growth factors, there were no stem cells in the infarcted tissue. Stem cells and myocytes alike had undergone apoptosis. With the growth factors, stem cells were found within the infarct. After 28 days, the growth factors had caused marked recovery of contractile force, and the treated hearts contained clusters of new myocytes, arterioles, and capillaries.

Comments: This paper offers a promise that regeneration of human myocardium can occur and be deliberately stimulated. Regeneration requires stem cells, but the stem cells will not necessarily need to be harvested from the patient, nor from a donor. In the large, mature mammals now studied (dogs), the cells are already present, and they can restore significant function, but they have to be pharmacologically supported. The experimenters above and their colleagues also have already reported some intriguing human studies (Urbanek K, Torella D, Sheikh F, De Angelis A, Nurzynska D, Silvestri F, Beltrami CA, Bussani R, Beltrami AP, Quaini F, Bolli R, Leri A, Kajstura J, Anversa P. Myocardial regeneration by activation of multipotent cardiac stem cells in ischemic heart failure.

Proc Natl Acad Sci U S A. 2005 Jun 14;102(24):8692-7. *Epub* 2005 Jun 2). Hearts have been examined from transplant recipients and from victims of acutely fatal infarctions. The bad news is that cardiac stem cells seem to be reduced in chronic ischemic cardiomyopathy. The good news is that some are still there. Also promising, 7 out of 20 acutely infarcted human hearts contained clusters of highly proliferating small developing myocytes within the infarct. Foci of regeneration were up to 5 square millimeters in area and included small blood vessels. This novel observation in human hearts coupled with impressive healing of dog hearts almost certainly indicates that deliberate and significant human heart regeneration will be effected. It will be interesting to see how cardiovascular anesthesiologists will prove to participate in the novel therapies.

Overexpression of mitochondrial transcription factor A ameliorates mitochondrial deficiencies and cardiac failure after myocardial infarction.

Ikeuchi M, Matshsaka H, Kang D, et al.
Circulation 2005; 112:683-90

Reviewed by KW Tim Park, MD
Santa Clara Valley Medical Center
San Jose, CA

Introduction: Myocardial infarction (MI) of the left ventricle (LV) leads to complex remodeling of the ventricle. Early on, the ventricular cavity dilates due to wall thinning of the infarct region. This is followed by progressive dilatation of the noninfarcted regions, associated with myocyte hypertrophy and interstitial fibrosis over weeks. These changes contribute to development of depressed cardiac function, clinical heart failure, and increased mortality.

Mitochondrial DNA (mtDNA) contains two promoters, the light-strand and heavy-strand promoters (LSP and HSP), from which transcripts are produced and then processed to yield mRNAs encoding the subunits of the oxidative phosphorylation system. Transcription from the LSP also produces RNA primer, necessary for initiating mtDNA replication. Myocardial transcription factor A (Tfam) is a nucleus-encoded protein that binds upstream of the LSP and HSP and promotes transcription of mtDNA. It has previously been demonstrated (Li H et al. PNAS USA 2000; 97:3467-72 and Wang J et al. *Nat Genet* 1999; 21:133-7) that targeted disruption of Tfam in myocytes induced deletion of mtDNA and dilated cardiomyopathy. In this study, the authors examined the hypothesis that an increase in Tfam expression may exert beneficial effects on cardiac remodeling and function after MI.

Methods: Human Tfam cDNA was inserted into the rabbit β-globin gene and used to generate transgenic (Tg) mice. The presence of the Tfam transgene was confirmed by polymerase chain reaction (PCR). Of four lines of Tg mice thus created, the line with the most robust expression of Tfam protein levels was used for this study. Tg and wild-type (WT) mice were either subjected to ligation of the left coronary artery or a sham operation. Hemodynamics were monitored. Four weeks after surgery, myocardial function was assessed by a 2D targeted M-mode tracings of the LV cavity on a parasternal short-axis view. Infarct size was assessed both at 24 hours and after four weeks by using Evans blue dye and 1.5% triphenyltetrazolium chloride solution at 24 hours and staining of transverse sections with Masson's trichrome at four weeks. Apoptosis was detected by staining LV tissue sections with transferase-mediated dUTP nick end-labeling (TUNEL) staining. Survival to 28 days was also noted. Western blotting, Southern blotting, and Northern blotting were used to measure protein, DNA, and RNA levels.

