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Beneficial Effects from β-Adrenergic Blockade in Elderly Patients Undergoing Noncardiac Surgery

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Background: **Perioperative β-blockade has been shown to improve long-term cardiac outcome in noncardiac surgical patients. A possible mechanism for the reduced risk of perioperative myocardial infarction is the attenuation of the excitotoxic effects of catecholamine surges by β-blockade. It was hypothesized that β-blocker–induced alteration of the stress response was responsible for the reported improvements in cardiovascular outcome. Several variables associated with the perioperative use of β-blockade were also evaluated.**

Methods: **Sixty-three patients were randomly assigned to one of three groups: group I, no atenolol; group II, pre- and postoperative atenolol; group III, intraoperative atenolol. Hormonal markers of the stress response (neuropeptide Y, epinephrine, norepinephrine, cortisol, and adrenocorticotropic hormone) were evaluated preoperatively and for 72 h after surgery.**

Results: **Perioperative β-blockade did not significantly alter the hormonal stress response. However, the β-blocked patients showed improved hemodynamic stability during emergence and postoperatively. They also received less fentanyl intraoperatively (27.7%, $P < 0.0001$), experienced faster early recovery, had lower pain scores, and required less analgesia in the postanesthesia care unit. Cardiac troponin I release was detected in 8 of 19, 4 of 20, and 5 of 20 patients in groups I, II, and III, respectively (not significant). Three patients in group I had cardiac troponin I levels consistent with myocardial infarction.**

Conclusion: **β-blockade does not reduce the neuroendocrine stress response, suggesting that this mechanism is not responsible for the previously reported improved cardiovascular outcome. However, it confers several advantages, including decreased analgesic requirements, faster recovery from anesthesia, and improved hemodynamic stability. The release of cardiac troponin I suggests the occurrence of perioperative myocardial damage in this elderly population, which appears to be independent of the neuroendocrine stress response. (Key words: Adrenal cortex hormones; cardiac troponin I; myocardial ischemia; neuropeptides; perioperative management.)**

REDUCED myocardial ischemia[1,2] and improved long-term cardiovascular outcomes[3] occur with perioperative β-blockade. The mechanisms underlying these beneficial effects are unclear. Attenuation of the excitotoxic effects of perioperative stress hormones, with the potential for inducing myocardial injury, may underlie the cardioprotective effects of β-blockade.[4–6] β-Adrenergic antagonists have also been shown to potentiate minimum alveolar concentration for volatile anesthetics and decrease nociception in a variety of experimental settings, suggesting the potential to decrease intraoperative anesthetic requirements.[7,8] Perioperative β-blockade, however, is relatively underused, particularly in elderly patients.[9] The reluctance to use perioperative β-blockade appears to be based on concerns of producing hemodynamic instability, bronchospasm, and postoperative congestive heart failure.[10]

This controlled study of elderly surgical patients was designed to evaluate two different anesthetic regimens incorporating β-blockade for their ability to ameliorate the perioperative stress response as measured by circulating hormone levels. It was hypothesized that perioperative treatment with atenolol would modulate the neuroendocrine stress response to anesthesia and surgery, suggesting a potential mechanism for the previously re-

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ported improved cardiovascular outcome in β-blocked patients. In addition, the impact of perioperative β-blockade on several aspects of intraoperative management and postoperative recovery was determined. These secondary end points included an assessment of hemodynamic stability, adequacy of anesthetic depth, anesthetic and analgesic requirements, recovery from anesthesia, and myocardial damage as indicated by the release of cardiac troponin I.

Materials and Methods

With institutional review board approval and written informed patient consent, 63 patients 65 yr of age or older scheduled for elective major noncardiac surgery were enrolled in one of following three groups in this randomized, prospective, open-label trial:

- Group I: Perioperative management without atenolol or any other β-adrenergic blocking drugs.
- Group II: Pre- and postoperative administration of atenolol.
- Group III: Intraoperative administration of atenolol.

Inclusion criteria included being scheduled for major elective noncardiac surgery that necessitated general endotracheal anesthesia and being 65 yr of age or older. Exclusion criteria included (1) preoperative treatment with β-adrenergic agonists, β-adrenergic antagonists, or glucocorticoids; (2) second- or third-degree heart block; (3) a nonsinus rhythm seen on an electrocardiogram (ECG); (4) clinically significant congestive heart failure or bronchospasm; (5) systemic infection; (6) surgery within the previous month; (7) neurologic disorders and current use of anticonvulsant or other psychoactive medications.

The study period included the immediate preoperative period through 72 h after surgery. All data were analyzed at the conclusion of the study.

Before surgery, all patients underwent a routine clinical evaluation that included detailed medical history, physical examination, laboratory tests, 12-lead electrocardiography (ECG), and chest radiography. Three separate preoperative measurements of arterial blood pressure (systolic, diastolic, and mean arterial pressure [MAP]) obtained on the ward established individual baseline values. Approximately 1 h before surgery, a radial artery cannula was inserted during local anesthesia after the patient received 50–100 μg fentanyl. Baseline blood samples were drawn 10 min later. No other premedication was administered.

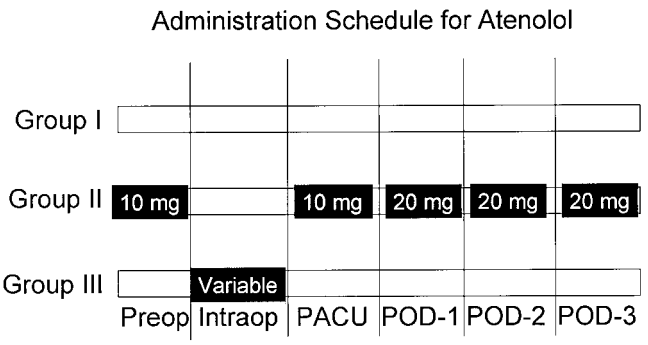

Fig. 1. Schematic diagram of intravenous atenolol administration for each group.

