Advocacy, the SCA and the value of being engaged

Recently, the president elect of the Society of Cardiovascular Anesthesiologists, Dr. Scott T. Reeves, had the opportunity to testify at the South Carolina Board of Medical Examiners meeting in Columbia, SC. The meeting included testimony of nurse practitioners from the SC Board of Nursing who introduced themselves as doctors and explained to the SC Board of Medical Examiners why there was no longer a need to have physician supervision for any advance practice nurse as well as the need to no longer place limits on their scope of practice. In their arguments to no longer place limits on their scope of practice they included placement of TEE, image acquisition and interpretation for surgical decision making to all CRNAs’ scope of nursing care.

The reason according to the SC Board of Nursing request to add TEE privileges was because several of their CRNA members had requested it although no documentation of training or experience was provided.

Dr. Reeves not only represented the SCA at this meeting but also the American Society of Echocardiography (ASE) as Chair, Committee of Perioperative Echocardiography as well as the Chairman of the Department of Anesthesia & Perioperative Medicine at the Medical University of South Carolina. In addition, support for the position that perioperative TEE is the practice of medicine came from the American Society of Anesthesiologists (ASA) as well as the American Society of Echocardiography (ASE) and the American College of Cardiology (ACC).

In the end, the South Carolina Board of Medical Examiners voted unanimously against the expanded scope of practice document and against the increase in scope for CRNAs doing TEE and added for the record that the Board considered the practice of transeosophageal echocardiography to be exclusively part of the practice of medicine.

This story is important and interesting on many levels. The first, of course, is that we should be made aware (if we were not already) of the agenda of some within the nursing community to expand their role of practice to include work which requires complex skill, knowledge and judgment that most experienced physicians have already recognized to be best performed in the hands of physician specialists.

On another level this story accentuates the value proposition reality of the physician specialist.

Training, certification, and credentialing are objective hurdles as well as subjective symbols that indicate a measure of experience and expertise that should be and can be expected from a patient. We physicians, who are specialists, differentiate ourselves by these standards of expectation because we are indeed different. Our value is ultimately defined by this difference. It is an objective difference and it is a difference that can and should be defined.

Finally, this story teaches us the value of being engaged, networked and involved. Dr. Reeves was able to represent at this meeting not only the voice of SCA, but the ASE as well. Many of us stay active in multiple societies and simultaneously wear multiple hats. This is a good thing and I wish to continue to encourage all of us to stay involved. It expands our understanding and our reach. The more we cross over, the better we are understood and the better we understand.

The SCA has always taken a position to remain engaged. Among current members on SCA’s Board of Directors, Chris Troianos for example, also serves on the ASA Committee on Economics and represents the SCA, Rob Sladen was Chair of the IARS Board of Trustees (whereas Jamie Ramsay, an SCA past president, is the current Chair), Jerrold Levy currently also serves as representative for Cardiothoracic and Vascular Surgery, Thrombosis Scientific Councils of the American Heart Association, Glenn Gravlee is the past president of the American Board of Anesthesiology (ABA), and Colleen Koch also serves on the IARS’ Board of Trustees. There are many, many more examples of collateral integration among our leadership in the SCA. This opportunity for networking is also true throughout our society. Among all of our members within the SCA most are also involved in other societies with many holding committee chair or officer positions. I am therefore going to ask our Membership Committee led by Dr. Glenn Murphy to work with our administrative office to begin recording in our membership database information about member collateral society membership including past and/or current positions, practice guideline authorship roles and other important roles and responsibilities. I have asked that our membership database be modified going forward to accommodate these changes, so that an example of what our SCA membership listing may look like is provided below:

Steven N. Konstadt, MD, MBA, FACC, Chair Department of Anesthesiology Maimonides Hospital, Brooklyn, New York, Indian Association Cardiobgic Anesthesia Education Committee member (2011-present)

Solomon Aronson, MD, MBA, FACC, FAE, FASE, Exec vice Chair Anesthesiology Duke Univ Medical Center past chair intraoperative council (2000-04) ASE, NBE Board of Directors (2004-2007), Joint Commission Council (2012-13)

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Scott T. Reeves, MD, MBA, FASE, Chair, Committee of Perioperative Echocardiography ASE (2011-12), Chairman of the Department of Anesthesia & Perioperative Medicine at the Medical University of South Carolina.

And so on… I believe these changes in our membership database will help us serve each other better in the future.

In keeping with the theme of the importance of networking and being engaged, I would also like to inform our membership about the status of the Flawless Operative Cardiovascular Unified Systems project (FOCUS). This multidiscipline safety project aimed at reducing Human Error in Cardiovascular Surgery initiated by the SCA and a project to which we in the SCA have been heavily committed is now managed by the SCA Foundation (SCAF). Beyond the clear mission to advance patient safety, one of the other goals of the SCA for initiating and supporting the FOCUS project was to provide opportunities for junior faculty in cardiovascular anesthesia careers to advance their visibility in the field. To date it is my pleasure to draw attention to two such individuals. Both Drs. Elizabeth Martinez (MGH) and Jake Abernathy (MUSC) are examples of how the SCA, by supporting FOCUS, has allowed younger members to have a huge career boost. Hopefully, there will be many others.

To date the references for the manuscripts that have been published (or soon to be published) by the SCA members involved in this important safety project are listed below:

- Spiess BD, Wahr JA, Nussmeier NA FOCUS - A Patient Safety Initiative. AHA Connection 8(1);17, Spring 2010
- Spiess BD Human Errors in Medicine: Change in Cardiac Operating Rooms through the FOCUS Initiative. JECT 2011;43:P33-P38

Going forward, I am also pleased to announce that these data soon will be available to the general SCA membership for purposes of epidemiologic research and observation hypothesis testing. For those members who are interested in accessing the data for investigational purposes, please contact the SCAF Executive Director, Chris Riely at clarissa@societyhq.com who will provide further information regarding the FOCUS Data Request policy and procedures. Data requests will then be forwarded to the FOCUS Steering Committee, Data Committee and Publications Committee for review.

The entire SCAF FOCUS Data Request Policy will be posted on the SCA and SCAF websites for your review. It is meant to facilitate SCA membership with generation of high quality manuscripts, while avoiding inconsistencies and redundancies. In addition the policy is meant to protect the scientific integrity of the data. The policy provides authorship guidelines such that all investigators have the opportunity to participate in and receive appropriate publication credit for the presentation of FOCUS data.
The Use of Extracellular Matrix in Cardiovascular Surgery

By Sanghun Kim, MD and Hong Liu, MD
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Although there were several attempts at development of biomaterials for orthopedic applications as early as 1970's, initial reference to the term “tissue engineering” can be trace back to a meeting held by National Science Foundation in late 1980’s.1 At a later meeting by the same organization, it was defined as “the application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve functions.”2

Since then interest in tissue engineering for cardiovascular applications has gradually gained momentum over the last few decades leading to development of biomaterials for use in cardiovascular medicine. Recently focus has shifted from merely replacing a portion of tissue with biomaterials to regenerating new tissue after implantation of bioengineered scaffold. This year’s Earl Wynands lecture at SCG’s 34th Annual Meeting will be delivered by Dr. Charles Vacanti on the topic of tissue engineering in the 21st century.

Importance of extracellular matrix was not appreciated by scientists and engineers in early stages of tissue engineering. However, it has taken a major role in recent years with the understanding that there is interplay between cells and the surrounding structures. Rather than merely occupying space around cells as a static entity, it has been shown that proteins within the framework communicate with cells and regulate growth, proliferation, differentiation, and migration of tissue at cellular level.3 In fact, it has been shown that extracellular matrix constantly undergoes remodeling through degradation and reassembly by the surrounding cells.4 In pre-clinical studies, the dynamic relationship between cells and extracellular matrix has been shown in wound healing, tissue regeneration, angiogenesis, and tumor invasions. For clinical applications, extracellular matrix has been successfully harvested from many mammalian tissue types including skin, dermis, fascia lata, small intestine submucosa, and pericardium. These materials are processed through proprietary methods developed by tissue engineering laboratories and are commercially available under different trade names.

CorMatrix ECM is available from CorMatrix Cardiovascular, Inc (Alpharetta, GA) and has been approved for usage in pericardial closure, cardiac tissue repair, and carotid repair by Food and Drug Administration. It is bioengineered acellular porcine extracellular matrix harvested from small intestine submucosa that is primarily composed of structural protein collagen.5 Based on laboratory research done by Badylak and his team of biomedical engineers from Purdue University, use of this material and processing method have been licensed to Cormatrix Cardiovascular, Inc (Alpharetta, GA) and Cook Biotech, Inc (West Lafayette, IN) for development of surgical implants for tissue regeneration and remodeling.

Initially developed as a possible solution to prevent complications from placement of vascular grafts used in surgery, CorMatrix ECM was shown to be effective as arterial grafts in carotid artery in an animal model in its ability to withstand forces and remodeling without causing calcification.6 Animal studies show that it can also act as a scaffold for repair and reconstitution of several tissue types including connective tissue, blood vessels, and myocardial tissue. The remodeled tissue showed functional cardiomyocytes with spontaneous contractility.7 Original scaffold is completely degraded after implantation over several months and induces a host cellular response that results in constructive remodeling instead of scar tissue formation.7

There are currently two preliminary studies that show promising results from using Cormatrix ECM in cardiovascular surgery in humans.8,9 In a retrospective study of 111 patients who received pericardial repair and reconstruction using Cormatrix ECM after coronary artery bypass graft surgery, there was decreased incidence of post operative atrial fibrillation with similar rate of other post operative complications.8 Although this finding led to statistically insignificant decrease in length of hospital stay, further research is warranted to investigate long term morbidity and mortality related to its use. In another study of 26 pediatric patients with congenital heart disease who required complex cardiac surgery in Europe, there was no incidence of surgical complications related to use of Cormatrix ECM both immediately after the surgery and up to a year after the surgery.9 Since it was used as a vascular graft to repair pulmonary artery, ascending aorta, arch, right ventricular outflow tract as well as a tissue graft for pulmonic, tricuspid, mitral, and aortic valve reconstruction in the study, this finding is very promising if follow up studies can show that there is vascular and myocardial tissue reconstruction with minimal adverse side effects due to host response during remodeling period.

There are also several anecdotal reports on use of Cormatrix ECM for cardiac surgery.10 It has been used in atrial septal repair after removal of atrial myxoma, aortic root enlargement in a case of patient prosthesis mismatch, and pericardial closure after left ventricular assist device implantation. It has met the functional role in surgical repairs without obvious immediate complications. In addition, its use for pericardial reconstruction is advocated for purported benefit to patients that may require another open heart surgery by preventing formation of adhesion between heart and sternum.

Although further studies are required to objectively assess utility of Cormatrix ECM for routine use in cardiac surgery, current literature suggests that there is a promising outlook for bioengineered extracellular matrix. Future studies evaluating long term effects in the human body would determine success of this product in clinical medicine.

References

An update on thromboelastometry in the setting of cardiac surgery

By Michael J. Frett, MD, Jeffrey W. Hartwig, DO, Jenny Kwak, MD
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Rapid assessment and correction of coagulopathy are essential in the setting of cardiopulmonary bypass (CPB). Routine lab tests following CPB include platelet count, prothrombin time, and activated partial thromboplastin time. While providing information about coagulation, they do not account for the physiologic conditions of the patient. The platelet counts provide a quantitative value with no information about platelet function. In addition, these tests are time consuming. Whole blood point-of-care testing is available, and the focus of this update is the recently FDA-approved rotational thromboelastometry (ROTEM; Tem Systems Inc., Durham, NC).

Thromboelastography was invented in 1948 and was initially used for hemostasis research. Recent methodological improvements have expanded its use to point-of-care testing in the operating room. Whole blood is placed in a cup and a pin is immersed in the sample. The tensile force created between the cup and the pin results from the interaction between activated platelet glycoprotein IIb/IIIa receptors and polymerizing fibrin during endogenous thrombin generation and fibrin degradation by fibrinolysis (1). As the blood in the cup clots and fibrin strands form, an increase in torque is created between the cup and the pin. The change in torque is then presented as a pictorial computer tracing, with the initial torque at the beginning of the test assumed to be zero.

The assays used in ROTEM are INTEM, HEPTEM, EXTEM, FIBTEM, and APTEM, and the parameters measured are coagulation time, clot formation time, angle of tangent at 2 mm, maximum clot firmness, and lysis onset time (85% of maximum clot firmness) (1-2). Each assay involves an activator or inhibitor to assess a specific part of coagulation. Phospholipids are used in INTEM to activate and monitor the intrinsic pathway. HEPTEM monitors the intrinsic pathway when unfractionated heparin is being used. For example, if INTEM is abnormal after CPB, the addition of heparinase in HEPTEM evaluates for residual heparin as a cause of abnormal coagulation. In EXTEM, tissue factor is added to activate and monitor the extrinsic pathway. FIBTEM monitors fibrinogen levels. In FIBTEM, tissue factor is added to activate the extrinsic pathway and cytochalasin D, a platelet antagonist, is added to isolate the effect of fibrinogen on clot firmness. APTEM assess for fibrinolysis. In APTEM, tissue factor is added to activate the extrinsic pathway and aprotinin is added to block hyperfibrinolysis. Data on clinical correlation between ROTEM variables with platelet counts and fibrinogen levels have begun to emerge with one study showing that FIBTEM quickly determines decreasing levels of fibrinogen (3).

Multiple studies have investigated the use of thromboelastography (TEG; Haemoscope-Haemonetics, Niles, IL) and ROTEM as point of care testing in cardiac surgical patients. While the methodology and basic principles are very similar between the TEG and ROTEM systems, measurements obtained from the two systems cannot be accurately used interchangeably (4). The main outcomes of most studies were perioperative bleeding and the amount of transfusions administered. Most studies demonstrated alterations in transfusion practice that did not necessarily translate to fewer overall transfusions, but rather an increase in therapy directed at dysfunctional components of the coagulation cascade. One group showed no change in intraoperative transfusion rates, but showed reduced postoperative and total transfusions administered in the TEG group (5). In addition, the amount of fresh frozen plasma and platelets transfused were reduced in the TEG group. Another group demonstrated a decrease in use of recombinant Factor VIIa in the ROTEM group (6). In the pediatric population, ROTEM decreased transfusions and changed the types of blood products transfused (7). Patients in the ROTEM group received fewer packed red blood cells and fresh frozen plasma but more platelets and fibrinogen concentrates.

The data suggest that the use of TEG and ROTEM in cardiac surgery patients have the potential to improve transfusion therapy in cardiac surgical patients. More information on outcomes and parameter thresholds used for transfusion will emerge with increasing availability of these systems.

References
2. www.roteminc.com
LITERATURE REVIEWS

Long-Term Follow-up of Participants with heart failure in the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT)


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Abstract
This is a follow-up study to the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The ALLHAT study was a randomized, double-blind study in high-risk patients with hypertension. Participants were at least 55 years of age, with a systolic blood pressure >140 mm Hg and diastolic pressure > 90 mm Hg and had preexisting cardiovascular or cerebrovascular disease. Patients with an ejection fraction (EF) < 55% and those that had symptoms of heart failure (HF) were excluded. Results of the ALLHAT trial showed that the incidence of new onset heart failure was lower in patients with hypertension on diuretic therapy than patients on a calcium channel blocker or angiotensin converting enzyme inhibitor (ACE-I).

The current study followed-up on patients from the ALLHAT trial who developed new onset HF; this consisted of 1761 participants. Mean follow-up time was 8.9 years. 76.5% of patients with HF died within that time. There was no difference in all-cause mortality between treatment groups. Rates of death were the same regardless of ejection fraction. The authors conclude that prevention of HF should be a focus in patients with hypertension, because once HF develops the mortality rate is high.

Comments
Heart failure is a major cause of morbidity and mortality with a large socioeconomic burden. The original ALLHAT trial was the largest study comparing antihypertensive medications in high-risk patients. The results of that study showed that diuretics should be part of the antihypertensive medical regimen for prevention of HF. The current study provides important follow-up information about the patients that developed HF. Hypertension and coronary artery disease have been found to be the most important risk factors in the development of HF in multiple large cohort studies. This study re-emphasizes previous findings but also gives us new information on outcomes in patients with poorly controlled hypertension. Prevention appears to be the key in decreasing mortality, as available therapies cannot sufficiently reverse or slow down the progression of disease.

Achievement of blood pressure control can be a daunting task in some patients that respond poorly to multimodal drug therapy. As new drugs become available, older thiazide type medications have become less popular. Yet this study supports the recommendations of the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the current US hypertension guidelines; which is to initiate thiazide type diuretic therapy as first-line treatment for hypertension. These medications have been available for greater than 50 years, have a well documented safety profile, are available in generic form and are inexpensive.

Acquired type 2A von Willebrand syndrome caused by aortic valve disease during valve surgery


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Background
Aortic valvular stenosis can cause an acquired type 2A von Willebrand Syndrome (aVWS). The mechanism is thought to be related to high fluid shear stress causing loss of high molecular weight multimers (HMWM) of von Willebrand factor (VWF). Impairment in both platelet adhesion and aggregation occurs making these patients highly susceptible to bleeding. Prophylactic perioperative administration of VWF/FVIII concentrates has been recommended in patients with aVWS. The authors hypothesized that the perioperative VWF HMWM defect is corrected during cardiopulmonary (CPB) before any hemostatic therapy and hence has minimal or no influence on perioperative bleeding and transfusion in corrective aortic valve (AV) surgery.

Methods
In this prospective observational study of 17 patients undergoing aortic valve surgery, an analysis of plasma samples for VWF concentration and activity was done. Ten patients undergoing coronary artery bypass grafting (CABG) were studied for comparison. Blood samples were collected before induction of anaesthesia, after weaning from CPB, and on the first post-operative day.

The VWF multimer pattern was assessed using agarose gel electrophoresis, Western blot and densitometric analysis. VWF antigen (VWF: Ag) and VWF collagen –binding capacity (VWF: CB) were determined using ELISA.

Results
A diagnosis of aVWS had not been made in any of the patients included in this study. In 12 of the 17 subjects (71%), VWF HMWM were absent before surgery. This normalized in 88% of the subjects at the end of CPB. The VWF: Ag concentration (50-160%) and VWF: CB (50-250%) was within or above normal at all times. Mean preoperative and end of CPB values of VWF: Ag and VWF: CB was comparable. The mean post-operative values of VWF: Ag were significantly higher than the preoperative and end of CPB values (p=0.001 and 0.0017, respectively). Similarly, the mean post-operative values of VWF: CB were significantly higher than the preoperative and end of CPB values (p=0.0007 and 0.0009, respectively). The transfusion requirement in these patients varied according to the complexity of the operation.

Discussion
The preoperative defect of VWF HMWM in patients undergoing AV surgery is corrected at the end of CPB before the administration of any hemostatic

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therapy. Diffuse bleeding seen after CPB is unlikely to be related to persistent aVWS and hence, the administration of VWF/F VIII concentrates in these patients is unnecessary.

Comment
This is an interesting study that looked at the perioperative evolution of VWF in patients undergoing corrective AV surgery. Surgical correction of the AV defect reduces the mechanical stress on VWF causing its normalization after surgery. At the same time, an acute intra operative inflammatory response triggered during cardiac surgery causes activation of endothelial cells triggering release of intact VWF HMWM. Correction of VWF defect in CABG patients supports this hypothesis which needs further investigation. Current guidelines for management of patients with aVWS require prophylactic administration of VWF/FVIII concentrate prior to surgery. This however seems unnecessary in patients undergoing corrective AV surgery.

Preoperative Aspirin Use and Outcomes in Cardiac Surgery Patients

Methods
This observational cohort study enrolled 4256 consecutive patients undergoing cardiac surgery in two tertiary medical centers. The 2868 patients met the inclusion criteria were divided into two groups: aspirin taking group (n=1923) and no aspirin group (n=945) 5 days before surgery. Data collected included demographics, patient history, medical record information, preoperative risk factors, preoperative medications, intraoperative data, postoperative cardiocerebral events, renal failure, and 30-day all-cause mortality. The main parameters were 30-day all-cause mortality, postoperative renal failure/dialysis required, and major adverse cardiocerebral events, renal failure, and intensive care unit stay and 30-day mortality. And preoperative aspirin therapy (vs non-aspirin) significantly reduced the risk of major cardiocerebral complications, renal failure, and intensive care unit stay and 30-day mortality. And preoperative aspirin does not increase the risk of readmissions in patients undergoing cardiac surgery.

Conclusions
This study concluded that preoperative aspirin therapy is associated with a significant decrease in the risk of major cardiocerebral complications, renal failure, and intensive care unit stay and 30-day mortality. And preoperative aspirin does not increase the risk of readmissions in patients undergoing cardiac surgery.

Risk of Acute Myocardial Infarction After the Death of a Significant Person in One’s Life: The Determinants of Myocardial Infarction Onset Study

Abstract
Investigators at Beth Israel Deaconess Medical Center, Boston, and other hospitals examined the effect of a close friend or relative’s recent death on the incidence of MI. In a case-crossover trial, 1,985 patients with angina and positive serum markers were interviewed after admission to the CCU in one of 45 participating hospitals. Among this group, 270 reported the death of a significant person within 6 months of the MI. Expected incidence rate of a
Clinical Implications of Electrocardiographic Left Ventricular Strain and Hypertrophy in Asymptomatic Patients with Aortic Stenosis: The Simvastatin and Ezetimibe in Aortic Stenosis Study


Circulation. 2012 Jan 17;125(2):346-53

Background

The prognostic impact of electrocardiographic left ventricular (LV) strain and hypertrophy (LVH) in asymptomatic aortic stenosis (AS) is not well described.

Methods and Results

Data was obtained in asymptomatic patients with AS randomized to simvastatin/ezetimibe combination vs. placebo in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Primary endpoint was the first incidence of myocardial infarction, non-hemorrhagic stroke, heart failure, aortic valve replacement (AVR) or cardiovascular death. Predictive value of electrocardiographic LV strain (defined as T-wave inversion in leads V4-6) and LVH (assessed by Sokolow-Lyon voltage criterion (RV5-6+SV1 ≥35 mV) and Cornell voltage duration criteria ((RV5+SV3+6 mV in women)°—QRS-duration ≥2440 mVsec), was evaluated by adjusting for other prognostic covariates. 1,533 patients were followed 4.3±0.8 years (6,592 patient-years of follow-up), 627 cardiovascular events occurred. Electrocardiographic strain was present in 340 (23.6%) patients; LVH by Sokolow-Lyon voltage in 260 (17.1%) and in 220 (14.6%) by Cornell voltage-duration product. In multivariable analyses, electrocardiographic LV strain was associated with 3.1-fold higher risk of in-study myocardial infarction (95% confidence interval [CI], 1.4 to 6.8, p=0.004). Similarly, electrocardiographic LVH by both criteria predicted, compared to no electrocardiographic LVH, 5.8-fold higher risk of heart failure (95% CI, 2.0 to 16.8), 2.0-fold higher risk of AVR (95% CI, 1.3 to 3.1, both p=0.001) and 2.5-fold higher risk of a combined endpoint of myocardial Infarction, heart failure or cardiovascular death (95% CI, 1.3 to 4.9, p=0.008).

Conclusions

Electrocardiographic LV strain and LVH were independently predictive of poor prognosis in asymptomatic AS.

Comments

This is a sub-study analysis of the Simvastain Ezetimibe in Aortic Stenosis (SEAS) multicenter trial. The authors used prospectively gathered data from a large cohort of asymptomatic patients with mild to moderate aortic stenosis to investigate the predictive value of LV strain and LVH on the risk of cardiovascular morbidity and mortality. The study encompassed a total of 1873 patients ranging from 45 to 85 years of age. Of those, 1533 of them were followed for an average of 4 years. After multiple data analyses and adjust-

References


Comments

The study builds on prior evidence that links bereavement to morbidity. In 1969, Parkes et al found a mortality rate 40% above the expected rate for widowers within the first 6 months of loss of spouse (1). A study from 2008 examined disease specific mortality in early widowhood and found increased rates of death in 15 of 17 causes, especially death from cardiovascular disease (2). Those authors concluded that the widowhood effect is not due to a single biological mechanism but is multifaceted and likely influenced by social support mechanisms (or lack thereof).

The present authors prudently highlight the limitations of their data. For example, their inclusion criteria for MI did not consider cardiac catheterization reports and did not reliably distinguish patients who might have actually been experiencing Takotsubo cardiomyopathy. Because the event rate was low, they were unable to determine if the relationship to the deceased influences MI rate. The implications of their findings are hypothesis-generating. For instance, mourners with elevated cardiovascular risk may benefit from social support mechanisms such as ensuring regular meals, sleep, and medication compliance.
ments for other prognostic covariates, the authors found IV strain and LVH to be good independent risk predictors for MI, heart failure, cardiovascular mortality as well as possible future aortic valve replacement surgery.

The authors emphasized the clinical value of electrocardiographic left ventricular strain and hypertrophy on predicting cardiovascular events. However, when correlating IV strain with an increased risk of myocardial infarction prior to AVR, one limitation of this study was inconsistent evidence of whether or not the patient had undergone angiography to identify any pre-existing coronary artery disease.

The authors stated that the original SEAS study randomized patients into two separate groups (drug vs. placebo) and found that there was no significant impact or alternation between the EKG variables when adjusted for the drug vs. placebo. The authors also mentioned that the study group receiving simvastatin did not show an appreciable difference or progression in their EKG findings of IV strain or LVH. Unfortunately, the authors presented neither the drug vs. placebo data nor the simvastatin data for review. The fact that the experimental data show that statins can potentially benefit cardiac hypertrophy raises questions on the potential existence of selection bias for this study.

Overall, this study illustrates a positive predictive value of IV strain and LVH on cardiovascular morbidity and mortality in patients with asymptomatic AS. The strongest indicator is the incidence of MI (4.1% with IV strain compared to 1.6% without IV strain) prior to AVR in patients with LV strain. Another limitation of this study is that the authors did not discuss whether or not other medication taken by the patient might have a potential effect on the EKG pattern. Further studies are warranted to answer these remaining questions.

**Main Outcome Measures**

The primary efficacy end point was platelet reactivity (measured in P2Y12 reaction units [PRUs]), assessed daily. The main safety end point was excessive CABG surgery–related bleeding.

**Results**

The dose of cangrelor determined in 10 patients in the open-label stage was 0.75 μg/kg per minute. In the randomized phase, a greater proportion of patients treated with cangrelor had lower levels of platelet reactivity throughout the entire treatment period compared with placebo (primary end point, PRU <240, >60% platelet inhibition; 98.8% (83 of 84) vs 19.0% (16 of 84) patients; relative risk [RR], 5.2 [95% CI, 3.3-8.1] P<.001). Excessive CABG surgery–related bleeding occurred in 11.8% (12 of 102) vs 10.4% (10 of 96) in the cangrelor and placebo groups, respectively (RR, 1.1 [95% CI, 0.5-2.5] P=.763). There were no significant differences in major bleeding prior to CABG surgery, although minor bleeding episodes were numerically higher with cangrelor.

**Conclusions**

Among patients who discontinue thienopyridine therapy prior to cardiac surgery, the use of cangrelor compared with placebo resulted in a higher rate of maintenance of platelet inhibition.

**Comments**

Disruption of coronary vascular endothelium either from acute plaque rupture or from chronic atherosclerotic process induces a hemostatic response marked by thrombin generation, tissue factor release, platelet aggregation, and eventual clot formation. Therefore, pharmacotherapy with antiplatelet agents, notably aspirin and thienopyridine (ticlopidine, clopidogrel, and prasugrel) drugs, is critical to both early and late success in management of coronary artery disease (CAD)- either by percutaneous coronary interventions (PCI) or coronary artery bypass (CABG) surgery. According with evidence-based practice, aspirin therapy is continued indefinitely; whereas, treatment with thienopyridines beyond 6 months post PCI with drug-eluding stents varies and debate persists as to when it would be safe to discontinue therapy.

In the setting of surgery, the perioperative management of antiplatelet therapy also raises important concerns regarding the appropriate timing for withholding antiplatelet treatment prior to surgery and for reinstituting it after the procedure. An estimated 5% of patients require surgery within the first year after stent implantation or following an acute myocardial infarction. Some reports suggest a rate of ischemic complications as high as 12.5% during the awaiting period between cessation of antiplatelet therapy and the planned surgical procedure.7,8 Albeit such high incidence of coronary events could be avoided by either continuing antiplatelet treatment up to the point of surgery and/or by administering other forms of anticoagulation, both surgeons and anesthesiologists are wary of undertaking the significant intraoperative and postoperative bleeding risks that can arise from chronic platelet inhibition with thienopyridines. In fact, there are many reports of major bleeding and associated massive transfusions in anticoagulated patients undergoing emergent and urgent procedures.

Several guidelines exist for “safe” withdrawal of antiplatelet therapy before surgical procedures. Monitoring of platelet function is commonly performed until the percent platelet inhibition is deemed safe for proceeding with surgery. While some form of thrombin inhibition is advocated with unfractionated heparin, low molecular weight heparin, or with a direct thrombin inhibitor (DTI) agent, there remain many unknown efficacy and safety issues. Given

**Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery: A Randomized Controlled Trial**


**Context**

Thienopyridines are among the most widely prescribed medications, but their use can be complicated by the unanticipated need for surgery. Despite increased risk of thrombosis, guidelines recommend discontinuing thienopyridines 5 to 7 days prior to surgery to minimize bleeding.

**Objective**

To evaluate the use of cangrelor, an intravenous, reversible P2Y12 platelet inhibitor for bridging thienopyridine-treated patients to coronary artery bypass grafting (CABG) surgery.

**Design, Setting, and Patients**

Prospective, randomized, double-blind, placebo controlled, multicenter trial, involving 210 patients with an acute coronary syndrome (ACS) or treated with a coronary stent and receiving a thienopyridine awaiting CABG surgery to receive either cangrelor or placebo after an initial open-label, dose-finding phase (n=11) conducted between January 2009 and April 2011.

**Interventions**

Thienopyridines were stopped and patients were administered cangrelor or placebo for at least 48 hours, which was discontinued 1 to 6 hours before CABG surgery.
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the aforementioned constraints, Angiollilo et al, randomized “bridging” patients on antiplatelet therapy who were scheduled to undergo CABG surgery to receiving either placebo or cangrelor. Cangrelor, a nonthienopyridine adenosine triphosphate analogue, is an intravenous (IV) antagonist of the P2Y12 receptor characterized by rapid, potent, predictable, and reversible platelet inhibition with rapid offset of effect. In this study, cangrelor drug infusion was initiated after thienopyridine therapy was discontinued and was continued throughout the preoperative period up to 1 to 6 hours before surgical incision. It was recommended that patients wait 5 days after discontinuation of ticlopidine and clopidogrel, and 7 days after prasugrel, before undergoing surgery.

Excessive CABG surgery–related bleeding (defined by surgical re-exploration, 24-hour chest tube output of more than 1.5 L, or packed red blood cell transfusion of more than 4 units) occurred in 11.8% vs. 10.4% in the cangrelor and placebo groups, respectively (P=0.763). There were no significant differences in major bleeding prior to CABG surgery. Cangrelor at an infusion dose of 0.75 mcg/kg/min achieved and maintained adequate levels of platelet inhibition throughout the treatment period. Prior to CABG surgery rapid recovery of platelet function was achieved after discontinuation of cangrelor infusion, as shown by similar levels of platelet inhibition compared to placebo.

The findings of this study are encouraging for preoperative management of patients on antiplatelet therapy who require surgery. Nevertheless, several important questions and concerns remain. For example, who are the individuals at greatest risk for coronary events during the bridging phase? There were few ischemic events in the placebo group, however, 20% of the patients in the placebo group maintained platelet inhibition by residual thienopyridine effect. The need for bridging may be avoided by timing surgery based on return of platelet activity, which has high variability. On the other hand, who are the patients at greatest risk for bleeding complication during and after surgery? Is there need for bridging therapy in patients insensitive to ticlopidine or clopidogrel? Are the costs of hospitalization for preoperative cangrelor administration feasible and financially sound especially with the introduction of oral alternatives such as ticagrelor? Should cangrelor be continued intraoperatively in those patients requiring CABG surgery with use of cardiopulmonary bypass? Lastly, what is the appropriate timing of resuming antiplatelet therapy in these patients after surgery?

References


Predictors and impact of postoperative atrial fibrillation on patients’ outcomes: a report from the Randomized On Versus Off Bypass trial.


Reviewers: Henry Liu, MD; Daisuke Inui, MD; Nakeisha Pierre, MD Tulane University Medical Center, New Orleans, Louisiana

Background

Postoperative atrial fibrillation (POAF) is a common complication after cardiac surgery. However there is no reliable predictor(s) for this common and severe complication. In this study, Dr. Almassi et al randomized 2103 patients into two groups (on-pump group and off-pump group) to illustrate the potential predictors for the pathogenesis of POAF, compare the two groups and the impact on the clinical outcomes.

Methods

There were 2203 enrollees in this ROOBY trial. Out of 2203, 2103 patients in the Randomized On Versus Off Bypass trial with no POAF was studied (1056 patients in the ONCAB group and 1047 patients in the OPCAB group). Patients with pre-existing atrial fibrillation were excluded. Univariate and multivariate analyses were used to identify the predictors of POAF and the impact of POAF on outcomes.

Results

Predictors of POAF: Older age (P < .0001), white race (P < .001), and hypertension (P < .002) were predictors of POAF on multivariate analysis. However, use of ONCAB versus OPCAB was not associated with increased rates of POAF.

Negative impact on clinical outcomes: In general, POAF led to higher rates of reintubation (ONCAB: 6.3% vs 0.8% no POAF, P < .001; OPCAB: 7.4% vs 1.8% no POAF, P < .0001) and prolonged ventilatory support (ONCAB: 7.1% vs 2.3% no POAF, P = .001; OPCAB: 9.2% vs 3.4% no POAF, P = .0005). The rate of any early adverse outcome was higher in patients with POAF (all patients: 10% POAF vs 4.7% no POAF, P < .0001; ONCAB: 9% POAF vs 4.3% no POAF, P = .008; OPCAB: 11% POAF vs 5.1% no POAF, P = .001). The 1-year all cause mortality was higher with POAF for both groups (ONCAB: 5.4% POAF vs 2% no POAF, P = .009; OPCAB: 5.1% POAF vs 2.6% no POAF, P = .07). POAF was independently associated with early composite end point (odds ratio [OR], 2.23; confidence interval [CI], 1.55-3.22; P < .0001), need for new mechanical support (OR, 3.25; CI, 1.39-7.61; P = .007), prolonged ventilatory support (OR, 2.93; CI, 1.89-4.55; P < .0001), renal failure (OR, 5.42; CI, 1.94-15.15; P = .001), and mortality at 12 months (OR, 1.94; CI, 1.14-3.28; P = .01).

Conclusions

In the Randomized On Versus Off Bypass trial, the strategy of revascularization did not affect the rate of POAF. Age, race, and hypertension were predictors of POAF. POAF may cause higher rates of reintubation, prolonged mechanical ventilation, and renal insufficiency. Diabetes is not a predictor. POAF was independently associated with a higher short-term morbidity and higher 1-year mortality rates.
**Effects of normothermic cardiopulmonary bypass on renal injury in pediatric cardiac surgery: a randomized controlled trial**


Reviewer: Mojca Remskar Konia, MD

University of Minnesota, Minneapolis, MN

**Abstract Excerpt**

The study by Caputo and co-authors is a randomized controlled study that compared renal injury in children who underwent repair of simple cardiac conditions with hypothermic or normothermic cardiopulmonary bypass. The study enrolled 59 patients (31 in the hypothermic group and 28 in the normothermic group). To determine the extent of renal injury the authors followed urinary albumin, retinal binding protein (RBP), and N-acetyl-β-D-glucosaminidase (NAG) preoperatively, at the end of bypass, 24, 48 and 72 hours postoperatively. Furthermore, serum urea, creatinine and hematocrit were determined at the end of bypass, 24, 48 and 72 hours postoperatively. Groups were compared for crossclamp time, cardiopulmonary bypass time, lower body temperature, in-hospital mortality, blood loss in the first 24 hours, fluid balance, platelet and fresh frozen plasma transfusion, inotropic support, diuretic use, postoperative ventilation time and postoperative hospital stay. The average age of included patients was 78 months (interquartile range, 39-130). Majority of patients underwent ASD and VSD repairs in both groups (hypothermic 71%, normothermic 79%). Only 3 patients had cyanotic heart condition. Except for the difference in body temperature and increased crossclamp and cardiopulmonary bypass times in hypothermic group, no differences were noted in the observed clinical parameters. There was also no statistically significant difference observed between groups for serum creatinine (-2.1; 95% CI, -6.51-2.31; RBP (0.96; 95% CI, 0.65-1.41), NAG (0.86; 95% CI, 0.56-1.36), (p>0.34), however urinary albumin was significantly lower in normothermic group (0.63; 95% CI, 0.42-0.95, p=0.03). Based on their results the authors concluded that normothermic cardiopulmonary bypass is not associated with worse renal injury compared to hypothermic cardiopulmonary bypass.

**Comments**

Renal dysfunction occurs in 5-20% of children after surgeries with cardiopulmonary bypass (1). It is believed to be multifactorial in causes and has frequently been related to the time of extracorporeal circulation. The longer the time the more likely the renal dysfunction (2). Hypothermia during bypass surgery has the main purpose of organ protection by reducing metabolic rate and oxygen consumption and decreasing the whole-body inflammatory response. However, we also know that hypothermia itself can induce damage, including renal injury. We know that rewarming from hypothermia causes injury to the renal tubular cells similar to the once observed in acute tubular necrosis (3). In fact, if the rewarming process is too vigorous the induced hypothermia can add to tissue damage (2). Hypothermia has also been shown to be associated with reduction in renal blood flow (4). The question of hypothermic vs. normothermic bypass cardiac surgery in pediatric population remains to be clarified. The existing data on the effects of hypothermia and normothermia on organ injury during cardiopulmonary bypass comes primarily from studies in adults and animals. In adult population not much difference has been observed between hypothermic and normothermic patients (5, 6). The presented study indicates that renal injury in the pediatric population may be the same or less in normothermic patients. However, one cannot overlook the fact that cases in the study were non-complex heart surgeries with short cardiopulmonary bypass times for which many of us would feel comfortable using normothermia. The question of the best approach in the more complex cardiac surgeries, surgeries in cyanotic patients or surgeries that require prolonged cardiopulmonary bypass time still remains unanswered. I would also like to comment on the number of included patients. The number is big enough to detect differences in biochemical markers, but not big enough to make conclusions about clinical outcomes. It is my understanding that the authors are collecting additional 240 patients to be able to comment on clinical outcomes and I am looking forward to those results.

This is the first randomized clinical trial that looked at the renal safety of normothermic cardiopulmonary bypass in pediatric population. The study indicates that normothermia may be safely used for noncomplex congenital heart surgery. Whether that is the case for cyanotic pediatric patients, complex heart surgery and prolonged cardiopulmonary bypass time remains to be determined.

**References**

Impact of Preoperative Angiotensin-Converting Enzyme Inhibitor Use on Clinical Outcomes After Cardiac Surgery


Reviewer: Jenny Kwak, MD
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Background
Angiotensin-converting enzyme inhibitors (ACEi) are commonly prescribed medications. ACEi affect ventricular remodeling and protect patients with coronary artery disease. However, there is controversy regarding the use of ACEi in the setting of coronary artery bypass grafting (CABG).

Methods
Outcomes of patients having CABG at a single institution were analyzed. Patients were identified using a clinical registry. Multivariable models were used to examine the association between preoperative ACEi use and outcomes. The primary outcome was in-hospital mortality, and both in-hospital and long-term outcomes were examined.

