High-Dose β-Blockers and Tight Heart Rate Control Reduce Myocardial Ischemia and Troponin T Release in Vascular Surgery Patients

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Background—Adverse perioperative cardiac events occur frequently despite the use of beta (β)-blockers. We examined whether higher doses of β-blockers and tight heart rate control were associated with reduced perioperative myocardial ischemia and troponin T release and improved long-term outcome.

Methods and Results—In an observational cohort study, 272 vascular surgery patients were preoperatively screened for cardiac risk factors and β-blocker dose. Beta-blocker dose was converted to a percentage of maximum recommended therapeutic dose. Heart rate and ischemic episodes were recorded by continuous 12-lead electrocardiography, starting 1 day before to 2 days after surgery. Serial troponin T levels were measured after surgery. All-cause mortality was noted during follow-up. Myocardial ischemia was detected in 85 of 272 (31%) patients and troponin T release in 44 of 272 (16.2%). Long-term mortality occurred in 66 of 272 (24.2%) patients. In multivariate analysis, higher β-blocker doses (per 10% increase) were significantly associated with a lower incidence of myocardial ischemia (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.51 to 0.75), troponin T release (HR, 0.63; 95% CI, 0.49 to 0.80), and long-term mortality (HR, 0.86; 95% CI, 0.76 to 0.97). Higher heart rates during electrocardiographic monitoring (per 10-bpm increase) were significantly associated with an increased incidence of myocardial ischemia (HR, 2.49; 95% CI, 1.79 to 3.48), troponin T release (HR, 1.53; 95% CI, 1.16 to 2.03), and long-term mortality (HR, 1.42; 95% CI, 1.14 to 1.76).

Conclusion—This study showed that higher doses of β-blockers and tight heart rate control are associated with reduced perioperative myocardial ischemia and troponin T release and improved long-term outcome in vascular surgery patients. (Circulation. 2006;114[suppl I]:I-344–I-349.)

Key Words: β-blockers ■ heart rate ■ ischemia ■ surgery

Large clinical trials have demonstrated the beneficial effect of β-adrenoreceptor blocking agents in preventing perioperative cardiac morbidity and mortality in patients undergoing major noncardiac vascular surgery.1–3 The ACC/AHA has therefore recommended the use of β-blockers in surgical patients who are at increased risk for postoperative adverse events.4 The mechanism by which β-blockers exert their cardioprotective effect remains not completely understood, but proposed mechanisms include reduction in heart rate, restoration of the myocardial oxygen supply–demand balance, and prolongation of coronary diastolic filling time.5,6 Despite the presumed benefits of perioperative β-blocker therapy, cardiovascular mortality and nonfatal myocardial infarction may still occur in patients using β-blockers, especially during the stressfull perioperative period characterized by rapidly changing physiological responses.7,8 Inadequate dosage of β-blockers and insufficient reduction of heart rate during the perioperative period may possibly explain the occurrence of adverse cardiac events in these patients.

Early postoperative episodes of myocardial ischemia, ie, during the first 48 hours after surgery, are an important correlate of adverse cardiac outcome after surgery.2 Continuous 12-lead electrocardiographic monitoring and measurement of cardiac troponins are accurate and reliable methods for the detection of perioperative myocardial ischemia. We conducted this study to assess whether higher doses of β-blockers and tight heart rate control during surgery are associated with a reduced incidence of perioperative myocardial ischemia as detected by continuous 12-lead electrocardiographic monitoring, with reduced troponin T release and with a reduced incidence of long-term mortality and cardiac events.

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Methods

Patients

The study population consisted of 273 patients undergoing elective major vascular surgery at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period July 2001 to August 2005. The study was performed with informed consent of all patients. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block, and atrial fibrillation were excluded. Before surgery, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mm Hg), diabetes mellitus (fasting glucose level ≥7.0 mmol/L, or insulin therapy), hypercholesterolemia (plasma cholesterol level ≥5.5 mmol/L or cholesterol-lowering medication), and renal failure (serum creatinine level ≥2.0 mg/dL [177 μmol/L]). The presence of definite coronary artery disease was indicated by a previous myocardial infarction, previous coronary intervention, or present stable angina pectoris. The use of chronic β-blocker therapy was noted and β-blocker dose was converted to a percentage of maximum recommended therapeutic dose (MRTD) according to the Food and Drug Administration’s (FDA) recommendations. β-blocker dose was determined according to established protocols.10 The left ventricle was divided into 17 segments and wall motion was scored on a 5-point scale (a score of 1 indicating normal; 2, mild hypokinesia; 3, severe hypokinesia; 4, akinesis; and 5, dyskinesia). The results were considered positive if wall motion in any segment decreased by ≥1 grades during testing. Patients who had a positive result on dobutamine stress echocardiography were considered to be at high risk for myocardial ischemia developing in the perioperative period.

Dobutamine Stress Echocardiography

Before surgery, all patients underwent dobutamine stress echocardiography for preoperative risk stratification, which was performed according to established protocols.10 The left ventricle was divided into 17 segments and wall motion was scored on a 5-point scale (a score of 1 indicating normal; 2, mild hypokinesia; 3, severe hypokinesia; 4, akinesis; and 5, dyskinesia). The results were considered positive if wall motion in any segment decreased by ≥1 grades during testing. Patients who had a positive result on dobutamine stress echocardiography were considered to be at high risk for myocardial ischemia developing in the perioperative period.

Holter Electrocardiography

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder; NorthEast Monitoring Inc), starting 1 day before surgery and up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 seconds every minute. The frequency response was 0.05 to 150 Hz. Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced investigators who were blinded to the patient’s clinical data. After excluding all abnormal QRS complexes, the ambulatory ECG recordings were analyzed for ST segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST segment changes, lasting at least 1 minute and shifting from baseline to more than 0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point. Heart rate was recorded and means of heart rate before, during, and after surgery were calculated. A measure of absolute heart rate change was used and expressed as the sum of the differences between the mean heart rate before, during, and after surgery. The mean heart rate after surgery was calculated from a standard 24-hour time period. For example, a patient with a mean heart rate of 75, 80, and 85 before, during, and after surgery, respectively, had an absolute heart rate change of 5+5=10 bpm.

Perioperative Management and Follow-Up

Before surgery, patients with beta-blockers were asked about medication adherence. Beta-blockers were withheld if patients presented with a systolic blood pressure <100 mm Hg or with a heart rate <50 bpm. The dosage of β-blockers on the day of surgery and after surgery was kept similar to the preoperative β-blocker dose. It was ascertained that β-blockers were administered on the morning of surgery and on each day after surgery until discharge. β-blockers were administered orally or by naso-gastric tube in patients who were not able to take medication orally. All patients received standard perioperative pain management. Surgical procedures were classified as abdominal aortic aneurysm repair (129 patients, 47%), lower extremity revascularization (100 patients, 37%), and carotid artery surgery (43 patients, 16%). In all patients, troponin T levels were measured on postoperative days 1, 3, and 7 and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured using a whole blood rapid test (TropT version 2; Roche Diagnostics, Mannheim, Germany). A value of >0.1 ng/mL was used to define positive troponin T levels.

During a median follow-up of 2.6 years, outpatient visits were scheduled every 3 months after discharge. Endpoints were mortality and cardiac events (cardiac death and nonfatal myocardial infarction). Nonfatal myocardial infarction was diagnosed when at least 2 of the following were present: elevated cardiac enzyme levels (CK level >190 U/L and CK-MB >14 U/L, or CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/mL), development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris. In case of death, the cause of death was identified. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. No patients were lost to follow-up.