Anesthetic Management

In all groups, anesthesia was induced with fentanyl (100–250 μg), propofol (1.7 mg/kg lean body mass) and rocuronium (0.8 mg/kg). Anesthesia was maintained with isoflurane, 66% nitrous oxide in oxygen, and continuous infusions of fentanyl (1 to 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and rocuronium. All groups were managed to maintain MAP within 20% of preoperative values and a heart rate (HR) between 50–80 beats/min. The methodology for each group is described subsequently. Treatment algorithms were specified in advance to ensure perioperative control of hemodynamic parameters. Hypotension was treated with phenylephrine and hemodynamically significant bradycardia was treated with atropine. Normovolemia and normothermia were maintained. Figure 1 shows the intravenous administration of atenolol for each group.

Group I. Intraoperative HR and MAP were maintained by adjusting the fentanyl infusion or the isoflurane concentration. No β-adrenergic agonists or antagonists were administered at any time during the study.

Group II. The following criteria were necessary before each atenolol dose: an HR of 55 beats/min or more; a systolic arterial pressure of 100 mmHg or more; absence of congestive heart failure, second- or third-degree heart block, and bronchospasm. Atenolol, 5 mg intravenous over 5 min, was administered approximately 30 min before the induction of anesthesia. A second dose of 5 mg atenolol was administered 5 min later if the criteria still were met. No intraoperative β-adrenergic agonists or antagonists were administered. Intraoperative HR and MAP were maintained by adjusting the fentanyl infusion or the isoflurane concentration. Fentanyl and isoflurane doses were not constrained. Atenolol doses were repeated at arrival in the postanesthesia care unit (PACU), with subsequent similar dosing every 12 h starting on

the first postoperative day and continuing until 72 h after surgery.

Group III. Fentanyl was administered at 1 to 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Isoflurane was limited to a maximum allowed end-tidal concentration of 0.4 volume percentage. After this dose was reached, atenolol was administered in 5-mg increments intravenously every 5 min to maintain an HR less 80 beats/min and a MAP within 20% of the preoperative MAP. No β-adrenergic agonists or antagonists were administered during the pre- or postoperative period.

Monitoring

Intraoperative monitoring included measurement of invasive arterial blood pressure, performance of five-lead ECG with continuous ST-segment monitoring (leads II and V5), measurement of pulse oximetry, and measurement of esophageal temperature (Merlin System, Hewlett-Packard, Waltham, MA). End-tidal carbon dioxide level and inhaled anesthetics concentrations were measured by mass spectroscopy (PPG Biomedical, Pittsburgh, PA). Data were acquired every 15 s by a computerized anesthesia record-keeping system (CompuRecord, Anesthesia Recording, Pittsburgh, PA). Bispectral analysis of the electroencephalogram was performed using the A-1050 monitoring system (Aspect Medical Systems, Natick, MA). The A-1050 computes an index ranging from 0 (deeply anesthetized) to 100 (fully awake). Bispectral analysis data were acquired every 5 s beginning shortly before induction of anesthesia until eye opening.

Laboratory Analysis

Blood samples were collected at the following time points: (1) preinduction; (2) intubation + 4 min; (3) incision + 4 min; (4) incision + 60 min; (5) 15 min after arrival in the PACU; and (6) 24 h and (7) 72 h after surgery. Arterial samples were obtained in the operating room and PACU and venous samples were obtained at the surgical ward. The samples were placed on ice immediately and the serum or plasma was separated using a refrigerated centrifuge. Aprotinin (50 μl, Bayer-Miles Laboratories, Kankakee, IL) was added to the samples used for adrenocorticotropic hormone (ACTH) and neuropeptide Y (NPY) determinations. All specimens were immediately frozen (−80°C) until analyzed.

Norepinephrine, epinephrine, NPY, ACTH, and cortisol measurements were performed by laboratory technicians blinded to the study group assignments. The following radioimmunoassays were used: norepinephrine and epinephrine (American Laboratory Products Company, Windham, NH): mean minimum detectable concentration (MMDC) for norepinephrine 15 pg/ml, for epinephrine 5 pg/ml; NPY (Advance Chemical Technology, Louisville, KY): MMDC 1 nmol/ml; ACTH (Incstar, Stillwater, MN): MMDC 15 pg/ml; cortisol (ICN Biomedicals, Costa Mesa, CA): MMDC 0.15 μg/ml. Cardiac troponin I (cTnI) levels were determined by fluorometric assay (Stratus II analyzer; Dade International, Miami, FL): MMDC 0.35 ng/ml. The following prespecified criteria were used to evaluate cTnI levels: $<$ 0.40 ng/ml = normal range for healthy individuals; 0.40–1.49 ng/ml = myocardial damage (micronecrosis), $\geq$ 1.5 ng/ml = myocardial infarction (sensitivity, 93%; specificity, 99%).

Analysis of Clinical Data

To eliminate artifactual data, 2-min medians were computed off-line. Statistical analysis was performed on consecutive 15-s averages of HR, ST-segment changes, and blood pressure and end-tidal isoflurane concentration and from 24 consecutive 5-s samples for the bispectral analysis data. Intraoperative blood pressure and HR were compared between groups using a previously described lability index.[11] Absolute fractional changes between consecutive 2-min medians (between times x and $x + 2$ min) for HR and MAP were calculated according to the formula

$$|\mathrm{FCM}| = \frac{|V_{x+2\mathrm{min}} - V_x|}{V_x}$$

where V is the 2-min median HR or MAP. A lability index for MAP was defined as an $|FCM| > 0.06$ for MAP. A lability index for HR was defined as an $|FCM| > 0.15$. The higher the lability index, the greater the instability in the measured variable.

The times from discontinuation of isoflurane to extubation and to orientation in the PACU (the ability to state date of birth) were recorded. Administered fentanyl doses for induction and maintenance were recorded and reported as $\mu g \cdot kg^{-1} \cdot h^{-1}$ of anesthesia. Total administered dose of morphine in the PACU and pain scores (visual analog scale score 0–10) 30 min after arrival in the PACU also were recorded. Suitability for PACU discharge was assessed every 10 min by a study physician and at least two PACU nurses who were blinded to study group assignments. The following discharge criteria were used: stable vital signs, satisfactory level of alertness (modified Observer's Assessment of Alertness/Sedation Scale score $\geq$ 4),[12] adequate pain control (visual analog scale score $\leq$ 3), and arterial oxygen saturation

greater than or equal to preoperative values (at room air).

Data from patients receiving postoperative epidural analgesia were excluded from analyses of pain scores, suitability for PACU discharge, and morphine usage. Patients who were transferred directly from the operating room to the intensive care unit were excluded from data analysis for recovery.

Medical charts were reviewed and the caregivers were interviewed daily for the occurrence of any adverse events. Physical examinations and interviews, including a semistructured interview to determine explicit intraoperative memory, were performed in the PACU and at 24, 48, and 72 h after surgery. A 12-lead ECG was obtained at least once for each patient postoperatively and interpreted by an anesthesiologist and a cardiologist blinded to group assignment.

Hemodynamic instability was defined by prespecified criteria: systolic arterial pressure less than 90 or greater than 180 mmHg, HR less than 40 or more than 100 beats/min. Clinically diagnosed adverse cardiac outcomes (as opposed to the cTnI measurements) were defined as myocardial infarction (new Q wave, persistent ST–T wave changes as defined by Minnesota Codes,[13] association with any elevation of creatine kinase with creatine kinase MB [muscle–brain] increase $> 5\%$), congestive heart failure (pulmonary edema diagnosed by chest radiography or at least two of the following symptoms: shortness of breath and rales, cardiomegaly, S_3 gallop, jugular venous distention, and peripheral edema diagnosed by an independent managing clinician); and cardiac death, as defined by standard criteria.[13] Intraoperative ischemic episodes were defined as new horizontal or downsloping ST-segment depressions greater than or equal to 0.1 mV, persisting 60 ms or more after the J point, or ST-segment elevations of 0.2 mV or more lasting more than 2 min. With ST depression at baseline, a further depression of 0.15 mV or more from that baseline was necessary.

Statistical Analysis

The sample size was calculated based on published data for NPY levels.[14,15] With an expected difference of 10 nmol/ml between group means, a standard deviation of 10 nmol/ml in each group, an $\alpha = 0.05/3$, and a $\beta = 0.8$, a sample size of 20 patients per group was necessary. A logarithmic transformation was applied to all hormone data to ensure a normal distribution before statistical analysis. Repeated-measures analysis of variance (with the Bonferroni correction) was used to evaluate differences over time between groups for the hormonal and hemodynamic data. Multiple *t* tests were used to compare the hormonal and hemodynamic data at each time point with the respective preoperative baseline measurements. Appropriate corrections for multiple comparisons were applied to the *P* values (Bonferroni correction). All other data were analyzed using an analysis of variance for parametric data or Kruskal–Wallis tests for nonparametric data. Appropriate *post hoc* procedures were used to isolate between-group differences, as indicated in the table and figure legends. Categoric data were analyzed using the two-tailed Fisher exact test. Analyses were performed using StatXact-3 software (Cytel Software, Cambridge, MA) for categoric data, all other analyses were performed using StatView software (Abacus Concepts, Berkeley, CA).

Results

Patient characteristics are listed in table 1. The three groups were similar (no significant differences) with respect to the type and duration of surgery. All patients were found to have coronary artery disease or to manifest at least two risk factors for coronary artery disease, as previously defined by Mangano *et al.*[3] Seventy-three percent of patients had preexisting ST-segment alterations. Data from the four patients who were withdrawn from the study were not included in the analysis (table 1).

Neuroendocrine Stress Response

Peak levels of norepinephrine, epinephrine, ACTH, and cortisol occurred in the PACU or at 24 h postoperatively in all groups (table 2). Norepinephrine levels tended to remain elevated during the entire study period; the other stress parameters returned to baseline levels before 72 h after surgery. Peak NPY levels occurred intraoperatively 1 h after incision, remained elevated in the PACU, and returned to (group I) or decreased below (groups II and III) baseline levels by 72 h. No statistically significant difference in the time course of the neuroendocrine response between groups was observed for norepinephrine, epinephrine, NPY, or cortisol. ACTH levels were lower in patients in group III (table 2).

Hemodynamic Responses

An overview of the intraoperative and postoperative HR and systolic rate-pressure product (RPP) at various

Table 1. Patient Characteristics

	Group I	Group II	Group III
Number of patients	20	23	20
Dropouts	1*	3†	0
Age (yr)	73 ± 6 [65–84]	76 ± 7 [65–88]	75 ± 7 [67–95]
Gender (F/M)	13/6	9/11	15/5
ASA physical status (II/III/IV)	8/9/2	6/13/1	8/7/5
Medical history			
Definite coronary artery disease	7	9	5
Myocardial infarction	6	9	5
Coronary bypass surgery	1	1	0
Percutaneous transluminal coronary angioplasty	1	0	0
Typical angina	4	3	2
Congestive heart failure	3	1	4
Mild chronic obstructive pulmonary disease	5	7	2
Cardiac risk factors			
Hypertension	13	14	17
Current smoking	4	7	3
Diabetes mellitus	2	3	2
Cholesterol >240 mg/dl	9	13	13
Renal insufficiency	0	1	1
Concomitant medication			
Ca^{2+}-blocker	9	4	5
Diuretics	2	6	9
Nitrates	3	2	1
Digoxin	4	1	0
ACEI	4	1	3
Preexisting ST alterations on ECG‡	14	15	14
Duration of anesthesia (h)	3.5 ± 1.7 [1.2–7.8]	4.1 ± 2.0 [1.1–9.1]	3.7 ± 1.1 [1.7–6.0]
Duration of surgery (h)	3.1 ± 1.6 [1.0–7.4]	3.3 ± 1.8 [1.0–8.0]	2.9 ± 1.0 [1.0–4.8]
Type of surgery			
Major abdominal	18	17	17
Intrathoracic	0	1	1
Hip replacement	1	2	2

Data are mean ± standard deviation [minimum, maximum]. The three groups were similar with respect to all patient characteristics.

ACEI = angiotensin converting enzyme inhibitor; ASA = American Society of Anesthesiologists.

* Postoperative treatment with glucocorticoids and β-blocker.

† One patient with a postoperative surgical complication (massive surgical bleeding), one patient with violation of the prescribed choice of anesthetics (propofol instead of isoflurane), one patient with fixed pacemaker rhythm.

‡ Preexisting ST segment alterations on the electrocardiogram (ECG) included left bundle branch block, digoxin-induced ST alterations, and ST alterations caused by left ventricular hypertrophy with associated strain.

time points is presented in figures 2 and 3. During emergence and extubation, HR and RPP were significantly lower in patients in groups II and III. HR and RPP remained significantly below preoperative values up to 72 h after surgery for groups II and III. In patients in group I, HR but not RPP remained significantly increased up to 72 h after surgery.

Intraoperative hemodynamic control was satisfactory in all groups (table 3). The percentage of time for which MAP remained less than 60 mmHg or HR remained less than than 50 beats/min was similar across groups. Compared with patients in group I, a significant decrease in the percentage of time HR remained at more than 80 beats/min was observed for patients in group III ($P = 0.006$; table 3). Lability indices for HR and MAP (table 3), which describe the instability of the measured variable, and the incidences of atropine and phenylephrine use (table 4) were similar for the three groups.

The incidence of perioperative hemodynamic abnormalities is presented in table 5. Episodes of hypotension (systolic arterial pressure < 90 mmHg) occurred in all three groups. Notably, the number of patients with postoperative tachycardia (HR > 100 beats/min) was significantly increased in group I compared with groups II and III (table 5).

Table 2. Perioperative Neuroendocrine Stress Response

	ACTH (pg/ml)			Cortisol (μg/dl)			Norepinephrine (pg/ml)			Epinephrine (pg/ml)			Neuropeptide Y (nmol/ml)		
Group	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
Preoperative	42 [37, 65]	41 [33, 58]	35 [27, 47]	23 [15, 30]	17 [16, 25]	19 [16, 25]	275 [210, 678]	555 [260, 835]	497 [338, 940]	92 [59, 159]	195 [113, 343]	117 [72,184]	12 [7, 20]	14 [9, 20]	11 [7, 18]
Intubation	44 [36, 65]	36 [30, 50]	35 [25, 41]	16‡ [12, 20]	18 [14, 30]	17‡ [14, 24]	265‡ [139, 435]	455 [145, 650]	331‡ [215, 585]	45‡ [18, 75]	52‡ [21, 91]	28‡ [19, 72]	17 [12, 24]	17 [9, 24]	11 [6, 17]
Incision	49 [36, 92]	36 [26, 44]	43 [24, 51]	15‡ [11, 21]	15 [13, 30]	18 [12, 25]	457 [200, 500]	365 [205, 670]	515 [396, 841]	74 [21, 181]	63‡ [23, 172]	101 [45, 223]	14 [10, 22]	15 [11, 27]	11 [6, 15]
Incision + 60 min	86† [52, 126]	72† [51, 96]	66† [47, 89]	35† [29, 54]	37† [31, 44]	35 [31, 45]	600 [374, 1156]	660† [465, 1175]	742 [464, 1190]	149† [103, 520]	256† [115, 445]	227† [137, 471]	22† [16, 31]	21† [16, 30]	20† [12, 27]
PACU	126† [80, 150]	96† [75, 140]	120† [78, 177]	40† [23, 62]	42† [32, 52]	48† [44, 58]	900† [483, 1470]	1,010† [660, 1,750]	748 [490, 1190]	600† [172, 771]	835† [413, 1,062]	710† [410, 1,000]	16† [9, 23]	15† [13, 29]	18† [9, 22]
24 h postoperation	47 [37, 78]	44 [36, 51]	40 [24, 44]	27† [20, 47]	27† [21, 47]	29† [20, 34]	700† [537, 625]	960† [620, 1,625]	905† [468, 1,465]	138† [113, 287]	244 [104, 404]	137 [84, 230]	10 [5, 14]	11‡ [3, 11]	8‡ [6, 10]
72 h postoperation	44 [39, 57]	41 [34, 56]	37 [29, 48]	18 [14, 31]	22† [15, 31]	24 [18, 31]	740† [408, 1,401]	830† [498, 1,500]	655 [413, 1,340]	121† [92, 212]	178 [88, 355]	130† [42, 210]	10 [10, 14]	10‡ [7, 14]	8‡ [6, 11]
ANOVA*		$P = 0.024$			$P = 0.86$			$P = 0.81$			$P = 0.45$			$P = 0.51$	

Circulating concentrations of stress hormones at the indicated time points. All data were log-transformed before analysis. Data are presented as median [25th percentile, 75th percentile].

* Repeated-measures ANOVA was used to evaluate differences over time between anesthetic groups for each hormone. Statistically significant differences between groups were found only for adrenocorticotropic hormone ($P = 0.024$). Pairwise comparisons for adrenocorticotropic hormone (Bonferroni–Dunn *post hoc* test with $P < 0.017$ significant): group I *versus* II, $P = 0.045$; I *versus* III, $P = 0.009$; II *versus* III, $P = 0.48$. Paired *t* tests with Bonferroni correction ($P < 0.008$ significant) compared each time point to preoperative baseline within each group.

† Significantly higher.

‡ Significantly lower than preoperative values.

ACTH = adrenocorticotropic hormone; ANOVA = analysis of variance.

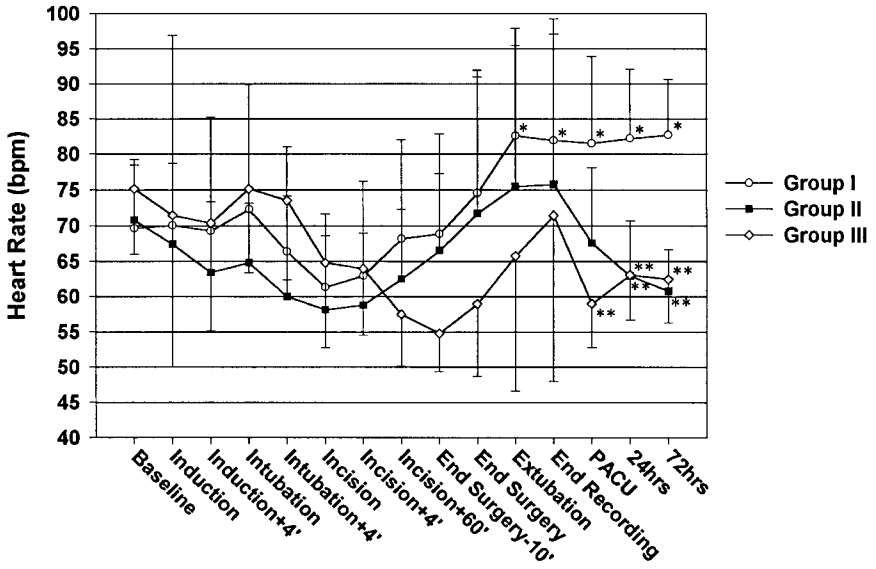

Fig. 2. Heart rate (HR, mean ± SD) at the various time points for each anesthetic group. Repeated-measures analysis of variance (P = 0.035) indicated that the groups differed in HR over time. Differences between groups were analyzed using the Bonferroni–Dunn *post hoc* test (with P < 0.017 significant): group I *versus* II, P = 0.014; group I *versus* III, P = 0.001; group II *versus* III, P = 0.80. Paired t tests with Bonferroni correction for multiple comparisons (with P < 0.01 significant) were used to compare HR at each time point with the respective preoperative baseline value for each group. *Significantly increased compared to baseline values; **Significantly decreased compared to baseline values.

Anesthetic Doses and Recovery from Anesthesia

All patients in group II received 10 mg intravenous atenolol preoperatively and at each scheduled postoperative dose. Patients in group III received a median dose of 20 mg atenolol intravenously, with a minimum of 10 mg and a maximum of 80 mg. Administered doses of anesthetic agents were significantly different among groups (table 4). By design, patients in group III received less isoflurane. On average, patients in group III received 37.5% less isoflurane than patients in groups I and II (P = 0.003). Patients in groups II and III received 27.7% less fentanyl than group I patients (P < 0.0001; table 4). Despite the differences in anesthetic doses, depth of anesthesia, as indicated by average bispectral analysis values, was similar in all three groups (group I: 54 ± 11; group II: 53 ± 10; group III 58 ± 2; analysis of variance P = 0.50). No reports of intraoperative recall were elicited from any patient.

Patients in groups II and III had significantly shorter early recovery times and met prospectively defined PACU discharge criteria sooner than patients in group I patients (table 6). Total morphine doses and pain scores in the PACU also were significantly lower in groups II and III (table 6).

Cardiac Troponin I and Cardiovascular Outcome

None of the patients experienced any adverse cardiac event as assessed by routine clinical examination. Spe-

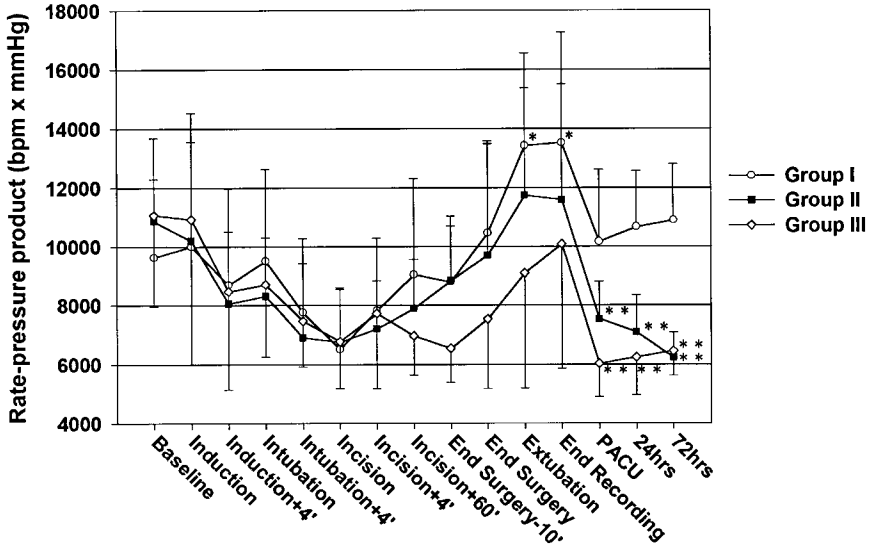

Fig. 3. Systolic rate-pressure product (RPP, mean ± SD) values at various time points for each anesthetic group. Repeated-measures analysis of variance (P = 0.02) indicated that the groups differed in RPP over time. Differences between groups were analyzed using the Bonferroni–Dunn *post hoc* test (P < 0.017 is significant): group I *versus* II, P = 0.016; group I *versus* III, P < 0.0001; group II *versus* III, P = 0.10. Paired t tests with Bonferroni correction for multiple comparisons (with P < 0.01 significant) were used to compare RPP at each time point with the respective preoperative baseline value for each group. *Significantly increased compared with baseline values. **Significantly decreased compared with baseline values.

Table 3. Intraoperative Hemodynamic Responses: Percent of Total Anesthesia Time

	Group I	Group II	Group III	*P*
HR <50 beats/min	0 [0, 27]	1.5 [0, 9]	2 [0, 17]	0.25
HR >80 beats/min	4 [2, 20]	1.5 [0, 10]	0 [0, 4]	0.04*
HR lability (15%)	3 [2, 5]	2 [1, 4]	2.5 [1, 4]	0.60
MAP <60 mmHg	0 [0, 4]	0 [0, 2]	2 [0, 7]	0.21
MAP >110 mmHg	5 [1, 8]	4.5 [2, 14]	1.5 [0, 6]	0.28
MAP lability (6%)	36 [25, 39]	31 [26, 41]	32 [26, 38]	0.96
SAP <90 mmHg	1 [0, 7]	1 [0, 4]	3 [0, 11]	0.12
SAP >160 mmHg	1 [0, 15]	4.5 [0, 7]	3 [0, 8]	0.92

For each patient the time during which the variable satisfied, the listed criteria was calculated for heart rate (HR), mean arterial pressure (MAP), and systolic arterial pressure (SAP) and expressed as a percentage of total anesthesia time (0–100%). A lability index for HR and MAP was calculated as described in the methods section. Data are median [25th percentile, 75th percentile]. Differences between groups were determined using the Kruskal–Wallis test. Groups differed significantly only in the percentage of time the HR remained above 80 beats/min.

* Group I *versus* II; $P = 0.14$; group I *versus* III; $P = 0.006$; group II *versus* III; $P = 0.07$ (Dunn *post hoc* test for multiple comparisons, $P < 0.05$ significant).

cifically, no episodes of intraoperative myocardial ischemia were detected intraoperatively or during retrospective review of the computerized ST-segment data. Postoperative 12-lead ECGs were evaluated for all patients and revealed no evidence of new postoperative myocardial ischemia or infarction.

No patient had detectable levels of cTnI preoperatively. Perioperative release of cTnI (≥ 0.4 ng/ml) was detected in 8 of 19, 4 of 20, and 5 of 20 patients in groups I, II, and III, respectively (fig. 4). Peak levels of cTnI occurred intraoperatively in 6 patients (two from each group) and postoperatively in 11 patients (group I: 6; group II: 2; group III: 3). Three patients in group I were found to have a clinically unrecognized postoperative myocardial infarction if the prespecified cTnI level more than 1.5 ng/ml was used to indicate myocardial infarction.

The 11 patients with postoperative increases in cTnI of 0.4 ng/ml or more had slightly but significantly higher postoperative HRs compared with patients without increases in cTnI (68 ± 14 *vs.* 78 ± 15 beats/min; analysis of variance $P = 0.002$). No correlation was found between hormonal markers of the neuroendocrine stress response and cTnI levels.

Discussion

The sympathetic neuroendocrine profiles (NPY, norepinephrine, and epinephrine) of the three anesthetic regimens were indistinguishable. The ACTH response was decreased in both β-blocker groups; however, cortisol levels were unaffected. Therefore, our principal hypothesis is rejected. Although our sample sizes were small, the study had an 80% statistical power to (and did) detect a minimum difference of 10 nmol/ml NPY in the average value between groups, which is the minimum difference we consider to be clinically significant. Both the pattern of peak concentrations for all measured hormones and the magnitude of responses of our patients are similar to previous reports in younger patients.[16,17] By design, less fentanyl (groups II and III) and isoflurane (group III) were necessary if atenolol was administered. Stress hormone levels would be expected to rise with decreasing doses of anesthetic agents.[18] However, neither neuroendocrine nor hemodynamic evidence of light anesthesia were present in any patient. Consistent with these findings, previous work indicates that esmolol reduces anesthetic requirements,[7,19] and propranolol potentiates opioid analgesia.[20] β-Adrenergic antagonists possess central nervous system–depressant antinociceptive and anxiolytic effects[7,21,22] thought to be caused by central β-blockade, although hydrophilic, esmolol, and atenolol attain plasma and cerebrospinal fluid ratios similar to those of lipophilic β-blockers.[23]

Classically, stress responses are subserved by the hy-

Table 4. Intraoperatively Administered Medication

	Group I	Group II	Group III	*P**
Mean end-tidal isoflurane (%)	0.40 ± 0.18	0.43 ± 0.19	0.25 ± 0.07	0.0006†
Fentanyl ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	1.8 ± 0.5	1.3 ± 0.2	1.3 ± 0.3	<0.0001‡
Phenylephrine (number of patients)	11	14	12	0.70
Atropine (number of patients)	1	0	0	0.32

The doses of anesthetic medications and the incidence of use of resuscitative medications are presented for each anesthetic group. Data are mean ± SD for isoflurane and fentanyl and number of patients who received atropine or phenylephrine intraoperatively.

* Differences between groups were assessed by analysis of variance for isoflurane and fentanyl and Fisher exact test (two-tailed) for phenylephrine and atropine. Pairwise group comparisons were performed using the Bonferroni–Dunn *post hoc* test with $P < 0.017$ significant.

† Isoflurane: group I *versus* II, $P = 0.45$; group I *versus* III; $P = 0.003$; group II *versus* III, $P = 0.0003$.

‡ Fentanyl: group I *versus* II, $P < 0.0001$; group I *versus* III; $P < 0.0001$; group II *versus* III, $P = 0.90$.

Table 5. Incidence of Perioperative Hemodynamic Abnormalities

	Day of Surgery											
	Before Surgery			During Surgery			PACU			Days 1–3 (ward)*		
Group	I	II	III	I	II	III	I	II	III	I	II	III
Systolic blood pressure < 90 mmHg	0	0	0	7	5	7	2	1	4	2	5	2
Systolic blood pressure >180 mmHg	2	0	2	5	3	1	7	4	3	3	1	1
Heart rate <40 beats/min	0	0	0	1	0	2	0	1	1	0	3	0
Heart rate >100 beats/min	0	0	0	1	0	0	10*	1	2	5**	0	0

The number of patients in each group exhibiting hemodynamic abnormalities at each time period, as described in the Methods section is presented. Data obtained on the ward were reported by the clinical staff. Differences between groups at each time period were determined by Fisher exact test (two-tailed, $P <$ 0.05 significant). Significantly more patients in group I exhibited a heart rate >100 beats/min in the postanesthesia care unit and on the surgical ward.

* $P = 0.0005$.

† $P = 0.002$.

pothalamic pituitary axis and the sympathetic nervous system.[24] The choice of anesthetic technique can significantly effect stress hormone responses,[25,26] and thus measurement of these responses became an important means for comparing techniques.[27,28] General anesthesia is thought to affect stress responses through action on the central nervous system, including the spinal cord.[29,30] Although β-antagonists are thought to act principally on peripheral receptors, they also have substantial anesthetic-modulating central effects.[7,21,22] We hypothesized that the addition of β-adrenergic blockade to an anesthetic regimen would significantly modulate humoral stress responses. A corollary of this hypothesis is that, in the absence of such modulation, humoral stress responses would increase in magnitude if alteration in the heart rate and blood pressure were blocked at a peripheral level.

Circulating hormone concentrations represent a composite of direct secretion, neural overflow, metabolism, excretion, and regional variations in hormone activity.[31] Norepinephrine in plasma largely represents the transmitter released by sympathetic nerves that has spilled over into the circulation.[32] In addition to releasing norepinephrine, sympathetic postganglionic neurons release neuropeptides. In particular, cells that release both norepinephrine and NPY innervate blood vessels,[33,34] particularly in the coronary circulation.[34] Tachycardia, left-ventricular failure,[35] and angina[36] are associated with increased NPY levels in cardiac patients. Thus, we selected NPY as our principle variable. Glucocorticoid levels were measured to assess hypothalamic–pituitary–adrenal activity and ensure that a stress response had occurred.

The group II regimen was modified from Mangano *et al.*,[3] principally by limiting the postoperative administration of atenolol to 3 days. This was consistent with our average duration of stay for the elderly patients included in this study but still allowed a certain degree of comparison to their larger study that included outcome measures. The group III regimen offers the advantage of easy integration into anesthetic care paradigms. In compari-

Table 6. Recovery Data

	Group I	Group II	Group III	*P*
Patients extubated in operating room	16/19	12/20	16/20	0.25
Extubation time (min)	22 ± 9	12 ± 5*	9 ± 6*	<0.0001
States date of birth (min)	25 ± 11	12 ± 8*	11 ± 9*	<0.0001
Fit for PACU discharge (hr)	4.9 ± 1.6	2.7 ± 1.5*	2.1 ± 1.1*	<0.0001
PACU morphine dosage (mg/hr)	2.4 ± 1.1	1.4 ± 0.7*	1.4 ± 1.1*	0.004
VAS (after 30 min in PACU)	4.6 ± 1.8	3.3 ± 1.8*	2.3 ± 1.3*	0.008

Data for main characteristics of recovery from anesthesia for each anesthetic group are presented. Recovery data were assessed as described in the methods section. Differences between groups were determined using the Fisher exact test for number of patients extubated (two-tailed, $P < 0.05$) or by analysis of variance followed by the Bonferroni–Dunn *post hoc* test for multiple comparisons ($P < 0.017$ significant). Data are mean ± SD or number of patients. Data from patients receiving postoperative epidural analgesia were excluded from analysis of pain scores, suitability for PACU discharge, and morphine usage (two patients each from group II and III). Patients who were directly transferred from the operating room to the intensive care unit were excluded from analyses for recovery (one patient from group I, and two patients from group II).

VAS = visual analog scale (0 = no pain to 10 = worst possible pain); PACU = postanesthesia care unit.

* $P < 0.05$ *versus* group I.

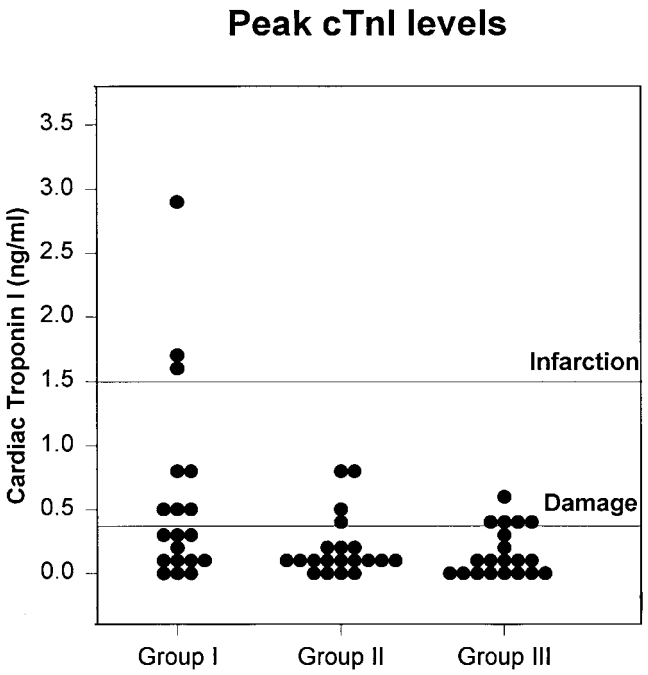

Fig. 4. Cardiac troponin I (cTnI) levels for patients in each anesthetic group. Peak levels of cTnI (only the highest level for each patient is presented) measured during the perioperative period are presented. Values are presented as nanograms/milliliter serum. Values above 0.4 ng/ml (*lower*) are indicative of micronecrosis. Values above 1.5 ng/ml (*upper*) are indicative of myocardial infarction.

son, group II necessitated clinical monitoring and evaluation in the postoperative period, which was in addition to standard nursing workloads.

