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Can Attenuation of the Perioperative Stress Response Prevent Intermediate or Long-term Cardiovascular Outcomes among Patients Undergoing Noncardiac Surgery?

Editor's Note: This is the second in a series of four Editorial Views on long-term outcomes after anesthesia and surgery. This series adds to other recent Editorial Views in ANESTHESIOLOGY and includes a discussion of broadening our research outside of the operating room to prevention of wound infections, cancer spread, cardiovascular morbidity and mortality, chronic postsurgical pain, and rare complications. ANESTHESIOLOGY will sponsor special sessions in 2010 on the topic of long-term outcomes at annual meetings of the Japanese Society of Anesthesiologists, the European Society of Anesthesiology, and the American Society of Anesthesiologists.

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THERE are at least two potential pathways through which perioperative events may increase the risk of intermediate (*i.e.*, 1 yr or less after surgery) and long-term (*i.e.*, more than 1 yr after surgery) cardiovascular outcomes. First, perioperative events (*e.g.*, myocardial ischemia) may result in unstable coronary artery plaques that are prone to fissure and cause acute thrombosis weeks to months later. Second, perioperative myocardial infarction (MI) may result in myocardial scaring that may lead months to years later to a major cardiovascular outcome (*e.g.*, heart failure, cardiac arrest, cardiovascular death).

Unfortunately, no direct imaging or molecular studies are available for evaluating whether perioperative events result in unstable coronary artery plaques. Less direct evidence that supports the first hypothesized pathway comes from three small prospective studies.[1–3] Wallace *et al.* undertook a nested cohort study within a 200-patient perioperative β-blocker trial.[1] This study demonstrated that perioperative myocardial ischemia (detected on Holter electrocardiography) on postoperative days 0–2 was a univariate predictor of 2-yr mortality (36 patients died; relative risk 2.06; 95% confidence interval [CI] 1.04–4.06).

Pasternack *et al.* undertook a prospective cohort study of 385 patients.[2] Logistic regression demonstrated that only total perioperative percentage time ischemic of 1% or more (based on continual electrocardiography monitoring for an average of 31 h after surgery) and age were statistically significant independent predictors of cardiovascular outcomes (44 patients died, and 17 suffered MI during 2-yr follow-up; estimates of association were not reported).[2]

Mangano *et al.* undertook a prospective cohort study of 444 consecutive patients with or at high-risk of coronary artery disease who were discharged home after surgery.[3] During the 2-yr follow-up, 47 patients suffered cardiac complications as defined by a broad composite that included cardiac death and nonfatal MI. Multivariable analysis demonstrated that postoperative myocardial ischemia (detected on Holter electrocardiography) was an independent predictor of long-term cardiac complications (hazard ratio 2.2; 95% CI 1.1–4.3).[3]

Several studies support the second hypothesized pathway that perioperative MI may lead to a major cardiovascular outcome months to years later. Five small studies (total of 753 patients) all demonstrated that an elevated troponin measurement after surgery was a statistically significant independent predictor of mortality (total of 98 deaths) within 1 yr of surgery.[4–8] Two small studies (total of 840 patients) both demonstrated that an elevated troponin measurement after surgery was a statistically significant independent predictor of mortality (total of 162 deaths) up to 4 yr after surgery.[9,10] The prospective cohort study by Mangano *et al.* also demonstrated that a perioperative MI was an independent predictor of a cardiac complication (hazard ratio, 20.0, 95% CI 7.5–53.0) at 2-yr follow-up.[3] Finally, a large (105,951 patients) Veterans Affairs study that used prospective and administrative data demonstrated that a perioperative MI was an independent predictor of 8-yr mortality (37,743 deaths, hazard ratio 1.5, 95% CI 1.4–1.6).[11]

There are at least two potential explanations for these study results. First, the groups of patients (*e.g.*, patients with and without perioperative myocardial ischemia) in each study had a similar extent of cardiovascular disease and a similar risk of subsequent events before surgery, and the occurrence of the perioperative event changed the patients' long-term prognosis. A second potential

