Postoperative use of b-blockers

Arnaoutoglou Eleni

Athens, 2011
The leading cause of postoperative morbidity and mortality?

Perioperative myocardial infarction

- Pathogenesis is complex: CAD, genetic predisposition, postoperative hypercoagulability, elevated levels of perioperative hormones
- >80% PMI occur early after surgery
- Etiology of Postoperative Myocardial Infarction: prolonged ischemia
ASSOCIATION OF PERIOPERATIVE MYOCARDIAL ISCHEMIA WITH CARDIAC MORBIDITY AND MORTALITY IN MEN UNDERGOING NONCARDIAC SURGERY

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Abstract Background. Adverse cardiac events are a major cause of morbidity and mortality after noncardiac surgery. It is necessary to determine the predictors of these outcomes in order to focus efforts on prevention and treatment. Patients undergoing noncardiac surgery sometimes have postoperative cardiac events. It would be helpful to know which patients are at highest risk.

Methods. We prospectively studied 474 men with coronary artery disease (240) or at high risk for it (231) who were undergoing elective noncardiac surgery. We gathered historical, clinical, laboratory, and physiologic data during hospitalization and for 6 to 24 months after surgery. Myocardial ischemia was assessed by continuous electrocardiographic monitoring for two days after surgery.
Avoid postoperative myocardial ischemia…

- Postoperative myocardial ischemia is an independent predictor of adverse cardiac outcome
- It is strongly associated with both short and long term cardiac morbidity
  
  Mangano et al, JAMA 1992
  Landesberg et al, Lancet 1993
  Yang, Can J Anesth 2010

- Postoperative period is more important
Avoid postoperative myocardial ischemia

• Little is known about the manner in which postoperative risk factors influence PMI

• PMI is often associated with: hemodynamic changes, particularly elevated HRs (pain, blood loss, fluid shifts)
Avoid postoperative myocardial ischemia

May the use of prophylactic b-blockers therapy reduce the incidence of postoperative MI???
Postoperative Prophylactic Administration of β-Adrenergic Blockers in Patients at Risk for Myocardial Ischemia

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Perioperative myocardial ischemia (MI) is associated with postoperative cardiac morbidity. Postoperative sympatholysis may reduce the incidence of MI. This study evaluated such a reduction postoperatively with the administration of prophylactic β-blockers in patients undergoing elective total knee arthroplasty with epidural anesthesia and postoperative epidural analgesia. One hundred seven patients were preoperatively randomized into two groups, control and β-blockers, who received postoperative esmolol infusions on the day of surgery and metoprolol for the next 48 h to maintain a heart rate less than 80 bpm. Patients were followed for ST segment depression by using a Holter monitor and adverse cardiac outcomes. Postoperative electrocardiographic ischemia was significantly more prevalent in the control group compared with the β-blocker group during esmolol blockade (0 of 52 vs 4 of 55; P = 0.04) and tended to be more common in the control group the next two days (8 of 55 vs 3 of 52; P = 0.135). In addition, the number of ischemic events (control, 50; β-blockers, 16) and total ischemic time (control, 709 min; β-blocker, 236 min) were also significantly different from the control group. Myocardial infarctions and cardiac events were more common in the control group, but these differences were not significant. Our results suggest that the use of prophylactic β-blocker therapy may reduce the incidence of postoperative MI.

(Anesth Analg 2000;90:1257–61)

b-blockers have been advocated to reduce the incidence of PMI as they reduce myocardial oxygen consumption and hence the incidence and degree of ischemia
The degree of cardio protection afforded by b-blockers is directly related to the degree of heart rate reduction!!!

Does Tight Heart Rate Control Improve Beta-Blocker Efficacy? An Updated Analysis of the Noncardiac Surgical Randomized Trials

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Duminda N. Wijeysundera, MD†
Keyvan Karkouti, MD, MSc†
Stuart McCluskey, MD, PhD*†
Gordon Tait, PhD*

BACKGROUND: Recent meta-analyses assessing the efficacy of perioperative β-blockade trials have failed to show a reduction in postoperative morbidity and mortality. Tight control of heart rate (HR) has been suggested to improve these outcomes. Meta-analyses have not considered the influence of tight HR control on the efficacy of perioperative β-blockade.

