Postoperative Myocardial Ischemia

Therapeutic Trials Using Intensive Analgesia Following Surgery

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Recent data suggest that postbypass and postoperative myocardial ischemia are related to adverse cardiac outcome following myocardial revascularization. Therapeutic trials to suppress postoperative ischemia are warranted. Because anesthetics can suppress a variety of physiologic responses to stress as well as myocardial ischemia intraoperatively, we examined whether use of intensive analgesia in the stressful postoperative period could decrease postoperative ischemia. In 165 patients undergoing elective myocardial revascularization, we standardized the anesthetic prior to bypass (sufentanil 5–10 μg/kg induction and 4.2–6.0 μg·kg⁻¹·h⁻¹ [infusion] supplemented with up to 0.5 mg/kg of diazepam). During bypass, patients were randomly assigned to receive either morphine sulfate (group M, n = 54, up to 2 mg/kg) or sufentanil (group S, n = 52, 1 μg/kg and 1 μg·kg⁻¹·h⁻¹). In the intensive care unit (ICU), group M received low-dose analgesia (morphine sulfate 1–10 mg intravenously every 30 min, average dose = 2.2 ± 2.1 mg/h), while group S continued to receive intensive analgesia (infusion of sufentanil at 1 μg·kg⁻¹·h⁻¹). Both groups received supplemental midazolam in the ICU (group M = 1.1 ± 1.1 mg/h; group S = 0.4 ± 0.6 mg/h; P = 0.01). All analgesic and sedative-hypnotic medications were discontinued at 18 hours following myocardial revascularization. Using continuous two-channel electrocardiographic (CCG) monitoring (CCG and CMS), we documented and characterized ECG changes consistent with ischemia during the preoperative, intraoperative (prebypass and postbypass), and postoperative (on- and off-treatment) periods. The total ECG monitoring time was 8,486 h, averaging 81 h per patient. During the prebypass (anesthetic control) period, groups M and S had a similar incidence, but group S episodes were more severe: maximum ST-segment change (median), S versus M: −1.8 mm versus −1.4 mm (P = 0.04). During the postbypass period, both groups had a similar incidence of ischemia, but episodes in group S were less severe: maximum ST-segment change, S versus M: −1.8 mm versus −2.7 mm (P = 0.0005). During the ICU-on-therapy period, the incidence of ischemic episodes was less in group S patients, and the severity was less: area-under-the-ST-time curve, S versus M: −21 mm·min versus −161 mm·min (P = 0.05). After discontinuation of the drug regimen in the ICU, the incidence and severity of ischemic episodes was similar. The incidence of hypotension, hypertension, and tachycardia was similar in both groups in both the intraoperative and ICU periods. Eight patients (8%) had adverse cardiac outcomes: two had fatal myocardial infarctions (both in group M); four had nonfatal myocardial infarctions (one in M and 3 in S); and two had ventricular failure (both in S) (P = not significant). We conclude that the severity of ischemic episodes can be diminished following myocardial revascularization by use of prolonged intensive analgesia. We infer that therapeutic trials designed to reduce postoperative ischemia should specifically include analgesic (and perhaps sedative-hypnotic) regimens, in addition to antiischemic and anti-thrombotic regimens. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: morphine; sufentanil. Heart coronary artery disease: myocardial ischemia. Monitoring: Holter electrocardiography. Surgery: coronary artery bypass graft surgery.)

Patients undergoing coronary artery bypass graft surgery are now older and are maintained longer on medical therapy; in addition, a larger number have had one or more previous myocardial revascularization or angioplasty procedures. Consequently, perioperative cardiac morbidity is increasing; postoperative myocardial infarction occurs in 1–25% and death in 0.5–14% of patients.1,2 It is expected that morbidity and mortality will continue to increase because of the rapid aging of the surgical population and greater prevalence of more advanced coronary artery disease.1

Solution of this problem requires identification of the reversible predictors of perioperative cardiac morbidity, followed by therapeutic trials aimed at modifying these predictors in an effort to decrease morbidity and mortality. Previous studies have focused mainly on the preoperative and intraoperative (prebypass) periods.3–10 However, the greatest increases in plasma catecholamines, stress hormones, heart rate, and left ventricular dysfunction occur following bypass and during the postoperative period.11–15 Consistent with this view are the recent findings that postoperative myocardial ischemia is the most important predictor of adverse cardiac outcome in high-risk noncardiac surgical patients.16 Similarly, in cardiac surgical patients, myocardial ischemia (defined by elec-
trocardiography (ECG) or echocardiography) was demonstrated to be most severe during the first 12 h following bypass,

11,17 and these preliminary data suggest that postoperative ischemia is related to outcome.