Statistical Analysis

Continuous data were expressed as mean (±SD) and analysis of variance (ANOVA) was used to compare means in different groups of β-blockers. Categorical data are presented as percentages and analyzed using the χ² test with Yates correction. The study group was divided in patients receiving no dose, low-dose (1% to 25% of MRTD), and high-dose (>25% of MRTD) β-blockers. Binary logistic regression analysis was used to study the effect of β-blockers and heart rate on the occurrence of myocardial ischemia and troponin T release. The C-index for the different multivariate logistic regression models was calculated to evaluate how well the model performed. Cox proportional hazards models were used to analyze the effect of β-blockers and heart rate control on postoperative survival and cardiac events. In multivariate analysis, adjustments were made for age, gender, cardiac risk factors according to the Revised Cardiac Risk Index (coronary artery disease, history of congestive heart failure, cerebrovascular disease, diabetes mellitus and renal failure), dobutamine stress test results, hypertension, statins, and angiotensin-converting enzyme inhibitors. Odds and hazard ratios are given with 95% confidence intervals. For all tests, P<0.05 (2-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc, Chicago, Ill). All authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

The baseline characteristics of the 272 patients (mean age 67.4±10.0, 80% male) are presented in Table 1. No significant differences were observed between baseline characteristics in the groups of patients with different doses of β-blockers. A total of 175 patients (64%) were using β-blockers; 3 of these patients (1.7%) presented with renal failure. Dobutamine stress echocardiography before surgery detected myocardial ischemia in 78 patients (29%). The majority of the 78 patients with a positive preoperative stress test received β-blockers (n =69, 88%). Mean duration of surgery (from intubation to skin closure) was 5.4±2.1 hours.
Mean duration of continuous 12-lead ECG registration was 62.9±13.8 hours. The mean heart rate during 12-lead ECG monitoring was 72.7±12.4 bpm. Mean absolute heart rate change was 9.7±7.1 bpm. Higher doses of β-blockers were significantly associated with lower heart rates during 12-lead ECG monitoring (78.8±11.8, 73.1±11.1, and 68.0±10.9 bpm in patients with no dose, low-dose, and high-dose β-blockers, respectively, \(P<0.0001\), and nonsignificantly with lower absolute heart rate change (11.3±8.8, 9.6±7.2, and 8.5±9.7 bpm in patients with no dose, low-dose, and high-dose β-blockers, respectively, \(P=0.092\)).

**Predictors for Myocardial Ischemia and Troponin T Release**

Myocardial ischemia was detected in 85 patients (31%). A total of 141 periods of myocardial ischemia were detected (33, 61, and 47 periods before, during, and after surgery, respectively). The number of ischemic events per patient ranged from 1 to 5. The median duration of ischemic events was 64.5 minutes (range, 9 to 1020 minutes) and the median ST-segment deviation was 1.5 mm (range, 1.0 to 5.4 mm). Troponin T levels >0.1 ng/mL were measured in 44 patients (16.2%). Troponin T values ranged from 0.1 to 8.14 ng/mL (median, 1.1 ng/mL).

In univariate analysis, higher β-blockers doses, lower heart rates, and lower absolute heart rate change were associated with a lower incidence of myocardial ischemia (for all, \(P<0.0001\), and with a lower incidence of troponin T release (for all, \(P<0.0001\)) (Figure). In multivariate analysis, these associations remained significant (Table 2). In a final multivariate model including β-blocker dose, heart rate, absolute heart rate change, and baseline clinical variables, we found that these variables remained independently associated with myocardial ischemia (β-blocker dose per 10% increase: hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.55 to 0.79, \(P<0.0001\); heart rate per 10-bpm increase: HR, 2.10; 95% CI, 1.52 to 2.91; \(P<0.0001\); absolute heart rate change per 10-bpm increase: HR, 1.46; 95% CI, 1.03 to 2.07, \(P=0.032\) (C-index, 0.86).

**Predictors for Long-Term Mortality and Cardiac Events**

During long-term follow-up, mortality, cardiac death and non-fatal myocardial infarction occurred in 66 (24.2%), 48 (17.6%), and 6 (2.2%) patients, respectively. Multivariate results are summarized in Table 3. In multivariate analysis, higher doses of β-blockers were significantly associated with a reduced incidence of mortality and cardiac events. Higher heart rates and higher absolute heart rate changes were associated with an increased incidence of long-term mortality and cardiac events. We also demonstrated that myocardial ischemia and troponin T release were significant predictors of
The dose of β-blockers, mean heart rate, and absolute heart rate change in relation to myocardial ischemia and troponin T release.
adverse long-term outcome. Interestingly, higher levels of troponin T release were associated with a higher incidence of mortality (HR per 1.0 ng/mL increase: 1.30; 95% CI, 1.03 to 1.68, \( P = 0.037 \)) and cardiac events (HR per 1.0 ng/mL increase, 1.40; 95% CI, 1.05 to 1.85, \( P = 0.027 \)).

### Discussion

The clinical characteristics of our study population demonstrate that coronary artery disease is highly prevalent among patients undergoing major vascular surgery. These patients are therefore at increased risk of adverse postoperative cardiac events and may benefit from perioperative \( \beta \)-blocker therapy.\(^1,^2^\) Several studies have demonstrated the association between perioperative \( \beta \)-blockers and myocardial ischemia reduction. In the study of Mangano et al, up to 10 mg atenolol or placebo was intravenously administered 30 minutes before and after surgery and up to 100 mg/d was orally given throughout the hospital stay (up to 7 days) to 200 noncardiac surgical patients. Continuous 3-lead Holter monitoring showed a 50% reduction of myocardial ischemia in the atenolol treated group during the first 2 postoperative days.\(^2,^11^\) Another study demonstrated in 26 patients with preoperative myocardial ischemia that strict heart rate control (heart rate of 20% below the ischemic threshold) using continuous esmolol infusion significantly decreased the rate of postoperative myocardial ischemia during Holter monitoring.\(^12^\) Two patients experienced a cardiac event: 1 in the placebo and 1 in the esmolol group. Both patients had extensive myocardial ischemia and were unable to maintain target heart rate control, suggesting that heart rate control, more than \( \beta \)-blocker therapy, may be the key element in reducing postoperative ischemia and adverse postoperative events.

Myocardial ischemia and troponin T release are markers for coronary artery disease and have been identified as predictors of adverse cardiac events after noncardiac surgery.\(^2,^13^\) This finding has been confirmed in our study. Moreover, our study also demonstrates that a higher level of troponin T was associated with worse outcome. During the past decades, much attention has been given to the prevention of postoperative cardiac events. The development of cardiac risk scores has allowed clinicians to identify patients at increased risk for adverse postoperative events.\(^14^\) Coronary artery revascularization before elective major vascular surgery has been proposed as preventive measure but does not seem to significantly alter the long-term outcome.\(^15^\) Cumulating evidence suggests encouraging effects of perioperative \( \beta \)-blocker therapy. However, most studies have not included heart rate, absolute heart rate change, and dosage of \( \beta \)-blockers into their analyses, omitting several important potential determinants of postoperative outcome. Our results suggest that higher doses of \( \beta \)-blockers, lower mean heart

### Table 2

#### Multivariate Models to Predict Myocardial Ischemia (Detected by Continuous 12-Lead Electrocardiographic Monitoring) and Myocardial Damage (Troponin T Release)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Myocardial Ischemia</th>
<th>Troponin T Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Dose of ( \beta )-blockers per 10% increase*</td>
<td>0.62 (0.51–0.75)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, per 10 bpm increase*</td>
<td>2.49 (1.79–3.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean heart rate before surgery, per 10 bpm increase*</td>
<td>1.51 (1.19–1.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean heart rate during surgery, per 10 bpm increase*</td>
<td>2.62 (1.88–3.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean heart rate after surgery, per 10 bpm increase*</td>
<td>2.12 (1.62–2.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Absolute heart rate change, per 10 bpm increase*</td>
<td>1.75 (1.25–2.45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, coronary artery disease, history of congestive heart failure, history of cerebrovascular events, diabetes mellitus, renal failure, hypertension, dobutamine stress echocardiography results, statins, and angiotensin-converting enzyme inhibitors.