METHODS: Using previously published search strategies, we identified all randomized trials evaluating perioperative β-blockers after noncardiac surgery. This search yielded 10 trials with 2176 patients. We used the data from these studies to correlate measures of HR control with major postoperative outcomes, primarily in-hospital myocardial infarction (MI). Odds ratio (OR) and 95% confidence intervals (CI) were calculated, and metaregression was performed correlating measures of HR control with MI.

RESULTS: The combined results of all studies did not show a significant cardioprotective effect of β-blockers, with considerable heterogeneity among the studies (OR = 0.76; 95% CI = 0.4–1.4; P = 0.38 heterogeneity; I² = 34%). However, grouping the trials on the basis of maximal HR showed that trials where the estimated maximal HR was <100 bpm were associated with cardioprotection (OR = 0.23; 95% CI = 0.08–0.65; P = 0.05) whereas trials where the estimated maximal HR was >100 bpm did not demonstrate cardioprotection (OR = 1.17; 95% CI = 0.79–1.80; P = 0.43) with no heterogeneity. Moreover, metaregression of the HR response to β-blockade against the log OR of postoperative MI demonstrated a linear association between the effect of β-blockade on the mean, maximal, and variation in HR and the OR of an MI (r² = 0.63; P < 0.001) where a larger effect of β-blockers on HR was associated with a decreased incidence of postoperative MI. Across all studies, β-blockade resulted in a reduction in perioperative HR (weighted mean difference: 8.6 bpm; 95% CI = 9.6 to −7.6; P = 85.3%) with considerable heterogeneity. This large heterogeneity in HR response to β-blockade was found to be related, in part, to the type of β-blocker, specifically, metoprolol, and the concomitant use of calcium channel blockers. Calcium channel blocker use and β-blockers other than metoprolol resulted in more effective control of HR. There was wide variability in the HR response to β-blockade. Twenty-five percent of patients receiving β-blockers had episodes when the HRs were more than 100 bpm, although 15% of placebo patients also had bradycardia, which would have required a dose reduction had they been administered β-blockers. Finally, this analysis found that perioperative β-blockade was associated with an increased incidence of bradycardia (OR = 3.49; 95% CI = 2.4–5.9) and congestive heart failure (OR = 1.68; 95% CI = 1.00–2.8).

CONCLUSIONS: The trials that achieve the most effective control of HR are associated with a reduced incidence of postoperative MI, suggesting that effective control of HR is important for achieving cardioprotection. Second, this analysis demonstrates that administration of β-blockers does not reliably decrease HRs in all patients, and may be associated with increased side effects. Judicious use of combination therapy with other drugs may be necessary to achieve effective postoperative control of HR.

POISE study

Beta-blockers:

• ↓ the risk for cardiac events (MI, AF, CI)
• ↑ the risk of severe stroke and overall death
But…

The doses used?
Timing of initiation of therapy?
Postoperative period is more clinically important
Bleeding, anemia, sepsis..
Limited number of assessments on surgical wards, supervision by physicians who have little experience with perioperative hemodynamics
Postoperative administration of b-blockers

In which patients?
• Withdrawal of chronic beta-blockade is associated with a significant increased risk of adverse cardiac events in different patient population

• Retrospective data suggest a significantly higher mortality if beta-blocker is discontinued postoperatively

Effect of β-blocker Prescription on the Incidence of Postoperative Myocardial Infarction after Hip and Knee Arthroplasty

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Background: The American College of Cardiology/American Heart Association guidelines recommend β-blockade for selected low- and intermediate-risk noncardiac surgery patients. The authors evaluated the effect of perioperative β-blockade on postoperative myocardial infarction (POMI) in low-risk patients undergoing intermediate-risk surgery.