Since the early postoperative period has been identified to be the highest risk period, therapeutic trials to suppress postoperative ischemia are necessary. Although a number of cardiovascular antiischemic therapies may be considered, few have direct effects on the stress response during the postoperative period. However, anesthetics and analgesics can have a marked effect on the stress response and therefore may be potentially important therapies for the control of perioperative ischemia. The pivotal work of Lowenstein et al.18 demonstrated that large-dose analgesia (morphine sulfate) could be used with safety in patients with minimal circulatory reserve, leading to the widespread acceptance of the high-dose opioid technique. Subsequent studies extended these findings, demonstrating that anesthetics can suppress the intraoperative stress response10–24 and intraoperative myocardial ischemia as well.11,16,25,26 Therefore, we questioned whether application of an intensive analgesic technique to the stressful postoperative period would decrease the incidence and/or severity of postoperative ischemia.

In order to assess the effect of prolonged intensive postoperative analgesia*** on the incidence and severity of myocardial ischemia, we randomly assigned patients to receive either continuous moderate-dose sufentanil analgesia or intermittent low-dose morphine analgesia (routine care) during the first 18 h following coronary artery bypass graft surgery. To detect myocardial ischemic episodes, the ECG was recorded continuously during the treatment period and for approximately 24 h following treatment.

**Materials and Methods**

**Patient Selection**

After obtaining the approval of our Committee on Human Research and written informed consent, we studied 106 patients (age range = 37–78 yr) scheduled for elective coronary artery bypass graft surgery at the San Francisco Veterans Affairs Medical Center, between August 1987 and March 1990. We excluded those patients with uninterpretable preoperative ECGs (left bundle-branch block) and those undergoing simultaneous valvular repair. Demographic and clinical data collected included: age, history of previous myocardial infarction, hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, previous coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, the anginal pattern, preoperative medications, and cardiac catheterization—including the number of significant coronary stenoses, left main coronary artery disease, and ejection fraction.

One-hundred and twenty-four patients were enrolled in the study. Eighteen patients (8 in group M and 10 in group S) were excluded from analysis. In ten excluded patients (4 in group M and 6 in group S), Holter recordings were uninterpretable because of new right bundle-branch block, left bundle-branch block, or Wolf-Parkinson-White syndrome that developed during the study period. Five excluded patients (3 in group M and 2 in group S) returned to the operating room for reexploration for persistent bleeding during the study period and received a second anesthetic. Three excluded patients (1 in group M and 2 in group S) had adverse events (pacemaker placement, intraaortic balloon pump, or acute myocardial infarction) prior to surgery.

**Electrocardiography**

Patients were monitored continuously using a two-channel Amplitude Modulated Holter ECG recorder (Marquette Electronics, Series 8500) during the preoperative period (mean = 55 h), the prebypass and postbypass intraoperative periods (5 h), and the postoperative “on-therapy” (14 h) and “off-therapy” (27 h) periods. Total ECG monitoring time = 8,486 h, averaging 81 h per patient. The frequency response of the recorders is 0.05–80 Hz at −3 decibels. Two bipolar leads, CC5 and CM5, were used.26 Silver/silver chloride electrodes were used, and skin impedance was <5 kΩ in all patients. The effect of positional variation on ECG morphology was measured before study with patients in the supine, upright, and left and right lateral decubitus positions. Patients were instructed to keep a diary of activity and symptoms during the pre- and postoperative periods and were questioned daily by a study physician.

Holter tapes were analyzed for ST-segment deviation after all abnormal QRS complexes, such as ventricular ectopic beats and beats with conduction abnormalities, had been excluded. The ST-segment was then trended continuously in the two leads for the duration of the tape. The baseline ST-segment level was defined as the average ST-segment over a stable period (usually 15–60 min) preceding each episode. All possible ischemic episodes were reviewed independently by two investigators blinded to patient identity and clinical course (MH and DTM). Electrocardiographic ischemic episodes were defined as reversible ST-segment changes lasting at least 1 min and involving either a shift from baseline (adjusted for positional changes) of ≥1.0 mm (0.1 mV) of ST-segment depression with a slope ≤ 0, or ≥2.0 mm ST-segment elevation at

*** We use the term "intensive analgesia" to denote continuous, moderate-dose opioid administration in the intensive care unit.
the J-point. ST-segment depression was measured 60 ms after the J-point, unless that point fell within the T wave, in which case it was shortened to a minimum of J + 40 ms. To be considered reversible, an ST-segment change had to return to baseline for at least 1 min. The lead (CC5 or CM5) with the most severe ischemic episode was chosen as the representative lead. For each episode, the following were measured: the maximum ST-segment change from baseline, episode duration, and the area-under-the-ST-time curve (AUC). In addition, because the varying amount of time that a given patient was monitored could result in differences in the absolute amount of ischemia detected, an ischemic burden (total ischemic minutes divided by the number of hours monitored) was also computed for each patient.