Control of Hemodynamic Responses

Maintenance of intraoperative hemodynamic parameters within prespecified limits was achieved with all three anesthetic regimens. The use of pre- and intraoperative (up to 80 mg) atenolol was well-tolerated. The incidence of significant bradycardia was not increased in the atenolol-treated patients, even if atenolol was combined with fentanyl and phenylephrine, which are known to provoke bradycardia. β-Blockade significantly reduced the incidence of tachycardia and high RPP, particularly during emergence and extubation and in the postoperative period, times which have been associated with increased hemodynamic instability and myocardial ischemia.[2,37] The hemodynamic effects of atenolol in group III patients persisted up to 72 h postoperatively. The expected duration of activity of atenolol (24 h); decreased perioperative renal clearance, particularly in elderly patients; and increased vagal tone after higher doses of atenolol may have contributed to this prolonged effect.[38] These data suggest that peri- and intraoperative administration of atenolol is safe, effective, and well-tolerated by elderly patients with significant coexisting diseases.

Anesthetic Doses and Recovery from Anesthesia

By design, group III patients received the lowest doses of isoflurane. Nonetheless, satisfactory levels of unconsciousness were achieved in all patients. The bispectral analyses were similar across groups and were within the range in which lack of recall is expected.[39] This is consistent with reports of satisfactory levels of unconsciousness produced by lower doses of volatile anesthetics than are necessary to control HR and blood pressure during surgical stimulation.[18,40,41]

More rapid recovery from anesthesia and reduced postoperative analgesic requirements were observed in the β-blocker groups. Significantly faster recovery was reported previously in patients receiving metoprolol and halothane anesthesia.[42] The magnitude of these differences warrants further investigation and may portend a significant clinical advantage, particularly for elderly surgical patients.

Myocardial Damage

β-Blockade has been studied as a means of decreasing myocardial ischemia and improving cardiac outcomes.[1,3] We selected cTnI as a surrogate for long-term cardiac outcomes. cTnI is unique to myocardium, and circulating levels of cTnI are not normally detectable. In patients with acute coronary syndromes, progressively increasing levels of cTnI are associated with an increased risk of death, presumably because of the increased amount of myocardial necrosis.[43] Detectable circulating levels of cTnI (> 0.35 ng/ml) below those used to define myocardial infarction are indicative of myocardial damage.[44,45] For the current assay, myocardial infarction was defined as cTnI level > 1.5 ng/ml. Lower levels of cTnI than measured in the current study have been associated with myocardial damage in congestive heart failure.[45] Increased cTnI level, consistent with myocardial damage, was present in 29% of our patients (17 of 59): 42% of group I patients, 20% of group II patients, and 25% of group III patients. The lack of statistical significance may represent a type II statistical error. However, the large percentage of patients exhibiting these levels suggests that this is not a rare event and warrants further investigation in a larger prospective study to determine the

ultimate usefulness of cTnI as a surrogate for cardiac outcome.

Several previous studies have explored perioperative β-blockade and its effect on myocardial ischemia in noncardiac surgery. Stone *et al.*[1] administered a single oral preoperative dose of β-blockers to patients with mild, uncontrolled hypertension. The incidence of myocardial ischemia was 28% in the untreated controls compared with 2% in the β-blocker–treated patients based on ECG criteria derived from a V_5 lead. Wallace *et al.*[2] administered intravenous atenolol preoperatively and intravenous or oral atenolol for up to 7 days postoperatively in patients with or at risk for coronary artery disease. The regimen was similar to group II in this study; however, Mangano et al.[3] and Wallace et al.[2] continued atenolol treatment for the duration of the hospital stay. Intraoperative myocardial ischemia was reported to be 18% in the control group and 12% in the β-blocker–treated group, which did not reach statistical significance. Postoperative ischemia over days 0–7, however, was significantly decreased in the β-blocker–treated group (24 *vs.* 39%). In the current study, no myocardial ischemia was detected by clinicians intraoperatively. A retrospective review of the computerized continuously recorded ST-segment data also failed to detect any episodes of intraoperative myocardial ischemia. In the postoperative period, a 12-lead ECG was obtained at least once for each patient, again failing to detect criteria for new myocardial ischemia. Several factors may explain these differences. Most important, previous studies excluded patients with left bundle branch block, digoxin effects, or ECG evidence of left-ventricular hypertrophy and strain, characteristics that obscure the ECG diagnosis of myocardial ischemia. In the current study a large percentage of patients (43 patients, 73%) showed preexisting ECG changes that complicated the diagnosis of myocardial ischemia. Thus, the ECG may under-report episodes of myocardial ischemia in our patients.

Limitations

Although the treating anesthesiologists were not blinded to group assignment, intraoperative management was directed at titrating HR and blood pressure to prespecified criteria. Because the hemodynamic effects of intravenous atenolol are relatively transparent and the incorporation of a placebo infusion would delay treatment of intraoperative hypertension and tachycardia, we thought that blinding was not justified. Because prespecified criteria were used, clinical care should have been affected only marginally. In addition, the observations in the postoperative period were blinded.

A limited number of parameters were used to assess the impact of β-blockade on the hormonal stress response; inflammatory and immunomodulatory parameters were not assessed.[46] The predictive value of perioperative cTnI levels for cardiac morbidity and mortality rates remains to be validated. All enrolled patients had either documented coronary artery disease or two or more risk factors for coronary artery disease. Such risk factors are common among geriatric patients. Nonetheless, it is not clear that our results would be applicable to elderly patients with no risk factors. A significantly larger clinical trial with long-term follow-up is necessary to address these issues.

In a recent editorial, Warltier[9] stated that "overwhelming" evidence demonstrated the beneficial effects of β-blockade in patients at risk for coronary artery disease and speculated that the relative underuse of these drugs resulted from misperceptions regarding the risk:benefit ratio for patients. The current study particularly emphasizes the idea that the perioperative use of β-blockers can decrease the amount of anesthetic administered to elderly surgical patients at risk for cardiovascular complications without altering the neuroendocrine response to surgery. A lack of alteration in neuroendocrine responses was associated with improved hemodynamic stability and faster recovery from anesthesia. Finally, our current data regarding perioperative cTnI levels are consistent with previous reports of decreased myocardial ischemia and suggest that β-blockade might reduce the incidence of perioperative microinfarctions.

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