Results: No sham-operated animals died. Survival was significantly higher in Tg-MI mice compared to WT-MI mice (100% vs. 66%, $P < 0.01$). The infarct size as a percent of the at-risk area was not significantly different, however, between Tg-MI and WT-MI mice ($83.1 \pm 1.1\%$ vs. $84.5 \pm 0.4\%$, P=NS). Blood pressures and heart rates were also similar between the groups. LV end-diastolic diameter was significantly increased and fractional shortening significantly decreased in WT-MI mice compared to the sham animals and these changes were attenuated in Tg-MI mice. Likewise, the lung weight/body weight ratio increased significantly in WT-MI mice ($8.3 \pm 0.6\%$) compared to sham animals ($5.3 \pm 0.1\%$) and this increase was attenuated in Tg-MI mice ($6.4 \pm 0.3\%$). Pleural effusion was much less prevalent in Tg-MI mice than in WT-MI mice (31% vs. 63%, $P < 0.05$). Collagen volume fraction, an index of myocardial interstitial fibrosis, was increased in the non-infarcted LV of WT-MI mice and this change was attenuated in Tg-MI mice. TUNEL-positive nuclei were rarely seen in sham-operated mice, whereas the number of such nuclei increased in the noninfarcted LV from WT-MI mice and this increase was significantly decreased in Tg-MI mice. mtDNA copy number, expressed as the ratio of mtDNA to nuclear DNA in the myocardial tissue, was increased in the Tg mice, compared to the WT. After coronary ligation, this number decreased significantly in the non-infarcted LV of the WT-MI mice (by 41%, $P < 0.01$), but remained at normal levels in Tg-MI mice. mRNA transcript levels for mitochondrial phosphorylation were lower in both WT-MI and Tg-MI mice compared to controls. However, mitochondrial enzymatic activities of complex I, complex III, and complex IV of mitochondrial phosphorylation were decreased in the noninfarcted LV of WT-MI mice, but not in Tg-MI mice. The enzymatic activities of complex II proteins, exclusively encoded by nuclear DNA, were not altered in either group. The overall number and size of mitochondria were similar in the two sham-operated groups, while the number was increased and the size decreased in WT-MI mice and these changes were attenuated in Tg-MI mice.

Discussion: The present study provides the first direct evidence that Tfam overexpression can prevent the decrease in mtDNA and mitochondrial respiratory defects in the post-MI hearts and attenuate cardiac chamber dilatation and dysfunction, as well as interstitial fibrosis and apoptosis. Although the mechanism of this benefit needs to be further elucidated, we can exclude certain mechanisms. First, the benefit is not due to sparing the magnitude of MI. Second, the benefit is not due to hemodynamic effects. Third, the benefit is probably not due to induction of mitochondrial biogenesis, as the post-MI increase in the number of mitochondria was actually greater in WT-MI mice than in Tg-MI mice. Importantly, the increase in the number of mitochondria did not seem to exert a beneficial effect. Rather, the benefit may result from binding and stabilization of the mtDNA by Tfam and from preservation of the enzymatic activities of the proteins of mitochondrial electron transport.

While the present study points to Tfam as a potential target of therapy in post-MI LV dysfunction, several questions remain to be elucidated. First, while overexpression of Tfam appears beneficial, similar results have not been obtained with overexpression of peroxisome proliferator-activated receptor γ coactivator-1α transgene, which acts upstream of Tfam. The reasons for the discrepant results remain unresolved. Second, it is not known whether Tfam overexpression needs to be present before the ischemic insult or may occur during or shortly after MI in order to realize the benefits. This is an important question to answer, if Tfam is to be exploited as a therapeutic target.

An essential role for mitochondrial aldehyde dehydrogenase in nitroglycerin bioactivation.

Chen Z, Foster MW, Zhang J, Mao L, Rockman HA, Kawamoto T, Kitagawa K, Nakayama KI, Hess DT, Stamler JS. Proc Natl Acad Sci U S A. 2005 Aug 23;102(34):12159-64. Epub 2005 Aug 15.

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Abstract: Nitroglycerin (TNG) is believed to dilate blood vessels because the drug, a nitrate ester ($R\text{-}ONO_2$), is converted to nitric oxide (NO). The chemical transformation of a nitrate to NO requires three electrons to come from some reducing agents somewhere. However, the biological reducing system for conversion of TNG to NO has been mysterious. The Stamler group argues compellingly that the reductive bioactivation of TNG occurs within mitochondria. Curiously, one of the important enzymes is mitochondrial aldehyde dehydrogenase, an enzyme which participates in the metabolism of ethanol.