HEMODYNAMICS

Systemic and pulmonary artery pressures (systolic, diastolic, and mean) were continuously measured and recorded during the intraoperative and postoperative periods. Transducers were balanced and calibrated electronically using a Marquette 7000 hemodynamic monitor and referenced 5 cm posterior to the sternum. Hemodynamic data were recorded every minute directly from the operating room and intensive care unit (ICU) monitors by a computer interfaced (RS232) with the bedside monitor. Time clocks on the Holter monitor and the hemodynamic monitor were synchronized prior to anesthetic induction. For each patient, an analog representation of the digitized data was created, and spurious abnormalities (e.g., catheter movement or transducer flushing) were eliminated manually before analysis. Heart rate was recorded from the Holter monitor. During the intraoperative prebypass period, we defined tachycardia as >20% increase in heart rate, hypertension as >20% increase in systolic blood pressure, and hypotension as >20% decrease in systolic blood pressure compared to preoperative control values. In the intraoperative postbypass and ICU periods, hypertension and hypotension were defined as a systolic blood pressure >160 and <90 mmHg, respectively, and tachycardia and bradycardia as a heart rate >100 and <50 beats/min, respectively.

ANEASTHETIC MANAGEMENT

On the morning of surgery, patients received diazepam 0.1 mg/kg orally and morphine sulfate 0.1 mg/kg intramuscularly as well as their usual cardiac medications. Clinical monitors included a seven-lead ECG, radial artery and pulmonary artery catheters, pulse oximetry, and mass spectrometry. In all patients, anesthesia prior to bypass was sufentanil 5–10 μg/kg for induction followed by an infusion of 4.2–6.0 μg·kg⁻¹·h⁻¹, supplemented with up to 0.5 mg/kg diazepam intravenously. Randomization of patients into the two anesthetic groups signified the beginning of the drug study periods (intraoperative—postbypass and ICU—on-therapy). During bypass, patients were randomly assigned to receive either morphine sulfate, up to 2 mg/kg in divided doses (group M, n = 54) or sufentanil 1 μg/kg as a bolus, followed by an infusion of 1 μg·kg⁻¹·h⁻¹ (group S, n = 52). In the ICU, group S continued to receive the infusion of 1 μg·kg⁻¹·h⁻¹, while group M received intermittent doses of morphine sulfate 1–10 mg intravenously every 30 min, as needed for pain. Both groups received midazolam 1–4 mg intravenously every 20 min as needed for anxiety, and vecuronium 2 mg every 20 min as needed for shivering during the rewarming period. (No patient required more than 10 mg morphine sulfate, 4 mg midazolam, or 2 mg vecuronium during these 20–30 min periods.) All sedation was discontinued at 18 h after cardiopulmonary bypass, based on our previous findings on the time course of postbypass ischemia.11,15

Throughout the perioperative period, clinically detected ischemia was treated in the usual fashion by controlling hemodynamics and using antischemic agents. The use of these agents was not prescribed by protocol but was recorded. In all patients, ventilation was controlled until the morning of the first postoperative day (at approximately 7:00 AM). Oxygen saturation of the arterial blood was continuously monitored and maintained at >97%; similarly, arterial partial pressure of carbon dioxide was maintained between 35–45 mm Hg.

OPERATIVE TECHNIQUE

Cardiopulmonary bypass was performed with a bubble oxygenator using hemodilution and moderate systemic hypothermia (26–28°C). Multiple-dose cold blood (4°C, hematocrit 20–25%) with potassium (20 mEq/l) cardioplegia and topical saline/ice slush was used for myocardial protection during cardiopulmonary bypass (mean duration 100 ± 28 min). Distal anastomoses were performed first during continuous aortic cross-clamping (mean duration 57 ± 17 min), followed by proximal vein grafting during partial aortic occlusion. One hundred patients (52 in group M and 48 in group S) received vein grafts; 91 patients (49 in M and 42 in S) received internal mammary artery grafts to either the left anterior descending or the first diagonal coronary artery. The pericardium was left open in all patients. The quality of the bypass grafts was assessed by surgeons who were unaware of the ECG findings. The grafts were graded qualitatively as excellent, very good, fair, or poor.