Methods: Patients who underwent elective hip or knee arthroplasty between January 1, 2002 and June 30, 2006 were identified. POMI was defined as a Troponin T value of more than 0.1 ng·ml⁻¹. Patients were divided into three groups: those prescribed a β-blocker on the day of surgery and throughout their hospital stay (or 7 days, whichever came first), those prescribed β-blockers within 48 hours of surgery, and those not prescribed β-blockers.

Results: Of the 643 patients analyzed, 497 were prescribed β-blockers, and 146 were not. The incidence of POMI was significantly lower in the group prescribed β-blockers compared to the group not prescribed β-blockers (1.4% vs. 11.1%, p < 0.001).

Conclusion: β-blockers reduce the incidence of POMI, and should be prescribed perioperatively to patients undergoing hip or knee arthroplasty.

78% of POMIs occurred in patients with no more than one cardiac risk factor suggesting that efforts to reduce the incidence of POMI should not be limited to high risk patients.
ACCF/AHA Fleischmann et al 2009
ESC Poldermans et al 2009

- IHD, MI or high risk surgery (IB)
- Intermediate-risk surgery (IIa,B)
- Initiation (30 days-1 wk),
- Target (60-70 b/min),
- Duration ???
- Postoperative tachycardia: diagnosis and management of potential underlying causes before up-titration!!!
May the use of the short-acting β-selective drug esmolol allow for individualizing drug dosage by titrating the drug to a specific hemodynamic end point thus providing for cardioprotection while minimizing drug-induced bradycardia and hypotension???
The Safety of perioperative esmolol: A systematic review and Meta-analysis of Randomized Controlled Trials
Yu et al. Anesth Analg 2011

- 67 small trials, short duration infusions > 24h in 125 pts
- ↓ myocardial ischemia
- ↓ hypotension as a continuous infusion
- Safety and efficacy!!!
### Incidence of postoperative hypertension

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Frequency of APH (%)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid endarterectomy</td>
<td>9–64</td>
<td>2, 4, 6, 7, 11, 13–15, 19</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>22–54</td>
<td>8, 17, 23–26</td>
</tr>
<tr>
<td>Abdominal aortic surgery</td>
<td>33–75</td>
<td>22</td>
</tr>
<tr>
<td>Radical neck dissection</td>
<td>10–20</td>
<td>3, 27</td>
</tr>
<tr>
<td>Intracranial neurosurgery</td>
<td>57–91</td>
<td>16, 28, 29</td>
</tr>
<tr>
<td>Elective general surgery</td>
<td>3–9</td>
<td>5, 20, 25</td>
</tr>
<tr>
<td>Elective surgery (noncardiac)*</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Release of flexion contractures</td>
<td>46</td>
<td>31</td>
</tr>
</tbody>
</table>

*Includes a mix of general, orthopedic, urologic, gynecologic, obstetric, neurologic, otolaryngologic, and minor vascular surgeries.

Am J Health-Syst Pharm 2004; 61: 1661-1673
Acute postoperative hypertension

Mechanism?

APH requires management?

Reverse or treat causes of APH

Ideal agent?
### Table 3—IV Drug Treatment for Postoperative Hypertension*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial dilators</td>
<td></td>
</tr>
<tr>
<td><strong>Nicardipine</strong></td>
<td>100–200-μg increments; 1–5 mg/h</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>50 μg/mL; begin at lowest dose (1–2 mL/h) and titrate upwards; usual dose 0.5–10 μg/kg/min</td>
</tr>
<tr>
<td><strong>Fenoldopam</strong></td>
<td>0.025–0.15 μg/kg/min</td>
</tr>
<tr>
<td>β-Adrenergic blockers</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>1–10 mg in incremental doses; repeat as necessary</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1–5 mg in incremental doses; repeat as necessary</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1 mg in incremental doses; repeat as necessary</td>
</tr>
<tr>
<td><strong>Esmolol</strong></td>
<td>10–50 mg; infusion of 50–200 g/kg/min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>5–20-mg incremental doses; repeat as necessary</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5–20-mg incremental doses</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>0.625–2.5 mg; repeat as needed (usually 4–6 hs)</td>
</tr>
</tbody>
</table>

*Treat pain, hypoxemia, and other underlying physiologic disturbances.