### Table 3

#### Multivariate Models to Predict Postoperative Mortality and Cardiac Events (Cardiac Death or Nonfatal Myocardial Infarction)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Long-Term Mortality</th>
<th>( P ) Value</th>
<th>Long-Term Cardiac Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazards Ratio (95% CI)</td>
<td>( P ) Value</td>
<td>Hazards Ratio (95% CI)</td>
</tr>
<tr>
<td>Dose of ( \beta )-blockers per 10% increase*</td>
<td>0.86 (0.76–0.97)</td>
<td>0.0080</td>
<td>0.71 (0.60–0.84)</td>
</tr>
<tr>
<td>Heart rate, per 10 bpm increase*</td>
<td>1.42 (1.14–1.76)</td>
<td>0.002</td>
<td>1.56 (1.22–2.00)</td>
</tr>
<tr>
<td>Heart rate prior to surgery, per 10 bpm increase*</td>
<td>1.21 (0.99–1.45)</td>
<td>0.052</td>
<td>1.28 (1.02–1.59)</td>
</tr>
<tr>
<td>Heart rate during surgery, per 10 bpm increase*</td>
<td>1.37 (1.09–1.70)</td>
<td>0.005</td>
<td>1.53 (1.20–1.97)</td>
</tr>
<tr>
<td>Heart rate after surgery, per 10 bpm increase*</td>
<td>1.45 (1.16–1.67)</td>
<td>&lt;0.001</td>
<td>1.62 (1.31–2.02)</td>
</tr>
<tr>
<td>Absolute heart rate change, per 10 bpm increase*</td>
<td>1.37 (1.06–1.77)</td>
<td>0.016</td>
<td>1.60 (1.20–2.13)</td>
</tr>
<tr>
<td>Myocardial ischemia during ECG monitoring*</td>
<td>2.23 (1.25–3.62)</td>
<td>0.0054</td>
<td>4.84 (2.38–9.84)</td>
</tr>
<tr>
<td>Troponin T release*</td>
<td>2.60 (1.49–4.55)</td>
<td>&lt;0.001</td>
<td>3.95 (2.11–7.42)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, coronary artery disease, history of congestive heart failure, history of cerebrovascular events, diabetes mellitus, renal failure, hypertension, dobutamine stress echocardiography results, statins, and angiotensin-converting enzyme inhibitors.
rates, and lower absolute heart rate changes were all important in the reduction of myocardial ischemia, troponin T release, and long-term events.

Reductions in heart rate lead to restoration of the myocardial oxygen supply–demand balance and prolongation of coronary diastolic filling time, being of benefit to the surgical patient with a compromised coronary circulation and exposed to the stressful period of surgery.\(^5,6\) In addition, it might be hypothesized that β-blockers improve outcome after major noncardiac surgery by its anti-inflammatory effect.\(^16\) It also has been demonstrated that elevated heart rates are associated with an increased risk of vulnerable coronary plaque disruption and that β-blockers could reduce the risk of disruption.\(^17\)

We defined absolute heart rate change by the cumulative difference between the mean heart rate before, during, and after surgery. It might be suggested that achieving continuous low levels of heart rate during the whole perioperative period may yield the optimal physiological condition to prevent adverse events. However, further studies are needed to confirm and validate the effect of perioperative heart rate change on postoperative outcome.

Although this study demonstrates strong evidence in favor of high doses of β-blockers, low heart rates, and low absolute heart rate changes, several limitations should be addressed. The major limitation in this study is that β-blockers were not randomly assigned to the patients. We used multivariate analysis to adjust for known possible confounding factors, such as cardiac risk factors according the Revised Cardiac Risk index, indications for β-blocker therapy and cardioprotective medication. Although our study focused on β-blockers, heart rate, and heart rate changes, future studies should evaluate the relation between blood pressure, cardiac output, and postoperative cardiac events. Our results may explain why several previously published studies failed to show a beneficial effect of β-blockers.\(^7,8\) Administration of β-blockers alone might not be sufficient for postoperative risk reduction. Close perioperative heart rate monitoring and heart rate control together with adequate doses of oral or intravenous β-blockers may improve prognosis and may therefore be recommended for all patients undergoing major vascular surgery.

**Disclosures**

None.

**References**


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