OUTCOME MEASUREMENTS

Patients were interviewed and examined by a study physician on each postoperative day until discharge. Post-
operative 12-lead electrocardiograms were obtained daily until hospital discharge. Creatine kinase levels with isoenzymes were obtained on postoperative days 0, 1, and 2 and when clinically indicated by symptoms including shortness of breath, chest pain, or syncope, and whenever ECG changes consistent with ischemia or infarction occurred. Adverse outcomes were noted by study physicians and validated separately by two investigators blinded to the patients’ clinical and monitoring data; disagreements were resolved by consensus, involving a third investigator if necessary. Adverse cardiac outcomes were defined as cardiac death, nonfatal myocardial infarction, and ventricular failure. Cardiac death was diagnosed if the patient died from a myocardial infarction, dysrhythmia, or heart failure caused primarily by a cardiac condition. A diagnosis of myocardial infarction required 1) an elevation of the creatine kinase MB isoenzyme (≥50 U/l) and 2) the development of new Q waves (≥40 ms, 25% R wave). A diagnosis of ventricular failure required a cardiac index < 2 L/min/m², necessitating the use of an intraaortic balloon pump.

**STATISTICAL METHODS**

Chi-square analysis with continuity correction or Fisher exact text was applied to categorical data. Student’s t test was used to test the difference between the means in two groups. Wilcoxon’s paired-sample test was used to compare nonparametric data. Multivariate analysis of variance using repeated measures was used to detect differences among periods (pre-, intra-, and postoperative). Episode characteristics (such as duration) were compared over the three periods by first averaging the durations of all episodes for each patient for each period and then using multivariate analysis as described. A P value of <0.05 (two-sided) identified statistically significant differences. Results are expressed as median values unless otherwise indicated.

**Results**

Clinical and demographic data are shown in table 1. The demographic data and preoperative medications were similar for patients in groups M and S. All 106 patients were men.

**ANESTHETIC-ANALGESIC MEDICATIONS**

During surgery, prior to bypass, the two groups received similar amounts of sufentanil and diazepam (table 2). During bypass, in group M the sufentanil was discontinued (total bypass dose 3.9 ± 3.2 μg/kg) and morphine administered (total bypass dose 0.58 ± 0.55 mg/kg); in group S, sufentanil was continued. The two groups received similar amounts of diazepam during bypass. In the postbypass period and in the ICU during drug adminis-

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Subjects (n = 106)</th>
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<tbody>
<tr>
<td><strong>Group M</strong> (n = 54)</td>
</tr>
<tr>
<td>Preoperative history</td>
</tr>
<tr>
<td>Age in years (range)</td>
</tr>
<tr>
<td>Age &gt; 65 yr</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
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<tr>
<td>Unstable angina</td>
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<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<td>Smoking</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Prior CABG Surgery</td>
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<tr>
<td>Prior PTCA</td>
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<tr>
<td>Preoperative medications</td>
</tr>
<tr>
<td>β-adrenergic blocker</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
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<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>Digitalis</td>
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<tr>
<td>Catheterization data</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>3</td>
</tr>
<tr>
<td>Left-main disease</td>
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<tr>
<td>Ejection fraction</td>
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</table>

Age and ejection fraction are expressed as mean ± SD.
M = patients receiving morphine analgesia; S = patients receiving sufentanil analgesia; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.
For all variables, no significant difference was found between group M and group S patients.
tation (for as long as 18 h postsurgery), group M patients received intermittent morphine, and group S patients continuous sufentanil. In the ICU during drug administration, group M received more midazolam than did group S; following drug administration (after 4:00 AM), the two groups received similar amounts of morphine and midazolam.

INTRAOPERATIVE SURGICAL DATA

No significant difference was found between group M and S patients in the number of grafts placed, the use of internal mammary artery grafts, the coronary arteries bypassed (including the left main coronary artery), the surgeons’ assessment of the revascularization, the aortic cross-clamp time, or the total time on bypass (table 3).

HEMODYNAMIC RESPONSES

Throughout the intraoperative and ICU periods, there was no significant difference in the amount of hypertension, hypotension, or tachycardia, expressed as a percent of the total time monitored, and averaged (mean ± SD) over the population (table 4). In addition, similar amounts of vasodilators and vasconstrictors were used in both groups.