James G. Ramsay Cardiac Management in the ICU Chest, 1999; 115: 138 - 144.
Avoid arterial hypertension after intracranial surgery....

Sympathetic overdrive →
systemic hypertension and tachycardia →
cerebral hyperemia →
the risk of postoperative intracranial edema and hemorrhage
Original contribution

**Esmolol blunts postoperative hemodynamic changes after propofol-remifentanil total intravenous fast-track neuroanesthesia for intracranial surgery**

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**Keywords:** Neuroanesthesia; Fast track; Total intravenous anesthesia; Remifentanil; Propofol; Esmolol

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**Abstract**

**Study Objective:** To investigate whether esmolol is effective in attenuating postoperative hemodynamic changes related to sympathetic overdrive.

**Design:** Clinical study.

**Setting:** Operating room of a university hospital.

**Patients:** 60 ASA physical status I, II, and III patients, age 18 to 65 years, scheduled for elective craniotomy for supratentorial neurosurgery.

**Interventions:** Patients were given total intravenous anesthesia (TIVA) during emergence from anesthesia and up to 60 minutes after extubation. Those patients who had hypertension (defined as an increase in systolic blood pressure >20% from baseline values) and tachycardia (defined as an increase >20% in heart rate from baseline) received a loading dose of 500 \(\mu\)g/kg esmolol in one minute, followed by an infusion titrated stepwise (50, 100, 200, and 300 \(\mu\)g/kg per min) every two minutes.

**Measurements:** The mean dose and duration of esmolol therapy were measured.

**Main Results:** Of 60 patients, 49 (82%) who received propofol-remifentanil TIVA developed significant tachycardia and hypertension soon after extubation. Treatment with esmolol (500 \(\mu\)g/kg in bolus maintained at a mean rate of 200 ± 50 \(\mu\)g/kg per min) effectively controlled hypertension and tachycardia in 45 of 49 patients (92%; \(P < 0.05\)) within a mean 4.30 ± 2.20 minutes. After extubation, mean esmolol infusion time was 29 ± 8 minutes.
Reduction of arrhythmias…

New-onset SVT is associated with increased mortality in postoperative noncardiac ICU patients

Christians KK, Am J Surg 2001
Brathwaite D, Chest 1998

SVT after CTS is associated with prolonged ICU or hospital stay

Neustein SM, J Cardiothorac Vasc Anesth 1998
Creswell LL, Semin Thorac Cardiovasc Surg 1999
Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications

Olaf Sander, MD; Ingeborg D. Welters, MD, PhD; Pierre Foëx, MD, DPhil; John W. Sear, MD, BSc, PhD

Objective: To assess the incidence of major cardiac events in critically ill patients with a high risk of cardiac complications presenting with an elevated heart rate.

Design and Setting: Observational, retrospective study in a 15-bed medical/surgical Intensive Care Unit (ICU) at a university hospital for a period of 12 months.

Patients: We studied patients with a high risk of cardiac complications, according to the revised Goldman index, who were treated for at least 36 hrs in the ICU. Patients presenting with prolonged elevated heart rate, defined as a heart rate >95 beats/min for >12 hrs in at least one 24-hr period of their ICU stay, were investigated. Cardiac high-risk patients not developing this criterion served as controls. Major cardiac events, defined as nonfatal myocardial infarction, nonfatal cardiac arrest, and cardiac related death, were the primary outcome measures.

Results: From a total of 791 patients, 69 patients were assessed as cardiac high-risk patients. Of 39 patients with prolonged elevated heart rates, 19 (49%) sustained major cardiac events, whereas in the control group of 30 patients, only four patients (13%) had a major cardiac event ($p = .002$; odds ratio, 6.2). Patients with elevated heart rate had to be treated 4.5 days longer in the ICU ($p = .01$), whereas the ICU and 30-day post-ICU discharge survival rates did not differ significantly.