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A strain of mice was caused to genetically lack the dehydrogenase. Knocking out the dehydrogenase caused the mice to be resistant to the hypotensive effect of intravenous TNG. The knockout did not reduce sensitivity to nitroprusside, which is expected to have a different mechanism for its conversion to NO. In vitro, aortic segments from knockout mice were resistant to dilation by TNG.

TNG is converted to NO which dilates blood vessels through activation of vascular smooth muscle guanylate cyclase. Accordingly, aortic segments from knockout mice generated lower levels of intracellular cyclic-GMP upon exposure to TNG.

Mitochondria were isolated from disrupted mouse liver cells and used in experiments in vitro. Interesting results were found with layers of rat lung fibroblasts, which generate cyclic-GMP in response to NO but generate very little cyclic-GMP in response to TNG. Exposure of the fibroblasts to TNG alone, or to mitochondria without TNG, elicited little cyclic-GMP. Together, mitochondria plus TNG elicited much cyclic-GMP in the fibroblasts. Cyclic-GMP production was blocked by hemoglobin, which destroys NO. It was also blocked by genetic deletion of the mitochondrial dehydrogenase or by inhibition of the dehydrogenase with choral hydrate.

TNG induces TNG tolerance. Aortic segments from TNG-tolerant mice behave similarly to segments lacking the mitochondrial aldehyde dehydrogenase or having the dehydrogenase inhibited by choral hydrate.

Comments: The chemist Ascanio Sobrero synthesized nitroglycerin in 1847. He noted that a trace amount of the vasodilator causes headaches. Alfred Nobel "tamed" TNG into dynamite. That is, he showed that spontaneous explosions of TNG were prevented by absorbing the liquid onto porous solids. Given non-exploding products, William Murrell described treatment of angina pectoris with TNG in 1876. Furchgott, Ignarro, and Murad shared the 1998 Nobel Prize in large part for showing that TNG is a vasodilator because it is converted to the same NO that is normally presented to vascular smooth muscle by endothelium. Yet, the molecular mechanism for the 3-electron reduction of TNG to NO remains mysterious.

Part of the mystery seems clarified. Mitochondria are full of reduction-oxidation enzymes, and those cellular organelles are now shown capable of transforming TNG into a diffusible substance that raises cyclic-GMP and dilates blood vessels and is scavenged by hemoglobin. One of the mitochondrial enzymes important in this regard is aldehyde dehydrogenase. That enzyme is genetically impaired in many individuals who tolerate ethanol poorly. The enzyme is subject to pharmacological inhibition by chloral hydrate and other drugs carrying an antabuse-like side-effect. Presumably, the ability of the dehydrogenase to react with TNG is competitively inhibited during the participation of the enzyme in the metabolism of ethanol.

The enzyme loses its ability to participate in the bioactivation of TNG upon prior exposure to TNG, and the Stamler group thus point to mitochondrial aldehyde dehydrogenase as the protein most responsible for TNG-induced tolerance to TNG.

It is puzzling that the dehydrogenase catalyzes the *oxidation* of acetaldehyde, but it participates in the *reduction* of TNG. The enzyme carries a critical active-site sulfhydryl group (R-SH) that normally attaches covalently to acetaldehyde during the dehydrogenation reaction. Perhaps the sulfhydryl group is a TNG reductant. Maybe NADH is the reductant. NADH is expected to carry only two electrons, and 3-electron reactions are expected by chemists to proceed via more than one step. The three little electrons for venerable TNG are not yet fully accounted.

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Child-Pugh and MELD classifications and the mortality following cardiac surgery.

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Patients with moderate to severe cirrhosis undergoing cardiac surgery have a high mortality. It is well known that liver dysfunction increases the risk of perioperative complications after anesthesia. [1-3] Cirrhotic patients have physiological changes including coagulopathy, malnutrition, relative vasodilation, fluid and electrolyte abnormalities making anesthesia more difficult but especially with the use of cardiopulmonary bypass.

The Child classification system identifies the severity of liver dysfunction from mild, moderate, to severe and has been utilized as a predictor of survival. The class is determined by five graded factors scored from 1 to 3 based on the presence of hepatic encephalopathy, total serum bilirubin level, presence of ascites, albumin level, and nutritional status with class A being a score of 5-6, B 7-9, and C 10-15. These criteria have subsequently been modified by Pugh to create Child-Pugh (CP) class replacing the most subjective factor, nutritional status, with prothrombin time. Another classification system, MELD (Model End Stage Liver Disease) score, has recently been developed to grade the severity of cirrhosis. The MELD score has a range from 6 to 40 and is based solely upon three objective factors, total serum bilirubin, international normalized ratio, and serum creatinine level. It has supplanted Child's criteria for determining the severity of hepatic cirrhosis and the urgency of liver transplantation. Several authors have utilized the MELD score to evaluate surgical risk in cirrhotic patients. [4,5]

To date, the population of cardiac surgical patients with cirrhosis has been sufficiently small which limit the ability to conduct large clinical trials. Several small studies have confirmed that Child-Pugh class B and C patients have a high mortality especially with the use of cardiopulmonary bypass. In those studies of cardiac surgical patients (total n = 96), liver dysfunction was classified according to Child/CP criteria and in one study by CP class and MELD score. Reported mortality for mild cirrhosis Child class A range from 0-3% and significantly higher mortality 41-80% for patients with moderate cirrhosis in Child class B. Although very few patients with severe cirrhosis in Child class C received operations, their mortality was 100%.

Klemperer et al 1998 identified 13 patients (8 Child class A, 5 Child class B) in a retrospective study with a preoperative history of cirrhosis. All patients underwent cardiopulmonary bypass for a variety of cardiac procedures. Significant postoperative complications occurred in 25% of Child class A patients and in 100% of Child class B patients. All patients with Child class A cirrhosis survived to discharge from the hospital. There were four deaths in class B patients. The causes of death were due mainly to major infection or hemorrhagic complications and not cardiac performance per se.[6] In a series of 10 patients, Kaplan et al reported similar findings with Child class B having a 50% mortality (3 of 6 patients) and no deaths with four class A patients. The causes of death were again not directly related to cardiac failure but rather hepatorenal syndrome, hemorrhage, or sepsis.[7] Bizouarn et al reported on early and late outcomes 12 cirrhotic patients (10 class A, 2 class B). In the immediate postoperative period, 50% of class A and 100% of class B patients developed significant complications. There was one death with class B patients and two deaths with class A, however, the two class A patients died during the follow-up period after discharge from the hospital. [8]

More recently, Hayashida reported on 18 patients (10 class A, 7 class B, and one in class C) undergoing cardiac operations. Fifteen of 18 patients had surgery with CPB while three patients had off pump coronary artery bypass grafting. All patients in Class B and C had major complications including bleeding, infection, renal failure, or respiratory failure. Sixty percent of class A patients had such outcomes. There were no deaths in class A and 50% mortality in class B patients that utilized CPB. All three

patients in class B that underwent bypass grafting without the use of cardiopulmonary bypass survived.[9] Off-pump CABG in moderate to severe cirrhosis may be advantageous as it avoids many of the complications associated with CPB such as poor coagulation profile, decreased vascular tone, massive fluid shifts, and whole body inflammatory response.[10] Suman have published by far the largest study to date with 44 total patients (31 class A, 12 class B, and 1 class C).[4] They report that Child score and MELD score are significantly associated with hepatic decompensation and mortality. Furthermore, they determined a cutoff Child score of >7 had a sensitivity and specificity of 86% and 92% for mortality, with a negative predictive value of 97% and a positive predictive value of 67%, respectively. Hepatic decompensation is defined by Suman as the appearance of new ascites, portosystemic encephalopathy, jaundice, coagulopathy, variceal bleed, or hepatorenal syndrome within three months following cardiac surgery. Only about 10% (3 of 31) of Child class A patients developed hepatic decompensation, while 66% (8 of 12) of Child class B and 100% (1 of 1) of Child class C had complications. Mortality in the series was 3% (1 of 31), 41% (5 of 12), and 100% (1 of 1) for Child class A, B, and C, respectively. In their final analysis, Suman suggested that Child score >7 is sufficient to predict a negative outcome after cardiac surgery. Although a similar cut-off value for MELD score is not firmly established, the data show comparable and significant association of Child score and MELD score with hepatic complications and mortality.

There is a paucity of data regarding the effects of cardiac surgery either with or without cardiopulmonary bypass on patients with hepatic cirrhosis. To date, there have been about five studies encompassing 96 patients with cirrhosis of various degrees and etiologies. Overall, these series report mortality for Child class A range from 0-3% and significantly higher mortality 41-80% for patients with moderate cirrhosis in Child class B. Although there is limited data (5 total patients), it is suggested that patients with moderate liver disease have better outcomes undergoing off pump surgery as opposed to CPB. Indeed, the use of CPB with moderate to severe cirrhosis is associated with increased postoperative bleeding, infections, renal failure, respiratory failure, and hepatic decompensation. Clearly, Child class B and C patients are at significant risk for death when undergoing cardiac surgery. Patients with moderate cirrhosis should weigh the benefits and risks of CPB. Patients with severe cirrhosis should not be offered cardiac surgery utilizing CPB. The efficacy of off-pump cardiac procedures for this group is still unresolved. However, the data also strongly supports the relative safety of cardiac surgery in patients with mild liver dysfunction. Child class A patients undergoing cardiac procedures have a reported mortality of 0-3% that is similar to the general population of cardiac surgical patients.

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Anesthetic preconditioning and perioperative myocardial protection

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Myocardial ischemia during the perioperative period is a serious risk factor for patients undergoing both cardiac and noncardiac surgeries. Up to 74% of patients with coronary artery disease experience perioperative myocardial ischemia during noncardiac surgery.[1] Prevention of ischemia has traditionally focused on maintaining the balance between myocardial oxygen supply and demand using β-adrenergic antagonists, α-agonists, and/or calcium channel blockers. New evidence suggests that volatile anesthetics at clinical concentrations (1 MAC) may also be useful in preventing perioperative myocardial ischemia.

Ever since Murry first reported that multiple brief episodes of ischemia and reperfusion reduced subsequent myocardial ischemia/reperfusion (I/R) injury[2] (termed ischemic preconditioning), researchers have endeavored to understand the underlying mechanisms responsible. Current research is focused on determining how interactions at the cellular, sub-cellular, and molecular levels impart protection against myocardial ischemia and infarction. Several key intracellular signaling pathways resulting in the opening of sarcolemmal and mitochondrial K-ATP channels have now been identified.[4] These K-ATP channels are thought to be one of the primary end effectors of preconditioning ultimately enabling the cell to withstand I/R injury. After sub-lethal ischemia, two distinct periods of protection have been identified. The first protective period occurs immediately and lasts about two hours. This is followed by a second period of protection appearing after 24 hours and lasting up to 72 hours.[3] These are commonly referred to as the early and delayed "windows" of preconditioning. Investigators have also discovered that the administration of volatile anesthetics produces a preconditioned state with features similar to that seen with ischemic preconditioning (IPC). As with IPC, anesthetic preconditioning (APC) mediates protective effects via intracellular messaging pathways ultimately resulting in the opening of sarcolemmal and mitochondrial K-ATP channels.[5] In 1997, Kersten reported that isoflurane imparted protection against I/R injury in dog myocardium.[5] Subsequent studies have shown that all currently used inhalational anesthetic agents are capable of producing myocardial protection against I/R injury with an efficacy comparable to IPC.[6]

Currently, a great deal of effort is aimed at trying to determine how ischemic and anesthetic preconditioning can be used to benefit patients in clinical settings. Ottani (1995) reported that the presence of pre-infarction angina was associated with a decreased infarction size and better post-operative ventricular function. Similarly, Kloner reported that pre-infarction angina decreased the 30-day post-operative cardiac event rate.[7,8] It has also been reported that patients undergoing balloon angioplasty who had short repeated periods of ischemia (inflation and deflation of the angioplasty balloon prior to definitive prolonged balloon inflation) had fewer symptoms, less ST elevation, less frequent in-hospital cardiac events, and a decreased one-year mortality compared with patients who did not receive the ischemic preconditioning prior to balloon angioplasty .[9,10] Intermittent occlusion of coronary artery during coronary artery bypass graft (CABG) surgery has also been shown to be beneficial. These protective effects are not seen in diabetic patients for reasons not clearly understood. In addition, certain drugs such as glybenclamide, a selective ATP-sensitive K+ channel blocker, have been shown to prevent preconditioning.

Despite the protective effects of IPC, routine use has not become widely accepted. Conversely, the use of volatile anesthetics prior to ischemia is easy to apply and is gaining greater acceptance for this application. Although earlier studies were controversial, recent studies consistantly demonstrate that volatile anesthetics decreased release of CK-MB, troponin, TNF-a, and

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BNP. In addition, there is evidence that APC results in better preservation of cardiac function following ischemia, and often less inotropic support is required.[12]

In summary, laboratory studies have demonstrated that exposing the myocardium to a volatile anesthetic before a period of ischemia provides significant protection against subsequent I/R injury. Despite encouraging results in the small numbers of published clinical studies, more clinical data are needed to further our understanding. A large, multi-center clinical study is warranted to determine whether the cardioprotective effects seen with APC translate into decreased morbidity and mortality in patients undergoing cardiac and noncardiac surgery.

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Conscious Neuraxial Anesthesia is a Viable Alternative to General Anesthesia in Cardiac Surgery.

PRO:

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Since the first report of a patient undergoing awake coronary artery revascularization in 2000[1], high thoracic epidural anesthesia for cardiac surgery has been established as an alternative to standard anesthetic techniques in various medical centres worldwide.[2-11] Currently, over 500 cases of patients from Europe, the US, Brazil and India undergoing awake CABG surgery with high thoracic epidural anesthesia alone have been published in case reports, observational cohort studies and controlled clinical trials. To date, approximately 2,000 procedures with this new anesthetic technique have been performed without reports of significant adverse events worldwide. Most of these patients underwent awake off-pump coronary artery revascularization using small lateral thoracotomy incisions, lower sternotomy incisions or full median sternotomy surgical approaches.[12] Only two case reports describe patients undergoing aortic or mitral valve surgery with high thoracic epidural anesthesia using cardiopulmonary bypass.[13,14]

Neuraxial techniques in awake cardiac surgery are restricted to high thoracic epidural anesthesia. Recent experiences as well as prospective randomized studies and meta-analyses have demonstrated advantages of high thoracic epidural analgesia combined with general anesthesia when compared to general anesthesia alone.[15-17] Clinical studies indicate that high thoracic epidural analgesia reduces the stress response to surgery, reduces the time to postoperative extubation and improves early postoperative pulmonary function. Further potential advantages of high thoracic epidural anesthesia include thoracic sympatholysis with subsequent improvement of coronary perfusion, decreased heart rate and endogenous stress response, and a reduced risk for myocardial ischemia perioperatively.[18]

So it seemed to be patently logical to apply high thoracic epidural anesthesia using local anesthetics combined with opioids as the sole anesthetic technique in awake patients undergoing CABG surgery. Published data confirm our own encouraging results and prove that high thoracic epidural anesthesia as the sole anesthetic technique in cardiac surgery can not only be performed in feasibility studies, but has been established as a valid alternative to general anesthesia in selected patients.[19]

As long as the application of larger amounts of sedatives is avoided, appropriate ventilation and oxygenation of awake patients intraoperatively is guaranteed.[19] Additional IV sedation intraoperatively is not mandatory since, apart from standard oral premedication, all patients benefit from the sedative effect of the epidural opioids reabsorbed. Undeniably, however, awake CABG is associated with a certain amount of psychological stress. But, in contrast to published presumptions,[20] compared to general anesthesia, the patient's stress response is not increased[21] and postoperative surveys have shown an extraordinary level of patient acceptance of this new anesthetic technique.[19]

The fundamental precondition for successful awake CABG surgery is an appropriate and highly defined patient selection. Thus, this anesthetic technique is not applicable to all kinds of coronary artery stenoses. Especially patients with left anterior descending artery (LAD) or right coronary artery (RCA) stenosis, that are easily accessible from the surgical point of view, may be operated on with high thoracic epidural anesthesia only, while revascularization of the left circumflex artery (LCx) requires Trendelenburg positioning and luxation of the heart and is therefore difficult to perform. In addition, patients with highly impaired left ventricular function depending on a certain cardiac sympathetic tone should be excluded from this new

technique. Further exclusion criteria arise from common contraindications of epidural puncture, such as compromised coagulation (thromboplastin time <80%, prothrombin time >40 sec, platelets <100/nl), bleeding disorders and the use of any antiplatelet drugs (e.g. ticlopidine, clopidogrel etc.) within the last 10 days. Finally, patients undergoing awake CABG surgery have to be extensively and properly informed about pro's and con's of this anesthetic technique, potential adverse events and the pre- and intraoperative course.

The controversy of awake CABG has been always a discussion of the potential risks of epidural hematoma and subsequent adverse neurological sequelae related to high thoracic epidural anesthesia. Based on the currently available data on 10,000 high thoracic epidurals combined with general anesthesia for cardiac surgery, epidural hematoma has been reported in only one patient.[22] In this patient, who underwent aortic valve replacement, epidural hematoma developed postoperatively after alteplase, a thrombolytic drug, was used to flush a dysfunctional central venous catheter. After immediate laminectomy, neurologic restitution and integrity was gained in this patient. However, this adverse event demonstrates that it is crucial to monitor cardiac patients with high thoracic epidural anesthesia meticulously and tightly in the postoperative period to detect epidural bleeding early. Apart from this case report, the potential risk of epidural hematoma in cardiac surgery seems to be comparable to non-cardiac procedures, especially when off-pump surgical techniques using low-dose heparinization only are performed.[23] It is self-evident that awake CABG should only be performed by anesthesiologists highly experienced with neuraxial blockade, e.g. high thoracic epidurals.

Advantages of CABG with high thoracic epidural anesthesia compared to general anesthesia have been described: safe and reliable hemodynamics intraoperatively,[18, 19] faster mobilization and even daily life activities a few hours after surgery,[24] short-term ICU stay or even bypass of the ICU,[8,19,25] shorter intrahospital stay and, in conclusion, a modern fast tracking technique for cardiac patients[8,26] with significant cost reduction potential and high patient acceptance.[19] Furthermore, case reports have demonstrated advantages in patients with significant pulmonary risk factors such as COPD or post tracheal reconstruction to prevent endotracheal intubation and, consequently, potential weaning difficulties postoperatively.[27] In addition, awake CABG allows for verbal intraopertive monitoring in patients with compromised cerebrovascular function, such as severe carotid artery stenosis.[28]

In conclusion of the published data to date and in strict consideration of defined exclusion criteria, neuraxial anesthesia for awake off-pump one and two vessel coronary artery revascularisation is a viable alternative to general anesthesia in highly selected patients. Especially patients with severe pulmonary coexisting disease and those with only a moderately impaired left ventricular function may benefit from high thoracic epidural anesthesia alone. However, more than by using standard anesthetic techniques, a team approach and excellent communication skills of the anaesthesiologist and the cardiac surgeon are crucial.

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"... As to diseases, make a habit of two things—to help, or at least to do no harm." – Hippocrates in the Epidemics, Bk 1, Sect XI

The combined use of general anesthesia (GA) and thoracic epidural anesthesia/analgesia (TEA) in cardiac surgery may lead to earlier tracheal extubation, decreased pulmonary complications and arrhythmias, and improved analgesia, although improvement in mortality and myocardial infarction rates as compared to GA alone has yet to be demonstrated.[1] In the 1980s, the off-pump technique in coronary artery bypass grafting (CABG) was revived. In 1998, the first CABG in a premedicated but conscious patient without GA was performed with TEA.[2] Thus far, limited experience suggests that conscious cardiac surgery may be safe and may have advantages.[2-9] There are, however, many concerns that must be addressed before the technique of awake cardiac surgery can be considered viable.

Anesthetic concerns

An overriding concern is the possibility of neuraxial hematoma. The incidence of neuraxial hematoma in the non-cardiac-surgery population that receives epidural anesthesia is one in 143,000.[10] The risk of hematoma after full- or half-dose heparin for cardiac surgery is probably higher. Based in part on a zero occurrence, this risk may range from 1:1,500 to 1:150,000.[11] Since the publication of that paper in 2000, at least two cases of epidural hematoma in patients having TEA for cardiac surgery have been reported.[12,13] Despite surgical decompression, one of them remained paraplegic.[13] In addition, there have been two reports of spontaneous epidural hematoma after cardiac surgery without epidural instrumentation.[14,15] The possibility thus exists that hematoma could spontaneously occur at sites of epidural placement. There have also been two other patients suffering from this complication after epidural catheterization intended for cardiac surgery scheduled for the next day.[16,17] Conceivably, if surgery had immediately followed, the consequence would likely have been worse.

Performing spinal decompression after CABG is daunting. The patient remains at risk of coronary insufficiency, has multiple tubes attached, and may be unstable.