OTHER RELATIONSHIPS

The time to extubation, the duration of ICU stay, and the duration of hospitalization did not differ significantly between groups (table 5). There also was no difference between groups in total fluid intake or output during and after surgery (during drug administration).

MYOCARDIAL ISCHEMIA

To assess the severity of ischemic episodes in individual patients, we plotted the ST-segment change in all patients with ischemia during any period (fig. 1) for group M and group S patients. During the treatment periods (postbypass, ICU-on-therapy), fewer group S patients had ST-segment depression of ≥2 mm (2 vs. 12 patients), and fewer had ≥3 mm depression (0 vs. 8 patients). Examples of the raw data for one group M and one group S patient are presented in figure 2. We also compared the severity of ischemic episodes for patients with ischemia during any period, as measured by ST-segment magnitude, duration, and AUC (fig. 3). During the preoperative period, ischemic episodes were equally severe in group S versus group M patients, as assessed by ST-segment magnitude.
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TABLE 4. Incidence of Hemodynamic Abnormalities

<table>
<thead>
<tr>
<th>Group</th>
<th>Prebypass (Control)</th>
<th>Postbypass (On Therapy)</th>
<th>ICU (On Therapy)</th>
<th>ICU (Off Therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M ± S</td>
<td>M ± S</td>
<td>M ± S</td>
<td>M ± S</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 ± 10% (0.94)</td>
<td>13 ± 20% (0.22)</td>
<td>5 ± 12% (0.77)</td>
<td>3 ± 4% (0.47)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 ± 13% (0.24)</td>
<td>1 ± 2% (0.65)</td>
<td>7 ± 10% (0.68)</td>
<td>9 ± 15% (0.23)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5 ± 6% (0.56)</td>
<td>13 ± 22% (0.65)</td>
<td>30 ± 29% (0.76)</td>
<td>25 ± 28% (0.11)</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD. ICU = intensive care unit; M = patients receiving morphine analgesia; S = patients receiving sufentanil analgesia. (mean values, S vs. M: −1.8 vs. −2.0 mm, P = 0.5; median values, S vs. M: −1.6 mm vs. −1.8 mm, P = 0.3), episode duration (mean values, S vs. M: 34 min vs. 45 min, P = 0.3; median values, S vs. M: 34 min vs. 36 min, P = 0.4), and AUC (mean values, S vs. M: −42 mm·min vs. −64 mm·min, P = 0.3; median values, S vs. M: −29 mm·min vs. −38 mm·min, P = 0.3). The results for the prebypass and other study periods are presented below.

Prebypass Period (Control Period)

During the prebypass period (similar anesthetics), the two groups had a similar incidence of myocardial ischemia (i.e., a similar number of patients with ischemia, a similar number of ischemic episodes), and a similar duration (minutes of ischemia per hour of monitoring). However, group S patients had more severe ischemic episodes, i.e., deeper maximal ST-segment depression (mean values, S vs. M: −1.9 mm vs. −1.5 mm, P = 0.01; median values, S vs. M: −1.8 mm vs. −1.4 mm, P = 0.04).

Drug Study Period: Intraoperative–Postbypass

During the postbypass on-therapy period the characteristics of the ischemic episodes were less severe in group S than in group M patients. Group S patients had less maximal ST-segment depression (mean values, S vs. M: −1.7 mm vs. −3.1 mm, P = 0.001; median values, S vs. M: −1.8 mm vs. −2.7 mm, P = 0.0005).

TABLE 5. Other Relationships

<table>
<thead>
<tr>
<th>Group</th>
<th>Group S</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation (h)</td>
<td>24 ± 8</td>
<td>0.14</td>
</tr>
<tr>
<td>Duration in ICU (days)</td>
<td>3.5 ± 1.9</td>
<td>0.21</td>
</tr>
<tr>
<td>Postoperative duration (days)</td>
<td>11.2 ± 4.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Total intake (ml/kg)*</td>
<td>111 ± 31</td>
<td>0.11</td>
</tr>
<tr>
<td>Total output (ml/kg)*</td>
<td>105 ± 37</td>
<td>0.64</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD. ICU = intensive care unit; M = patients receiving morphine analgesia; S = patients receiving sufentanil analgesia. No differences were significant between groups.

* Total = intraoperative plus postoperative in the ICU.