Results
The study population included 5,946 patients, of which 55% had preoperative ACEi therapy. The group with ACEi therapy was more likely to have diabetes mellitus, hypertension, ejection fraction less than 40%, and recent myocardial infarction and less likely to have pre-existing renal failure. Postoperative use of an inotrope or intra-aortic balloon pump was also more frequent in the ACEi group. Both groups had similar rates of in-hospital mortality (odds ratio [OR] = 1.1, 95% CI = 0.8-1.4, p = 0.76), perioperative MI, stroke, and new-onset renal failure. There was no difference in prolonged ICU stay or hospital length of stay. There was no independent association between ACEi and long-term survival (hazard ratio [HR] = 1.0, 95% CI = 0.9-1.2, p = 0.54), but ACEi therapy was associated with increased risk of hospital readmission for heart failure (HR = 1.2, 95% CI = 1.1-1.4, p = 0.007).

Conclusions
There was no association between preoperative ACEi use and adverse in-hospital outcomes or long-term survival after CABG.

Comments
This was a large study, but it was limited by its retrospective and observational design. Due to its design, there was no information regarding the specific ACEi and dosage used or whether or not the ACEi was held for any amount of time preoperatively. Despite its limitations, it showed that preoperative ACEi before CABG is safe. The cohort with ACEi therapy had a higher risk profile but had similar mortality and survival with a median follow-up time of 3.6 years. The longerterm effects of preoperative ACEi therapy on high risk patients and the increased risk of hospital readmission for heart failure in patients on ACEi therapy may be of interest in future studies.

Truncations of Titin Causing Dilated Cardiomyopathy


Reviewers: Sean Birmingham, MD and Dalia Banks, MD
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Background
A well-accepted important cause of cardiomyopathy is genetic mutation. A genetic cause of dilated cardiomyopathy (DCM) has been implicated, with 30-50% of patients with DCM having a relative with DCM. Over 40 genetic mutations, primarily encoding the sarcomere or cytoskeleton, have been associated with DCM. Titin, the largest human protein with 33,000 amino acids, has been linked to DCM. Titin is critical for sarcomere assembly and modulation of the contractile force. The gene encoding this sarcomere protein is TTN. It has been incompletely studied due to its large size, technical sequencing challenges and extensive cost. Recent advances in sequencing techniques allow for more rapid sequencing of long stretches of DNA without the expense of previous techniques. This study attempted to use next generation sequencing as well as traditional techniques to identify distinct TTN mutations in patients with DCM, hypertrophic cardiomyopathy (HCM) and patients with cardiomyopathy.

Methods
The authors identified 312 patients with idiopathic dilated cardiomyopathy within three cohorts, A, B, and C, 231 subjects with HCM, and 249 control subjects without cardiomyopathy. Genomic DNA was collected from each subject and used to construct DNA libraries. The 145 kb TTN gene was enriched by filter-based hybridization. Group C had the TTN sequenced by traditional Sanger dideoxy sequencing while next-generation sequencing techniques were used on groups A and B, patients with HCM and the controls. Statistical analysis included Fisher's exact test, exact conditional tests of independence, or goodness-of-fit tests for association, cross-cohort and cross group analysis. Clinical characteristics in each DCM cohort were compared using two-tailed, unpaired t-tests. Two-point lod scores for 19 families with DCM were calculated and indicated disease penetrances.

Results
There were no significant differences between subjects with and without TTN truncating mutations with regards to age at diagnosis, left ventricular end-diastolic dimensions, ejection fraction, rates of cardiac transplantation, implantation of DAD or death. 97% of the targeted bases were sequenced at least 20 times in DCM cohorts A and B, subjects with HCM and controls. 931 rare TTN variants in the 792 subjects were identified that were predicted to change the titin amino acid sequence. 72 unique TTN truncating variants were identified in 67 subjects with DCM, 3 with HCM, and 7 control subjects. They analyzed nonsense, frameshift, splicing and copy number variants and classified these variants as TTN truncating variants. The three subjects with HCM had three TTN truncating variants but also had pathogenic mutations in established HCM genes. The frequency of variants between HCM and control subjects did not significantly differ (1% and 3% respectively). TTN variants were significantly more frequent among DCM subjects than among HCM subjects (P<3X10-16) and control subjects (P=3X10-14). Overall frequencies of TTN truncating mutations in DCM subjects in group A were 28% and group

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B 24%. Group C, which used an older sequencing technique, had a 9% TTN mutation rate. TTN mutation type did not influence rates of cardiac transplantation, LVAD implantation or death among subjects or family members due to cardiac causes. Segregation analysis in 20 families confirmed the co-inheritance of truncating mutations and that the penetrance of TTN mutations was greater than 95% for patients over 40 years old. They also found that men with TTN mutations had adverse events at a significantly earlier age than women (P=4x10-5).

**Conclusion**

The authors concluded that TTN truncating mutations are the most common known genetic cause of DCM. They felt that these mutant alleles produce shortened titin protein with abnormal properties that cause dilated cardiomyopathy. They also concluded that TTN truncating mutations rarely if ever cause HCM as the three subjects with TTN variants also had mutations in established HCM genes. The reduced frequency of mutations in group C suggests that detection of mutations was better with next generation sequencing techniques than with traditional dideoxy sequencing.

**Comments**

This study is the first to clearly show that the mutation in the TTN gene can account for 25% of DCM in patients with a known family history and about 18% of DCM cases without known family history in a large sample population. Previously, only a very few number of TTN mutations have been clearly linked to DCM due to difficulty in comprehensive sequencing of the TTN gene. An interesting finding was that men had adverse events at an earlier age than women. The “suggestion that sex would substantially influence an autosomal monogenic cause of heart failure is unexpected.” The authors acknowledge, “further study of the functional consequences of TTN truncating mutations on myocardial physiological features and myocyte signaling is warranted.” The role of next-generation sequencing in clinical genetic screening has yet to be determined. The authors propose that detection of DCM should increase by 50% by using next generation sequencing analyses in clinical genetic screening. Identifying these mutations should make it easier to find family members with undiagnosed disease. This should allow for earlier DCM diagnosis, implementation of interventions to prolong the asymptomatic period, earlier monitoring for arrhythmias and potentially slow down disease progression.