We also speculate that the need to withdraw the epidural catheter under reasonable hemostatic conditions could lead to unnecessary transfusion with coagulation factors and platelets, especially after cardiopulmonary bypass (CPB). More postoperative blood tests may be needed to facilitate catheter withdrawal in valve cases in which anticoagulation is required postoperatively.

To minimize the risk of neuraxial hematoma, investigators inserted the epidural catheter the day before surgery, a move that makes same-day-admission impossible. Ensuring that the epidural is inserted at least an arbitrary hour before heparinization is seldom a problem, but is impossible if the patient becomes unstable and needs to go on CPB quickly. Postponing surgery due to a "bloody tap" (incidence of 3-4%) is inconvenient for all parties involved. There is also no guarantee that there will not be a "bloody tap" the next time around. All in all, no precaution would completely eliminate the risk of neuraxial hematoma when TEA is used in cardiac surgery.

Another potential problem is the failure to insert an epidural catheter. Three percent of patients in Karagoz's series could not be catheterized.[2] Multiple attempts put the patient at risk of neuraxial complications[18,19] even if no catheter is inserted, and no purported benefits of TEA could be derived.

Many cardiac patients have impaired ventricular function and/or are on β-blockers. High TEA may cause extensive sympatholysis. Vasopressors used in such cases may have detrimental effects on the coronaries and grafts.[20,21]

Paralysis of the diaphragm is another potential complication if the TEA reaches C5 or higher. Due to intercostal blockade, any degree of diaphragmatic paralysis would be detrimental. Conversion to GA was needed in one of the seven patients in Meininger's report.[7] An inadequate block may also necessitate conversion to GA,[5] or require supplementation with local anesthetics at the jugular notch or xiphoid process level, as seen in 8% and 42% of the patients.[2,6] Several questions are unanswered: What is the incidence of incomplete bilateral blocks? Does analgesia of the skin covering the sternum guarantee a stress-free sternotomy? Is impaired ventilation due to TEA less harmful than the effects of intubation and mechanical ventilation. Overall, titration of the epidural block to a satisfactory level may be tedious with no guarantee of success.

Surgical concerns

Spontaneous respiration can interfere with surgery. A patient undergoing aortic valve replacement needed CPB for over two hours due, in part, to the negative impact of the breathing pattern on surgical progress.[8] Pneumothorax in cardiac surgery has reported incidences of 10% and 28%.[2,3] Four of the 137 patients in Karagoz's series and two of Aybek's 31 patients required intubation because of it.[2,3] Furthermore, two patients (out of 151) in one of the reports required conversion to GA because of coughing.[4] Rarely, hemorrhage and cardiovascular instability may require conversion to GA, just when the clinicians need to focus on efficiently rectifying the problem(s).

For patients undergoing CABG with TEA, saphenous venous graft harvesting mandates a lumbar neuraxial block, thus increasing the risks of neuraxial complications, cardiovascular instability, and local anesthetic toxicity. Therefore, the majority of cases reported were one- or two-vessel bypasses using internal mammary arteries. In some cases, the radial artery was used. In summary, conscious cardiac surgery imposes significant limitations on surgical options and progress.

Patient concerns

Some patients would require intraoperative sedation,[5,6] which must be titrated carefully because respiratory depression compounds the problem of muscle paralysis from the TEA. It is common for patients undergoing a high risk operation to be anxious. Having a chest opened and having to stay still for several hours are stressful. One could also imagine the anxiety (relief in some patients perhaps) evoked when told that surgery can only continue by converting to GA – a non-reassuring sign to some. Anxiety is undesirable in patients with coronary insufficiency. Even though patients expressed satisfaction after a successful CABG under TEA and sedation,[4,5,7] one wonders if it was not due in part to the relief of surviving the experience. In other words, without comparison with a similar group of patients under GA, any claim of superior satisfaction after TEA is premature.

In summary, there are many potential problems, some extremely serious, associated with conscious neuraxial anesthesia for cardiac surgery. The potential gain seems relatively minimal, and for the most part, unproven. One case of emergency evacuation of spinal hematoma and/or paraplegia in a post-cardiac patient would negate all of the so-called benefits derived from many uncomplicated awake cardiac cases. Fast track and off-pump cardiac surgery have successfully evolved using GA alone. The use of TEA for conscious cardiac surgery, in spite of its theoretical advantages, represents a leap into the unknown that, for the moment, seems too risky to justify.

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