Drug Study Period: ICU–On-therapy

During the ICU-on-therapy period, the characteristics of the ischemic episodes were less severe in group S than

![Graph showing ST deviation over time for Group M and Group S patients during preoperative, prebypass, postbypass, ICU on-therapy, and ICU off-therapy periods.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931330/)
in group M patients. Group S patients had less severe episodes as assessed by the AUC (mean values, S vs. M: −51 mm·min vs. −207 mm·min, P = 0.04; median values, S vs. M: −21 mm·min vs. −161 mm·min, P = 0.05).

ICU Off-therapy Period

Upon discontinuation of the study treatment, both groups had a similar incidence and severity of ischemia. No rebound effect occurred in group S patients during the ICU off-therapy period.

Other Episode Characteristics

The characteristics of the ischemic episodes, represented as a percentage change from the prebypass—control value, are shown in figure 4. Substantial changes in the characteristics of ischemia occurred in the morphine analgesia group during the postbypass and ICU-on-therapy periods. However, continuous analgesia with sufentanil suppressed these changes.

No difference was found between the sufentanil and morphine groups in the heart rate at onset of ischemia during any study period (median heart rate, S vs. M: prebypass 61 versus 70 beats/min, P = 0.6; postbypass 87 versus 80 beats/min, P = 0.7; ICU on-therapy 94 vs. 92 beats/min, P = 0.3; ICU off-therapy 97 vs. 93 beats/min, P = 0.7).

Combining the results for all patients, the incidence of myocardial ischemia appears to be greatest during the first 8 h following myocardial revascularization (fig. 5) and then decreases gradually such that by 18 h after revascularization (the morning of the first postoperative day), fewer than 10% of patients are ischemic. Both the sufentanil and morphine groups exhibited this characteristic, with the severity of sufentanil episodes being significantly less, as described above.

ADVERSE CARDIAC OUTCOMES

Eight patients (8%) had in-hospital adverse cardiac outcomes, hierarchically classified as fatal myocardial infarct-
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Fig. 3. Characteristics of ECG ischemic episodes contrasted during each study period for group M and group S patients who were ischemic during any study period. Shown are the mean ST-segment deviation (top), ST-segment duration (middle), and the area under the ST-segment–time curve (AUC) (bottom). The asterisks denote significant differences between the group M and group S patients (*P = 0.01; **P = 0.001; ***P = 0.04).

Discussion

The results of our study suggest that the severity of myocardial ischemic episodes can be diminished significantly following myocardial revascularization using intensive analgesia. Our study therefore extends the pivotal work of Lovenstein et al.\textsuperscript{14} and others,\textsuperscript{20–22} who demonstrated the efficacy of higher-dose analgesia for control of intraoperative hemodynamics. From our results, we infer that therapeutic trials designed to reduce postoperative ischemia should specifically include analgesic (and perhaps sedative–hypnotic) regimens, in addition to anti-ischemic and antithrombotic regimens.

Previous Studies

Previous studies of perioperative cardiac morbidity in patients undergoing coronary artery bypass graft surgery have focused mainly on the pre- and intraoperative (pre-bypass) periods\textsuperscript{6–10} in an attempt to define reversible predictors of morbidity. These studies are important because they suggest the potential efficacy of intraoperative high-dose analgesia in ameliorating adverse hemodynamic and other cardiovascular changes. However, multiple stresses also occur during the postbypass and postoperative periods, including pain on emergence from anesthesia, fluid shifts, temperature changes, impaired pulmonary gas exchange, sleep deprivation, coagulation abnormalities, platelet activation with mediator release, and changes in arachidonic acid metabolism.\textsuperscript{19–22,28,29} As a result, the greatest changes in adrenergic activity (sympathetic and parasympathetic), plasma catecholamine levels,\textsuperscript{19} hemodynamics and ventricular function,\textsuperscript{30} and coagulation\textsuperscript{1,28} occur after bypass and during the postoperative period. Thus, the ability to alter cardiac morbidity after coronary artery bypass graft surgery may reside in strategies aimed at modifying postbypass physiologic variables.

Recently, we found that myocardial ischemia (electrocardiographic or echocardiographic) is most frequent and severe during the first 18 h following bypass.\textsuperscript{11,15,17} This high incidence and severity of postoperative ischemia occur despite the achievement of apparently successful myocardial revascularization. These findings parallel those of ventricular function studies,\textsuperscript{30} demonstrating that the most substantial changes in left and right ventricular function occur during the early postoperative period.