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Table 1. Intermediate and Long-term Impact of Perioperative β-blockers

First Author (yr)	Year	β-Blocker (Targeted Dose)	Primary Outcome	Duration f/u	Tx Group, Events/Patients	Cx Group, Events/Patients	Effect (95% CI)
Mangano[13]	1996	Atenolol (50% MDTD)	Total mortality	24 months	13/99	23/101	RR = 0.58 (0.31 to 1.07)*
Poldermans[14]	2001	Bisoprolol (started at 25% MDTD, allowed titration to 50%)	Cardiac death or nonfatal MI	22 months	9/59	32/53	OR = 0.16 (0.01 to 0.39)†
Juul[15]	2006	Metoprolol CR (25% MDTD)	Cardiac composite 1	18 months	99/462	93/459	HR = 1.06 (0.80 to 1.41)
Yang[16]	2006	Metoprolol (25% or 50% of MDTD depending on weight)	Cardiac composite 2	6 months	28/246	30/250	RRR = 6.2% (−58.4 to 43.8%)
Zaugg[17]	2007	Bisoprolol (25% or 50% of MDTD depending on hemodynamics)	Cardiac composite 3	12 months	25/110	24/109	HR = 0.97 (0.55 to 1.69)

* Authors did not include all deaths in their analysis; Table 1 includes all deaths in an intention-to-treat analysis. † Unilike all other trials, patients continued study drug during long-term follow-up.

Cardiac composite 1 = composite outcome including: all-cause mortality, acute myocardial infarction (MI), unstable angina, or congestive heart failure; cardiac composite 2 = cardiac death, nonfatal myocardial infarction, unstable angina, or new congestive heart failure, new atrial or ventricular dysrhythmia requiring treatment; cardiac composite 3 = cardiovascular mortality, nonfatal myocardial infarction, unstable angina, congestive heart failure, and cerebrovascular insult; CI = confidence interval; Cx = control; f/u = follow-up; HR = hazard ratio; MDTD = maximum daily therapeutic dose; metoprolol; CR = extended-release metoprolol succinate; OR = odds ratio; RR = relative risk; RRR = relative risk reduction; Tx = treatment.

explanation is that perioperative myocardial ischemia and infarction are markers of more severe underlying cardiovascular disease and thus a worse prognosis.

If the first explanation is correct, then preventing perioperative myocardial ischemia or MI may prevent intermediate or long-term cardiovascular outcomes; if the second explanation solely accounts for the demonstrated associations, then preventing perioperative myocardial ischemia or MI is unlikely to affect distant events.

Although it is not possible to draw firm conclusions on the basis of the current evidence, the consistency of the signal in the adjusted analyses across the perioperative studies and the strong evidence that myocardial ischemia and MI alter intermediate and long-term prognosis in the nonoperative setting suggests that perioperative events independently alter intermediate and long-term cardiovascular prognosis. Therefore, exploring whether interventions that prevent perioperative myocardial ischemia or MI result in a decrease in intermediate or long-term cardiovascular complications is warranted.

Can Perioperative β-blockers Prevent Intermediate or Long-term Cardiovascular Outcomes

Before considering the intermediate and long-term impact of administering a β-blocker around the time of noncardiac surgery, it is relevant to determine whether a β-blocker can attenuate the perioperative stress response. A meta-analysis of high quality β-blocker randomized controlled trials (RCTs) among patients undergoing noncardiac surgery demonstrated at 30-day follow-up a lower rate of myocardial ischemia among patients assigned a β-blocker (43 of 1,059 patients) compared to control (76 of 1,059 patients, odds ratio 0.42, 95% CI 0.27–0.65, I^2 20%), and a lower rate of nonfatal MI among patients assigned a β-blocker (174 of 5,610 patients) compared to control (240 of 5,426 patients, odds ratio 0.72, 95% CI 0.59-0.87, I^2 0%).[12]

Five trials have reported whether the favorable perioperative effects of a β-blocker translate into intermediate or long-term cardiovascular benefits (table 1).[13–17] Only one small trial (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study [DECREASE]) with few events (112 patients, with 41 patients experiencing the primary outcome) and methodological limitations (unblinded and recruitment was stopped early for an unexpected very large treatment effect)[18] demonstrated a statistically significant long-term benefit with β-blocker therapy.[14] Unlike all the other trials, patients in this trial continued the study drug during the long-term follow-up[14]; therefore, DECREASE addresses a different question than the other trials that evaluated the intermediate or long-term effects of a β-blocker only given around the time of surgery.

