Non-Cardiac Thoracic Surgical and Endovascular Perioperative MACE: Quick, Easy Prediction and Mitigation Strategy

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Abstract

This article is the second of the two part series focusing on predicting and reducing perioperative major adverse cardiac events (MACE) resulting from the procedures cardiothoracic surgeons perform. The first addressed cardiac surgery (1). This article addresses non-cardiac procedural complications

Key words: perioperative MACE; thoracic surgery; endovascular revascularization; surgical revascularization

Introduction

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At least 4% of the world's population, 300 million people, undergo non-cardiac surgery yearly (2). Up to 9.6% suffer major adverse cardiac events(MACE) within 3 mo. of major elective surgery(3), the most common major, deadly complications(4). Although perioperative MACE can be quickly, easily, and reasonably accurately estimated (5-7), seemingly there's little we can do proactively to mitigate it. This review covers: (1) estimation of perioperative MACE; (2) current options available to reduce MACE (8, 9); and (3) suggests new, proactive, simple, safe, promising pharmacologic approaches that might further reduce MACE (10-12).

Estimating Mace

(1) Lee's Revised Cardiac Risk Index (Lrcri, 1999)

This is probably the most frequently used tool (3). A score of 0(absent) or 1(present) is given for:

- PHx coronary disease(CAD):AMI,CABG,PCI,+stress test,angina,nitrate use,ECG pathologic q's
- PHx congestive heart failure(CHF)
- PHx transient ischemic attack(TIA),stroke(CVA)
- PHx insulin dependent diabetes mellitus(IDDM)
- PHx creatinine >2
- High risk surgery(≥50 y/o thoracic/abdominal, CEA,AAA repair, suprainguinal revascularisation)

Score= Risk MACE(acute myocardial infarction[AMI],ventricular fibrillation[vf], cardiac arrest, complete heart block, pulmonary edema, cardiac death

Score Risk

- ➤ 0 = 0.4%
- ➤ 1 = 1.0%
- ➤ 2 = 2.4%
- ➤ ≥3 = 5.4%

These percentages are higher for age > 70 y/o, unstable angina w/I 6mo.,left bundle branch block(LBBB) on ECG, and acute decompensated CHF, especially if left ventricular ejection fraction(LVEF) is <40%.

LRCRI's advantage is that it's easily and quickly scored. Disadvantages include: use of CK mb, not troponin, to diagnose AMI; exclusion of emergency surgery, endovascular or infrainguinal procedures; no accounting for frailty or inactivity; and of the operations Lee categorized high (up to 5%) risk in 1999, today some are, at most, of moderate risk. Reguardless, adhere to Lee's list for scoring and use current risk data relating to newer procedures employed since 1999 to decide if their risk should be scored high

(2) Acs Nsqip Mica Risk Score (2013)

This is likely the 2nd most often used among several risk scores. The physician needs a calculator into which the following 5 variables are entered to obtain operative risk:

- Type of surgery
- Functional status
- Creatinine >1.5
- ASA class
- Age

In comparison to LRCRI, it's more accurate for vascular surgery MACE and predicting death.

Mitigating Mace

Sadly, under the present Guidelines, options are limited .Using the 3 Lee's MACE categories (AMI, life-threatening arrhythmias, acute CHF), we can:

a) **AMI(1%-3% incidence[4,13](CAD**):
   Delay elective surgery to avoid acute thrombosis
       i. 6-12 mo. post coronary drug eluting stent(DES) or AMI
       ii. 1 mo. post coronary bare metal stent(BMS)
       iii. 2-4 wk. post coronary plain old balloon angioplasty(POBA)

   If dual antiplatelet therapy (DAT) must be stopped, continue aspirin if benefit>risk; consider bridging with i.v. antiplatelet Rx (Hematologist can assist)

   Continue beta blockers but do not start w/I 1 day of surgery (POISE TRIAL) so as to avoid hypotension, CVA, or death

   Start a statin at least 2wk. prior to vascular or high risk surgery (reduces AMI 44%)

   Myocardial perfusion imaging (MPI) stress testing should be considered in frail or inactive patients (<4 METS) who have known CAD or risk factors.

b) **Arrhythmia:** No preventative recommendation for VT, cardiac arrest, complete heart block

c) **Pulmonary Edema**

       i. If patient's CHF is decompensated, there is an 8% 1 mo. perioperative death rate(13), so delay until compensated
       ii. Continue home CHF medications(ACEI/ARB discontinued only if for HTN, not CHF, to avoid hypotension during anesthesia)

If the patient has had a TIA, cerebrovascular imaging should be done within 6 mo. of surgery. Surgery should be delayed up to 6 mo., since the risk of a CVA is increased 2x-34x depending upon the time between the TIA and surgery.

Going Beyond the Guidelines to Mitigate Mace

In the first article of this two-part series, regarding reducing perioperative MACE from cardiac surgery based upon my non-surgical MACE-reduction using the antianginal ranolazine (RAN), on- and off-label in 3 of Lee's MACE categories(AMI, ventricular arrhythmias, CHF) provided therapeutic blood levels (2-6 micromolar) can be achieved, RAN reduced MACE up to 50% (1). As a reminder, RAN has 2 unique cardio-protective mechanisms of action:

- Strong use-dependent inhibition of neuronal sodium channel 1.7($Na_{v1.7}$) in its open state via the local anesthetic receptor. This reduces high Sympathovagal Balance (SB) and can also correct Cardiac Autonomic Neuropathy (CAN = critically low Parasympathetic tone [RFa < 0.10 bpm^2]), both of which can be present in CAD and CHF (31%-59% of Guideline-treated patients). When SB was ≤ 2.5, 80% of our patients were MACE-free (r=0.0048, p=0.02140; when SB was > 2.5, 55% of patients suffered MACE (cardiac death, acute coronary syndromes, elective revascularization, ventricular tachycardia/fibrillation, CHF admission) (r=0.0117, p=0.0108). SB > 2.5 increased MACE 7- fold in 483 patients we studied with risk factors or established CAD or CHF, mean f/u 4.92 vrs,

- Inhibition of the cardiac $Na_{v1.5}$ late inward sodium current (INa) by attaching to $Na_{v1.5}$'s amino acid F 1760. $Na_{v1.5}$'s opening 1 msec. (the early I_{Na}) results in the upstroke of the QRS complex and systole. Any stress, including surgery, can result in faulty gating of this sodium channel, causing a marked increase of the late I_{Na} . The resulting high myocellular Na^+ is exchanged for Ca^{++} via the Na^+/Ca^{++} exchanger (NCX).Therefore, both Na^+ and Ca^{++} are elevated, resulting in increased diastolic dysfunction, increased triggered ventricular arrhythmias due to early and delayed afterdepolarizations (EAD/DAD), diastolic compression of the coronary microvasculature yielding myocardial ischemia, and depression of left ventricular ejection fraction (LVEF).The Ca^{++} overload results in mitochondrial dysfunction, reduced ATP, and increased oxidative stress-all of which may occur during any reperfusion injury of surgery, also depressing LVEF, which RAN mitigates.

Reducing Perioperative Ami Risk

We added RAN to CAD therapy in 51 anginal patients and MACE (unstable angina, AMI [STEMI, non-STEMI],elective coronary revascularization, cardiac death) was compared to a well-matched cohort of 59 asymptomatic CAD patients. Mean follow-up was 6.1 yrs. Symptomatic CAD patients are well known to have a worse prognosis than asymptomatic patients. However, RAN reduced MACE 37% (p=0.0274): non-STEMI, unstable angina, and death by 31%, even though only 35% had an ischemic (+) MPI stress test.

Reducing Perioperative Ventricular Arrthytmias

Premature ventricular contractions (PVCs) are caused by (1) disorders of impulse conduction (reentrant, fixed-coupled) or (2) impulse initiation: (a)triggered (common),non-fixed coupled, caused by early or delayed afterdepolarizations(EADS,DADs),or (b) enhanced automaticity (less common). Another unique mechanism of action of RAN is that it reduces EADs and DADs. We treated 59 patients with triggered PVCs, typically refractory to other drugs with RAN. Ninety-five% of patients responded, including a 91% reduction in runs of VT. No proarrhythmia occurred (nor has any ever been reported; in fact, RAN protected against proarrhythmias in animal experiments).

Reducing Perioperative Pulmonary Edema Risk

Acute, decompensated CHF carries an 8% perioperative death rate. We compared changes in LVEF, SB, and MACE (cardiac death, VT/VF,CHF admissions) in 109 NYHA class 2-4 CHF(systolic and diastolic) patients, all fully ACC/AHA guideline-treated,54 of whom had RAN added (mean follow-up 23.4 mo.).RAN increased LVEF in 70% of patients on average 11 EFUs(p=0.018)(23% of patients had ≥15 EFUs increase);LVEF was unchanged or decreased in those 55 patients not receiving RAN.The increase in LVEF can occur within 1 week.

MACE was reduced by 40%: deaths by 57%,VT/VF by 53%, CHF admissions by 22%.RAN decreased SB from 2.42 to 1.98(p=0.019).The other patients' SB increased from 2.61 to 4.28(p=0.039).This is of major

importance, since when SB was ≤2.5,81% of patients were MACE-free; when SB was >2.5, 59% of patients suffered MACE(identical to the results in the CAD study).In a separate study including 132 CHF patients, SB >2.5 had a sensitivity of 0.59,OR 7.03(CI 4.59-10.78), specificity of 0.83,PPV of 0.64, NPV of 0.80 for MACE.

Is there a downside to RAN? Not that I can fathom. In the 14 yrs. since its launch, I know of not a single death attributed to it. Its most frequent side effects (6%) are headache, dizziness w/o BP change, nausea, and constipation. It steady states by 72hr (precisely when perioperative MACE peaks), is metabolized by CYP3A (so cut statin dose ½),and interacts with P-gp (reduce digoxin dose ½) and OCT2(limit metformin to 1700 mg/d). Do not use in patients with stage 4 or 5 chronic renal disease.The other absolute contraindication is RAN allergy.

I plan to do a RAN perioperative MACE reduction trial. Until its completion, what can we do? Based upon my publications:

- ❖ CAD pts. with a PHx of angina,nitrate use,dyspnea(? angina equivalent)
- ❖ Pts. with a PHx CHF
- ❖ Pts. with frequent PVCs, couplets, or runs of VT

Should be taking RAN regardless of needed surgery, not because of it. So why not start 500mg b.i.d.p.o.,attempting to increase to 1000mg b.i.d. p.o. after 3d,at least 1-4wks.preoperatively?If surgery is an emergency or urgent, start RAN 1000mg bid ASAP.

Would Preoperative (R)Alpha Lipoic Acid((R)Ala) Be Helpfull Preventing Perioperative Sudden Cardiac Death In Type 2 Diabetics (Dm Ii)?

We just completed a prospective, open-label cohort 133 DM II patient study (83 took the natural antioxidant, over the counter, (r) ALA; 50 controls, mean follow-up 6.31 yrs.). (r)ALA (mean dose 300mg b.i.d.) reduced sudden cardiac death (SCD) by 43%(p=0.0076) via preventing the decrease in cardio-protective parasympathetic activity caused by Diabetic Autonomic Neuropathy and Cardiovascular Autonomic Neuropathy (CAN), present (often asymptomatically) in at least 65% of DM II patients. The reduction in SCD began within 3 months. So I have all my DAN and CAN DM II patients on (r) ALA unless autonomic function testing (which typically has not been done) by me is normal.

References

1. Murray G.Cardiac perioperative MACE: could ranolazine safely reduce it ≥ 35%?.J Thoracic Disease and Cardiovascular Surgery, 1(1).
2. Weiser T, Haynes A, Molina G, Lipsitz S, Esquivel M, Uribe-Leitz T, et. al (2015) Estimate of the global volume of surgery in 2012:an assessment supporting improved health outcomes.Lancet. Apr;385cSuppl 2:511.
3. Puig-Barbera J,Martinez-Calderon S,Vila-Sanchez M.Cardiac complications of major elective non-cardiac surgery:Incidence and risk factors.
4. Sabate S, Mases A, Guilera N, Canet J, Castillo J, Orrego, et.al. (2011) Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery.British Journal of Anaesthesia,107(6):879-90.
5. Lee T,Marcantonio E,Mangione C,Thomas E, Polanjczyk C, Cook F,et.al (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.Circulation. Sep 7; 100(10):1043-1049.
6. Bilimoria K,Liu Y,Paruch,J,Zhou L,Kmiecik T,Ko C,et.al (2013) Development and evaluation of the universal ACS NSQIP surgical risk calculator:A decision aide and informed consent tool for patients and surgeons.J Am Coll Surg. Nov;217(5):833-842.
7. Gupta P,Gupta H,Sundaram A,et.al (2011) Development and validation of a risk calculator for prediction of cardiac risk after surgery.Circulation.124:381-387.
8. Fleisher L, Fleischmann K, Uretsky B, Wijeysundera D,Auerbach A, et al (2014) ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery.JACC.2014 Dec.;64(22):e77-137.
9. Kristensen S, Knuuti J, Saraste A, Anker S, Botker H, et al (2014) ESC/ESA guidelines on non-cardiac surgery:cardiovascular assessment and management.Eur J Anaesthesiol.31:517-73.
10. Murray G,Colombo J (2016) Ranolazine therapy reduces non-st-segment elevation myocardial infarction and unstable angina in coronary disease patients with angina.Int J Anjgiol.25:159-164.
11. Murray G (2016) Ranolazine is an effective and safe treatment of adults with symptomatic ventricular contractions due to triggered ectopy. Int J Angiol; 25:242-51.
12. Murray G,Colombo J (2019) Routine measurements of cardiac parasympathetic and sympathetic nervous systems assists in primary and secondary risk stratification and management of cardiovascular clinic patients.Clinical Cardiol Cardiovascular Med.,3:27-33.
13. Sellers D, Srinivas C,Djaiani G (2018) Cardiovascular complications after non-cardiac surgery.Anaesthesia.2018 Jan.;73(S1):34-42.

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