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Review Article

Cardiac Perioperative MACE: Could Ranolazine Safely Reduce it ≥ 35%?

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Abstract

The Society of Thoracic Surgery Score and Euro II Score are tools for estimating major adverse cardiac events (MACE [death {or morbidity}, renal failure, stroke, prolonged ventilation, CSW infection, reoperation, prolonged admission]) after cardiac surgery.

Key words: ranolazine; perioperative MACE; cardiac surgery

Short Title: Ranolazine and Cardiac Perioperaive MACE

Introduction

The Society of Thoracic Surgery Score and Euro II Score are tools for estimating major adverse cardiac events (MACE [death {or morbidity}, renal failure, stroke, prolonged ventilation, CSW infection, reoperation, prolonged admission]) after cardiac surgery. Although deaths average approximately 3%, predicted mortality can exceed 20% [1]. Hyperlactatemia occurs in 1.3%, most commonly due to acute congestive heart failure (CHF) [2].Chronic CHF patients suffer Vasoplegia in 29% [3]. Troponin elevations are frequent, although an AMI diagnosis incidence is 3% (up to 12%), most commonly after surgery involving the mitral valve or cardiac arrest [4-7].Post- operative ventricular arrhythmias (POVA) are present in 1.7% of patients, more commonly in the elderly, those with chronic CHF, after emergency surgery, or when left ventricular mass index is > 188m/m^2 [8,9].

We are as poor in mitigating perioperative MACE as we are as good at predicting it. Amiodarone and chronic beta blockade help some [4,10], but we need more. I propose ranolazine may be our safe pharmacologic salvation, as a result of my 14 years' experience with its use in coronary disease, congestive heart failure, and ventricular arrhythmia (also atrial fibrillation). I will briefly detail my published studies done in non-surgical patients below; I have no reason to suspect that any of ranolazine's profound benefits (37-40% MACE reduction) would not occur perioperatively.

RANOLAZINE

Ranolazine has 2 main mechanisms of action (MOC) [11-15]:

i. 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 are present in CAD and CHF(31%-59% of guideline-treated patients[11-14]).We found when SB was ≤ 2.5, 80% of 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 (11) in 483 patients with risk factors or established CAD or CHF, mean f/u 4.92 yrs (**Table 1**).

Events

	Sensitivity	OR	Specificity	PPV	NPV
SB > 2.5(all)	0.59	7.03(CI 4.59-10.78)	0.83	0.64	0.80
+MPI (CD)	0.31	1.93(CI 0.90-4.16)	0.88	0.67	0.62
LVEF≤0.33(CHF)	0.67	3.46(CI 1.49-8.05)	0.67	0.50	0.81

For predicting MACE, **SB > 2.5(p<0.001) *outperformed* +MPI(reversible defect[s]) in all 3 groups, *outperforming* Framingham in Group 1, & 2DE LVEF ≤ 0.33 in Group 3.**

In CDR patients, Framingham Risk Score (14.5% vs 12.15%) was not useful

Table 1: Sympathovagal Balance (SB) prediction of MACE

ii. Inhibition of the cardiac $Na_{v1.5}$ late inward sodium current(I_{Na}) 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 the 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 [15] (EAD/DAD, Figure 1, Table 2), 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 occur during the reperfusion injury of cardiac surgery (16), depressing LVEF. Ranolazine mitigates this [16,17].