The largest trial (Diabetic Postoperative Mortality and Morbidity [DIPOM], 921 patients with 192 patients experiencing the primary outcome) demonstrated no effect on major cardiovascular outcomes at 18 months of follow-up. Although some authors have suggested that the difference in results of the β-blocker trials is the result of variations in the dosing (*i.e.*, high dose *vs.* low dose), the current evidence does not support this perspective (table 1); it is more likely that the differences relate to chance and methodological quality (*i.e.*, the high-quality trials demonstrate a consistent signal).

Although the current trials do not provide encouraging evidence that a perioperative β-blocker affects intermediate or long-term cardiovascular outcomes, there is still a limited amount of data. The PeriOperative ISchemic Evaluation (POISE) Trial (perioperative extended-release metoprolol succinate with a target dose of 50% of the maximum daily therapeutic dose *vs.* placebo) included 8,351 patients and will report the 1-yr follow-up data next year; 22 countries have completed their direct patient follow-up, and Canada will complete its 1-yr follow-up through its national databases in 2010.[19] If POISE demonstrates a benefit from a perioperative β-blocker at 1 yr, clinicians and patients will have to balance this benefit against the 30-day excess of death and stroke with a β-blocker, as demonstrated in POISE and the high-quality RCTs.[12,20]

The prior perioperative β-blocker discussion, except for a few patients in the trial by Mangano *et al.*, relates to patients who were not taking chronic β-blocker therapy before surgery. Therefore, these trials do not inform the intermediate or long-term effects of continuing, withholding, or titrating β-blockers around the time of noncardiac surgery among patients who have a history of taking a β-blocker chronically. Potentially relevant issues to the short, intermediate, and long-term effects include the following: the potential exacerbation of cardiac ischemia that may occur from stopping a β-blocker acutely before a patient undergoes surgery, and the β-blocker dose that is safe in the nonoperative setting may still exacerbate clinically significant hypotension after surgery and result in the negative consequences demonstrated in POISE.[20] Until a large high-quality trial is undertaken to directly inform this issue, physicians will have to use indirect evidence to individualize the perioperative management of each patient who is chronically on a β-blocker.

Can Perioperative α_2 Agonists Prevent Intermediate and Long-term Cardiovascular Outcomes

RCT evidence suggests that α_2 agonists can attenuate the perioperative stress response (*e.g.*, reduce perioperative myocardial ischemia).[21,22] Wallace *et al.* undertook an RCT evaluating the effect of 4 days of perioperative clonidine in patients undergoing noncardiac surgery.[23] Clonidine demonstrated an absolute risk reduction of 5.4% for mortality at 30 days (total of 5 deaths, $P = 0.048$) and an absolute risk reduction of 14% for mortality at 2 yr (total of 38 deaths, $P = 0.035$). These encouraging but limited data (Wallace is the only clonidine trial that followed patients beyond 30 days) highlight the need for further RCTs to examine whether perioperative clonidine reduces long-term mortality.

Conclusion

Perioperative cardiovascular events appear to affect intermediate and long-term cardiovascular outcomes. The current β-blocker evidence is not encouraging, but we will have more data in 2010. Although the clonidine evidence is encouraging, there is a need for confirmatory trials. Considering that globally 200 million adults undergo noncardiac surgery annually highlights why there is an urgent need for large high-quality RCTs to establish ways to ensure that patients obtain the benefits of their noncardiac surgery without suffering a major cardiovascular outcome that compromises their quality or duration of life in the short, intermediate, or long-term.

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