Outcome data from cardiac surgical patients are limited, but several studies have suggested or demonstrated an association between perioperative ischemia and adverse outcome.\textsuperscript{10,17,31} Using intermittent ECG data to define prebypass ischemia, Slogoff and Keats\textsuperscript{10} found that prebypass ischemia was associated with postoperative myocardial infarction; however, the postbypass and postoperative periods were not studied. Two studies have examined the prognostic importance of new segmental wall-motion abnormalities.\textsuperscript{17,31} Using intermittent transesophageal echocardiography, Smith et al.\textsuperscript{31} found that intraoperative segmental wall-motion abnormalities were more predictive of postoperative myocardial infarction than were electrocardiographic changes. Using continuous transesophageal echocardiography, Leung et al.\textsuperscript{17} found that segmental wall-motion abnormalities following cardiopulmonary bypass, but not those in the prebypass period, appeared to predict adverse cardiac outcomes.

Thus, it appears that myocardial ischemia that occurs
in the postbypass and postoperative periods may play a critical role in the determination of cardiac morbidity following surgery.

**The Present Study**

Currently, the usual postoperative analgesic management following bypass surgery includes small intermittent doses of an opioid, usually morphine, given in response to complaints of pain or other signs of distress, such as tachycardia or hypertension. These signs most likely reflect sympathetic stimulation, for which small intermittent doses of opioid can only partially blunt the peak effects. Because myocardial ischemia in the postoperative period may be related to increased sensitivity of platelets to epinephrine, decreased fibrinolysis, and decreased left ventricular function, it may be necessary to suppress more fully the activation of the sympathetic nervous system. Cardiovascular therapies (nitrates, β-adrenergic blocking agents, and calcium-channel blocking agents), though potentially effective in blunting ischemia, have little effect on the activation of the sympathetic nervous system. Opioids, however, can decrease heart rate, wall tension, and catecholamines without compromising left ventricular function. These characteristics suggest that such drugs might be useful in the prevention of myocardial ischemia in the postoperative period.

Our study contrasted this usual regimen of intermittent administration of a low dose of opioid (morphine sulfate)
with continuous administration of a moderate dose of opioid (sufentanil). The dose of sufentanil administrated during the postbypass and in the ICU periods was 1 \( \mu g \cdot kg^{-1} \cdot h^{-1} \). Based on the work of Shafer and Varvel, \(^{34}\) using their mathematical models, we estimate that approximately 20 min would be required for a 20% decrease in effect-site concentration, 120 min for a 50% decrease, and 900 min for an 80% decrease. Their data also suggest that opioid concentrations must decrease by 80–90% for adequate ventilation after an opioid–oxygen anesthetic. Assuming that a sufentanil concentration of 0.25 ng/ml is necessary to permit adequate ventilation on emergence (table 2 of their study\(^{34}\)), and given our extubation times for sufentanil (3–6 h following discontinuation of infusion), we estimate that the opioid concentration during infusion of sufentanil during the postoperative period was between 0.5 and 1.0 ng/ml. Although this is less than the concentration required for maintenance with oxygen only (2–8 ng/ml), it is within the opioid concentration range for oxygen–nitrous oxide only. Furthermore, because midazolam was used in our patients, we estimate that the opioid concentration to ablate responsiveness, given our midazolam–sufentanil regimen, would be between 0.5 and 4.0 ng/ml sufentanil. Thus, our postoperative regimen was not markedly dissimilar from an anesthetic regimen capable of blunting intraoperative noxious stimuli, nor from one that could blunt postoperative stimuli.

In comparison, the relative amount of morphine sulfate administered during the study periods was substantially less. Although there are no data in humans directly comparing sufentanil to morphine, and although such comparisons are quite difficult, we can extrapolate from the available data\(^{22,85}\) that sufentanil is at least 100 times more potent than morphine. Thus, in the operating room during cardiopulmonary bypass in the present study, the morphine group received approximately the same amount of opioid as the sufentanil group. However, in the ICU, patients in the sufentanil group received at least five times more opioid than did those in the morphine group (16 \( \mu g/kg \) of sufentanil \( \text{vs. 0.33 mg/kg of morphine} \)), with the average hourly dose of morphine administered being 2.2 mg/h.