Conclusions: In this study, we provide evidence for an increased incidence of major cardiac events in critically ill, cardiac high-risk patients with a prolonged elevated heart rate during their ICU stay. In addition, elevated heart rate was associated with a significantly longer ICU stay. (Crit Care Med 2005; 33:81–86)

Keywords: heart rate; arrhythmia; myocardial infarction; survival rate; risk assessment; intensive care
Reduction of arrhythmias…

• 16 trials, 2571 participants, 4-90 days, discharge from hospital, propranolol, metoprolol, sotalol, atenolol

• β-blockers reduced the frequency of life-threatening perioperative ventricular arrhythmias in patients undergoing CS, not in non-CS
Reduction of arrhythmias...


• 26 trials, 4058 participants, 4-45 days, discharge from hospital, ns, propranolol, atenolol, metoprolol, sotalol, acebutolol

• β-blockers reduced the incidence of AF 63% after CS
Reduction of arrhythmias…


• 3000 participants, discharge from hospital, ns, 4-10 days, 3 mts, metoprolol, sotalol, nadolol, atenolol, propranolol, acebutolol, timolol

• β-blockers reduced the frequency of SVT arrhythmias after CS, but not after non CS
Treatment of new-onset atrial fibrillation in non cardiac intensive care unit patients: A systematic review of randomized controlled trials

Salmaan Kanji, PharmD; Robert Stewart, MD; Dean A. Fergusson, MHA, PhD; Lauralyn McIntyre, MD, MSc, FRCPC; Alexis F. Turgeon, MD, MSc, FRCPC; Paul C. Hébert, MD, MSc, FRCPC

Objective: Atrial fibrillation is a common problem associated with morbidity and mortality in critically ill patients; however, evidence-based treatment recommendations are lacking. The objective of this systematic review was to evaluate the efficacy of pharmacologic rhythm control of new-onset atrial fibrillation in noncardiac, critically ill adults.

Data Source: Citations identified from an electronic search of Medline, the Cochrane register of controlled trials, and Embase databases (1966 to August 2006) were independently reviewed by two investigators.

Study Selection: All prospective randomized controlled trials evaluating pharmacologic rhythm conversion regimens for new-onset atrial fibrillation in (noncardiac surgery) critically ill adult patients were included. The primary end point was atrial fibrillation resolution.

Data Extraction: Using a standardized data extraction form, data related to study design, population characteristics, pharmacologic intervention, and outcome measures were collected.

Data Synthesis: Four trials met inclusion criteria from 1995 citations screened. Of the 143 evaluable patients in these trials 89 (76%) had atrial fibrillation while the remaining ones had other atrial tachyarrhythmias. Drugs evaluated for rhythm conversion included amiodarone (n = 25), procainamide (n = 14), magnesium (n = 19), flecainide (n = 15), esmolol (n = 28), verapamil (n = 15), and diltiazem (n = 27). The definition of treatment success ranged from conversion within 1 hr to conversion within 24 hrs. No study evaluated maintenance of conversion, and one study included hemodynamically unstable patients. Lack of methodologic homogeneity prevented any pooled analysis.

Conclusions: Using the current published literature, we cannot recommend a standard treatment for atrial fibrillation in noncardiac critically ill adult patients. Clinical trials evaluating rhythm conversion in critically ill populations outside of cardiac surgery are lacking. Further trials that address goals of care in hemodynamically stable and unstable patients and utilize standardized definitions of successful cardioversion are required. (Crit Care Med 2008; 36:1620–1624)

Key Words: atrial fibrillation; supraventricular arrhythmia; intensive care; critical care; systematic review
<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Design</th>
<th>Blinding</th>
<th>Patients</th>
<th>N</th>
<th>Intervention</th>
<th>Patients with AF</th>
<th>Definition of Cardioversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman (1993)</td>
<td>Randomized comparator controlled</td>
<td>No</td>
<td>Med/surg</td>
<td>24</td>
<td>Amiodarone (3 mg/kg bolus then 10 mg/kg over 24 hrs) vs. Procainamide (10 mg/kg bolus then 4 mg/min × 2 hrs, then 3 mg/kg × 2 hrs then 2 mg/kg × 20 hrs)</td>
<td>16/24</td>
<td>Within 12 hrs</td>
</tr>
<tr>
<td>Moran (1995)</td>
<td>Randomized comparator controlled</td>
<td>No</td>
<td>Med/surg</td>
<td>42 (34 evaluable)</td>
<td>Amiodarone (5 mg/kg bolus then 10 mg/kg over 24 hrs) vs. Magnesium (37 mg/kg bolus, then 25 mg/kg/hr × 24 hrs)</td>
<td>18/34</td>
<td>Within 24 hrs</td>
</tr>
<tr>
<td>Barranco (1994)</td>
<td>Randomized comparator controlled</td>
<td>No</td>
<td>Med</td>
<td>30</td>
<td>Flecaïnide (2 mg/kg bolus then 1.5 mg/kg over 1 hr) vs. Verapamil (0.15 mg/kg bolus then 0.005 mg/kg/min × 1 hr)</td>
<td>11/30</td>
<td>Within 1 hr</td>
</tr>
<tr>
<td>Balzer (1998)</td>
<td>Randomized comparator controlled</td>
<td>No</td>
<td>Surg</td>
<td>55</td>
<td>Esmolol (12.5–50 mg repeated bolus until HR &lt;110 beats/min then 50–100 mcg/min) vs. Diltiazem (20 mg bolus then 10–20 mg/hr)</td>
<td>44/55</td>
<td>Within 12 hrs</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td>143</td>
<td></td>
<td><strong>89/143 (76%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

HR, heart rate; AF, atrial fibrillation.
Figure 2. Conversion rates (and 95% confidence intervals) for all drugs evaluated. Conversion rates reported as percents with 95% confidence intervals for reported conversion rate at 12 hours for each drug except flecainide and verapamil which are presented as 1 hour conversion rates.
The Role of the Perioperative Period in Recurrence After Cancer Surgery

Anita Gottschalk, MD,*** Soral Sharma, MD,† Justin Ford, MD,‡ Marcel E. DuFourez, MD, PhD,‡ and Mohamed Touatine, MD‡

A wealth of basic science data supports the hypothesis that the surgical stress response increases the likelihood of cancer recurrence and metastasis during and after cancer surgery. Recent advancements in molecular biology and immunology have revealed that cancer cells can evade the immune system and stimulate angiogenesis, leading to tumor recurrence and metastasis.

The idea that surgery promotes local cancer recurrence and distant metastasis is not new. In fact, in the 19th century, observation concerning the negative impact of surgical manipulation on cancer progression was documented. A Committee in 1869, called "The Surgical and Medical," examined the effect of surgery on the recurrence of cancer, believing that only surgery (the operation of the organ of cancer) should be removed, because other organs would be affected by the treatment.

Today, evidence suggests that surgical removal of cancer is associated with the risk of local recurrence and distant metastasis. Nonetheless, despite our advances in cancer treatment techniques, metastatic recurrence still remains the leading cause of death from cancer.

Several theories have been advanced to explain the frequent incidence of cancer recurrence, most notably residual disease, dissemination of tumor cells at the time of surgery, and possible tumor dormancy. When cancer cells are quiescent before progressing growth, surgery can cause profound metabolic, immunological, inflammatory, and angiogenic impact. This surgical stress response includes the release of inflammatory mediators that have been directly and indirectly implicated in cancer growth. These mediators can cause an upregulation of major proinflammatory pathways, resulting in a disruption of normal tumor homoeostasis, thus promoting local and distant metastasis. Importantly, the type of anesthesia may play a role in this process and could indirectly promote angiogenesis or cell development. In this article, we briefly review possible mechanisms involved in the effect of surgery on cancer recurrence and discuss how anesthetic management could potentially influence these mechanisms, thereby affecting long-term patient outcome.

IMMUNITY AND CANCER

The idea that the immune system recognizes cancerous cells as "foreign" and thereby destroys them was first enunciated by Paul Ehrlich in 1885, and was later expanded by Burnet and Tomlinson in the Immunochemical hypothesis. They suggested that the immune system could actually eliminate cancer cells before they are clinically detected. It was clear, however, that the immune system is able to destroy cancer cells completely, as evidenced by the persistence of tumors despite a competent immune response. Subsequently, the concept of immunodetection was born. Under this theory, the immune system is believed to "inadvertently" promote tumor progression by clearing some tumor cells and thereby selecting for those cells that are most resistant to immune-system clearance. The process of immunodetection is divided into 3 steps:

1. The first step is the "elimination phase" where cells of the innate and adaptive immune system recognize and destroy tumor cells. The second step is the "squillization phase" where is postulated that the immune system hyper-reacts to kill the tumor cells to check for a variable period of time. The third step is called "escape" whereby tumor cells evade immunity and become overt tumor. The mechanisms underlying these events are not completely understood and include alterations in antigen presentation, secretion of immunoregulatory agents, and stimulation of inhibitory pathways. Thus, the immunosuppressive effects of surgery through the release of proinflammatory mediators and the cytokines could shape the journey of residual minimal disease toward immune evasion and growth. This hypothesis remains without an effective support at this time.
Possible targets for metastatic prevention by the anesthesiologist...
Perioperative Use of β-blockers and COX-2 Inhibitors May Improve Immune Competence and Reduce the Risk of Tumor Metastasis

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2Department of Biochemistry, Tel Aviv University, Tel Aviv, Israel
3Outcomes Research(TM) Institute, Louisville, KY, USA

Background: COX inhibitors and β-blockers were recently suggested to reduce cancer progression through inhibition of tumor proliferation and growth factor secretion, induction of tumor apoptosis, and prevention of cellular immune suppression during the critical perioperative period. Here we evaluated the perioperative impact of clinically applicable drugs from these categories in the context of surgery, studying natural killer (NK) cell activity and resistance to experimental metastases.

Methods: F344 rats were treated with COX-1 inhibitors (SC560), COX-2 inhibitors (indomethacin, etodolac, or celecoxib), a β-blocker (propranolol), or a combination of a COX-2 inhibitor and a β-blocker (etodolac and propranolol). Rats underwent laparotomy, and were inoculated intravenously with syngeneic MADB106 tumor cells for the assessment of lung tumor retention (LTR). Additionally, the impact of these drug regimens on postoperative levels of NK cytotoxicity was studied in peripheral blood and marginalizing pulmonary leukocytes.

Results: Surgery increased MADB106 LTR. COX-2 inhibition, but not COX-1 inhibition, reduced postoperative LTR. Etodolac and propranolol both attenuated the deleterious impact of surgery, and their combined use abolished it. Surgery decreased NK cytotoxicity per NK cell in both immune compartments, and only the combination of etodolac and propranolol significantly attenuated these effects. Lastly, the initiation of drug treatment three days prior to surgery yielded the same beneficial effects as a single pre-operative administration, but, as discussed, prolonged treatment may be more advantageous clinically.

Conclusions: Excess prostaglandin and catecholamine release contributes to postoperative immune-suppression. Treatment combining perioperative COX-2 inhibition and β-blockade is practical in operated cancer patients, and our study suggests potential immunological and clinical benefits.

Key Words: COX-2 inhibitors—β-Adrenergic blockers—Metastases—Perioperative.

• Powe DG et al. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget 2010
In conclusion....

Beta-blockers postoperatively

- Avoid postoperative myocardial ischemia
- Avoid acute hypertension after surgery
- Reduction of arrhythmias
- Metastatic prevention