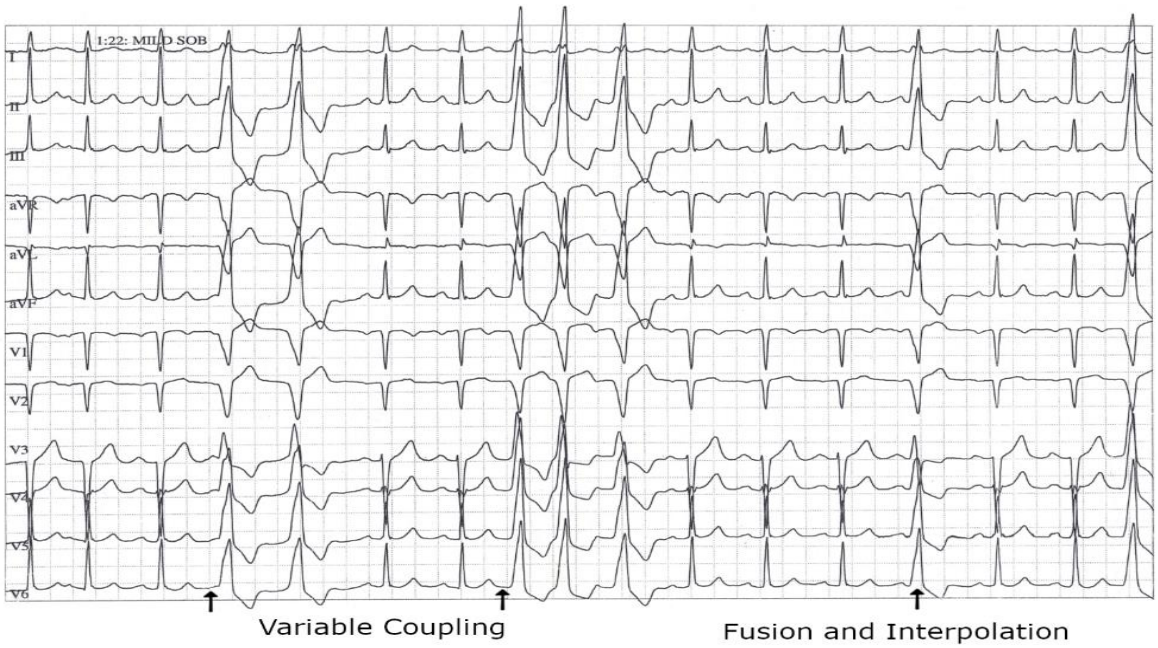

Figure 1: ECG typical of patients with PVCs due to EADs/DADs

	PreRAN	PostRAN	p value
Total QRS	102,667	99,826	p=ns
Isolated PVC	13,329	3,837 (-71%)	p<0.001
V bigeminy	4,168	851(-80%)	p<0.001
V couplets	374	81(-78%)	p<0.001
Runs VT	56	5(-91%)	p<0.001

Table 2: 24 HR. HOLTERS OF PATIENTS RESPONDING TO RANOLAZINE*

*95% (56/59) of patients had their ventricular ectopy reduced by ranolazine.PVC = premature ventricular contractions;RAN = ranolazine;V = ventricular;VT= ventricular tachycardia

In our studies, when ranolazine was **added** to guideline therapy in 81 CHF patients, over 1-2 yr. mean f/u in these 2 studies, high SB corrected in 83% of patients (p=0.033), and CAN improved in 67% (12), LVEF increased in 70% of patients an average of 11 ejection fraction units(EFUs) (p<0.001)(Table 3)(13). Improvement begins within 1 week. MACE (cardiac death, ventricular tachycardia/fibrillation, hospital CHF admission) was reduced by 40% [13].

CHANGE IN LVEF

	ΔEFU ≤ -7	-6 ≤ ΔEFU ≤ +6	ΔEFU ≥ +7	p
RANCHF (N=54)	1 (2%)	27 (50%)	26 (48%)	<0.001
NORANCHF (N=55)	8 (15%)	43 (78%)	4 (7%)	<0.001

Table 3: Ranolazine(RAN)CHFpatientsvs.controls(NORAN)

In our CAD study[14], mean f/u 6 yrs., ranolazine reduced MACE(acute coronary syndromes, elective revascularization,cardiac death) by 37%(p=0.0105). In our triggered Ventricular arrhythmia study (15),(Figure 1, Table 2), 95% of patients responded to ranolazine.

RANOLAZINE AND CARDIAC SURGERY MACE

In light of these studies, ranolazine should reduce perioperative CHF, ventricular (and atrial) arrhythmias, and ischemia. It might reduce the vasoplastic syndrome as well. In this syndrome, there is a dramatic increase in sympathetic (S) tone.The resulting high beta 2 stimulation of the vasculator contributes to the refractory vasodilatation characteristic of this syndrome [3]. Ranolazine should reduce S, allowing vessels to be more responsive to vasopressor therapy.

Is there a downside to ranolazine? 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% of patients) are headache, dizziness w/o BP change, nausea, and constipation.There may be a tiny,clinically insignificant creatinine increase, and Hgb A1C decreases by 0.6% 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 ranolazine allergy.It can be used with any antiarrhythmic.Torsades de pointes requires [1] prolongation of the QT interval (usualy to > 500 msec); [2] afterdepolarizations; and [3] transmural dispersion of repolarization. Ranolazine only prolongs the QT 6 msec, reduces afterdepolarizations, and does not cause dispersion of repolarization [13,15].

Conclusions

Based upon my publications, ranolazine should reduce perioperative complications:

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

should be taking ranolazine regardless of needed surgery, not just because of it. 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 1000mg b.i.d. as soon as the patient can start it.

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