Why is the severity of ischemic episodes less in the sufentanil group? Clearly these patients received more opioid than did those in the morphine group; however, neither mean heart rates and systolic blood pressures nor the use of vasopressors and vasodilators differed significantly between the two groups. Thus, gross differences in the indices of myocardial oxygen demand do not appear to be a likely explanation. However, more subtle differences in sympathetic stimulation, though unproven, may exist. Patients given low-dose morphine analgesia appear to have had more sympathetic stimulation (although our study lacks biochemical confirmation) because they received significantly more midazolam than patients given sufentanil analgesia. Thus, we can postulate that the administration of an intensive analgesic in the postoperative period may have suppressed activation of the sympathetic nervous system more completely, thereby having beneficial effects on the sensitivity of platelets to epinephrine,\(^{33}\) on fibrinolysis,\(^{39}\) on regional left ventricular function,\(^{39}\) and on coronary artery vasoconstriction. However, this is only conjecture, and the mechanism for the decreased severity of postoperative ischemia remains uncertain. In fact, it is unclear whether the differences found were due to the significantly different doses of opioid received, the mode of administration, or the agents themselves.

Thus, therapeutic trials are necessary to determine the relative efficacy of different techniques and agents as well as the optimal dosing and duration of administration of analgesics as well as other agents, such as \( \alpha_2 \)-adrenergic agents or propofol.

**Other Findings**

No significant difference in adverse cardiac outcomes (heart failure, myocardial infarction, and death) was found between the two groups of patients. However, because of the low incidence of adverse outcomes, further clinical testing in larger groups of patients is necessary to determine whether decreasing the incidence and severity of postoperative ischemia decreases the number of adverse cardiac outcomes. Our findings regarding the temporal distribution of postoperative ischemic episodes (fig. 5) suggest that the maximal changes occur during the first 8 h. These findings are consistent with our previous results in similar patients,\(^{59}\) which demonstrated that the maximum change in ventricular function occurs within the first 8 h after revascularization. The mechanism is uncertain, but we hypothesize that factors such as the adequacy of myocardial preservation, the completeness of revascularization, the mechanical effects of bypass, and postbypass supply–demand stresses all contribute. Our findings elucidating the time course of the postbypass ischemic changes may be useful for design of future therapeutic trials.

No substantial deleterious effects were associated with use of continuous intensive analgesia in the postoperative period. Specifically, the time to extubation did not differ between the two groups. In addition, the time spent in the ICU and the duration of hospitalization were no different, but these are more subjective measures and are reflective of other nonphysiologic factors, as attested by the apparently prolonged stays at our institution. (For example, the ICU stay reflects both ICU care and step-down care, also performed in our ICU.) Finally, it is our impression that use of the continuous intravenous technique in the ICU is a change in care and would require education of the nursing staff and clinicians.
STUDY LIMITATIONS

The present study is important in being the first to show modulation of postoperative ischemia using intensive postoperative analgesia; but, it has several potential limitations.

1. We cannot state whether the ST-segment abnormalities observed on ambulatory ECG monitoring truly indicate myocardial ischemia. An absolute reference standard does not exist, and, even if available, would be difficult to apply because of the spontaneous occurrence of perioperative ischemia. Thus, to validate such spontaneously occurring ischemic changes, the “gold standard” must be continuously measured; however, few reference standards (such as biochemical assays) can be used continuously, over prolong intraoperative periods. Therefore, establishing the predictive importance of perioperative ST-segment abnormalities may be the only way to ascertain their ischemic “validity.”

2. We chose only one dose of sufentanil for our experimental group, and although it demonstrated an effect on the severity of ischemia in the ICU period, a smaller dose may be equally effective. In contrast, a larger dose might have reduced both the incidence and severity of postoperative ischemic episodes. If this technique is to be widely applied, dose–response studies are necessary.

3. Although we have shown the ability to blunt postoperative myocardial ischemia using a high-dose infusion of sufentanil, conclusive outcome data linking postoperative ischemia to perioperative cardiac morbidity in cardiac surgical patients are lacking. Therefore, a large outcome study examining the relationship between perioperative myocardial ischemia and perioperative cardiac morbidity is necessary.

CLINICAL IMPLICATIONS AND CONCLUSIONS

The results of our study suggest that the severity of ischemic episodes can be diminished following myocardial revascularization using intensive analgesia. Although we are not necessarily recommending the use of continuous intensive analgesia in the postoperative period, we do recommend that additional therapeutic trials be performed to determine the optimal postoperative analgesic or sedative–hypnotic regimen for reduction of postoperative ischemia and perioperative cardiac morbidity. Therapeutic trials designed to reduce postoperative ischemia should specifically incorporate such analgesic (and/or sedative–hypnotic) regimens, in addition to antiischemic and antithrombotic regimens.


30. Mangano D: Biventricular function after myocardial revascularization in humans: Determination and recovery patterns during the first 24 hours. ANESTHESIOLOGY 62:571–577, 1985


Appendix

The SPI (Study of Perioperative Ischemia) Research Group consists of: